Prevention of Yellow Fever in Persons Traveling to the Tropics

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Yellow fever (YF) is a potentially lethal mosquito-borne viral hemorrhagic fever endemic in Africa and South America. Nine million tourists annually arrive in countries where YF is endemic, and fatal cases of YF have occurred recently in travelers. In this article, we review the risk factors for YF during travel and the use of YF 17D vaccine to prevent the disease. Although the vaccine is highly effective and has a long history of safe use, the occurrence of rare, fatal adverse events has raised new concerns. These events should not deter travelers to areas where YF is endemic from being immunized, because the risk of YF infection and illness may be high in rural areas and cannot be easily defined by existing surveillance. To avoid unnecessary vaccination, physicians should vaccinate persons at risk on the basis of knowledge of the epidemiology of the disease, reports of epidemic activity, season, and the likelihood of exposure to vector mosquitoes.
with only 11 reported cases since 1950 [6, 7]. YF is a zoonosis; it is transmitted from monkeys to humans by the agency of vector mosquitoes. The risk of a traveler acquiring YF is determined by immunization status, geographic location, season of travel, length of exposure, occupational and recreational activities partaken of while traveling, and the rate of YF virus transmission at the time. Although reported cases of human disease are the principal guide to the level of YF transmission, they may be absent (because of a high level of immunity in the population) or not detected (because of poor surveillance). Few YF cases are officially reported, because the disease occurs in remote areas that lack specific diagnostic facilities. For example, in an outbreak in The Gambia that spanned ~6 months (1978–1979), the incidence of YF virus infection was 33% and the incidence of severe disease with jaundice was 4.4%, with a case-fatality rate of 19.4%. Only 30 cases were officially reported out of a probable 8400 cases and 1600 deaths [8]. Remarkably similar incidences of infection and disease have been recorded in many other YF outbreaks in Africa [6]. Presently, epidemic activity is ongoing in the Ivory Coast, Guinea, and Liberia. One may estimate that an unimmunized person entering an area of epidemic activity would have risks of YF illness and death of 1:267 and 1:1333, respectively, for a 2-week trip.

During interepidemic periods in Africa, the incidence of overt disease is less than the threshold of detection of existing means of surveillance. Interepidemic conditions may last years or even decades in specific countries or regions. "Epidemiological silence" may provide a sense of false security and lead to travel without the benefit of vaccination. Surveys in rural West Africa during "silent" periods indicate that the incidence of YF illness is 1.1–2.4 cases per 1000 persons and the incidence of death due to YF is 0.2–0.5 deaths per 1000 persons, which are less than the threshold of detection of the existing means of surveillance [9]. The risks of illness and of death due to YF in an unvaccinated traveler are estimated to be 1:1000 per month and 1:5000 per month, respectively (for a 2-week journey), the risks of illness and death are 1:2000 and 1:10,000, respectively, although the risks vary considerably according to season. In West Africa, the most dangerous time of the year is during the late rainy and early dry seasons (July–October). These estimates, which are based on risk to indigenous populations, may overestimate the risk to travelers who take precautions against getting bitten by mosquitoes and who have less outdoor exposure than do indigenous residents.

The incidence of YF in South America is lower than that in Africa, because virus transmission between monkeys and mosquitoes occurs in the canopy of the forest, isolated from human contact, and because vaccine coverage is high. The risks of illness and death are probably 10 times lower in South America (i.e., 1:20,000 for illness and 1:100,000 for death for a 2-week journey) than they are in rural West Africa, but the risks vary greatly according to specific location and season. As in Africa, virus transmission between mosquitoes and monkeys may be epidemiologically silent, although some monkey species succumb to infection. Virus transmission is highest during the rainy season (January–March) in Brazil. The low reported incidence of YF (generally a few hundred cases per year) has resulted in lullied concern among travelers. In Brazil, for example, where the majority of the population lives in coastal regions outside of the zone of endemicity, unimmunized recreational or vocational travelers to the interior of the country are the usual persons to be affected by YF. Three of the 4 patients from the United States and Europe who acquired YF in 1996–1999 were exposed in South America [7, 10, 11]. Although it is not as dramatic as the situation in Africa, the 1990s represented a period of increased enzootic and epizootic YF transmission in South America. Brazil and Peru are currently experiencing an expansion of YF virus activity, and the risk to travelers is higher than usual.

**GEOGRAPHIC CHARACTERISTICS OF YF AND COMMENTS ON THE INTERNATIONAL HEALTH REGULATIONS**

Because it is not possible to define the risk of exposure to YF on the basis of surveillance data, all persons traveling outside urban areas of countries where YF is endemic should be vaccinated. The zone of endemicity and areas that have sustained recent epidemics are shown in figure 1. Urban outbreaks have been reported from the Ivory Coast and Nigeria recently, and recommendations regarding rural versus urban travel need to be continuously reconsidered (as discussed in the next paragraph). Autochthonous cases of YF have also been reported in selected cities and periurban areas in Bolivia and Brazil. The threat of more-wide spread urban YF in the Americas is a serious concern, which may change vaccination recommendations in the future.

It is difficult to obtain specific information about the geographic characteristics of YF even from health professionals in their indigenous geographic areas. Moreover, the epidemiological status of YF is never static, and what is true one year may not be the next. For example, Iguazu Falls, a favorite tourist destination on the Brazil-Argentina border, is usually not a high-risk area, but it may be so during exceptional periods of epizootic expansions, such as those that occurred in 1966 and 2001. Travel to urban areas within the zone of endemicity, such as Iquitos (Peru), Manaus or Brasilia (Brazil), or Enugu (Nigeria), generally present a low risk, which, however, cannot be taken as zero risk. Because urban (Aedes aegypti–borne) YF occurs regularly in West Africa, vaccination is recommended for persons traveling to towns and inland cities within the zone of endemicity. Cases of YF are currently being reported within...
CASES OF YF IN TRAVELERS AND EXPATRIATES RESIDING IN COUNTRIES WHERE YF IS ENDEMIC

Cases reported since 1970 are listed in table 1. These cases illustrate a number of points: (1) all patients traveled to remote, rural areas; (2) the duration of exposure was relatively brief in some cases; (3) there was no evidence of an ongoing epidemic in the location of exposure, although YF activity may have occurred in the recent past or in surrounding areas; (4) the disease was fatal in most cases, suggesting that there may have been other cases with mild or abortive infection that were missed; (5) there was a potential for introduction of YF to receptive areas and secondary spread by the urban vector, A. aegypti; and (6) most patients had not been vaccinated. It is possible that the cases that occurred among vaccinated travelers resulted from the use of vaccine that had deteriorated during storage. However, in various clinical trials of YF vaccines, 1%–5% of vaccine recipients have not responded to vaccine, as determined by a neutralization test; this suggests that primary vaccine failure may occur at a low incidence [6, 16].

YF VACCINE

The live, attenuated YF 17D vaccine is delivered as a single subcutaneous inoculation of 0.5 mL. The vaccine induces neutralizing antibodies (the mediator of protection) in 90% of vaccine recipients within 10 days after inoculation and in 99% within 30 days after inoculation. Immunity is very durable and probably lifelong [17], although revaccination is recommended at 10-year intervals. No cases of secondary vaccine failure (i.e., YF occurring in an individual who had been shown to respond to the vaccine but who lost protective immunity over time) have been identified. The vaccine may be simultaneously administered with most other vaccines, including measles, BCG, inactivated and oral polio, diphtheria-pertussis-tetanus, meningococcus, hepatitis B, hepatitis A, oral cholera, oral typhoid, and parenteral typhoid vaccines [18–23]. If other live viral vaccines, such as the measles and the measles-mumps-rubella vaccines, are not administered simultaneously, administration should be separated by 1 month. There are no data on co-administration with Japanese encephalitis (JE) vaccine (another flavivirus), although interference is unlikely. Prior infection or immunization with JE does not interfere with YF vaccination [24, 25], but cross-protection due to prior dengue infection probably reduces the response to YF vaccine [26].
attenuated JE and dengue vaccines come into use, research will be needed on interactions between those vaccines and YF 17D. YF 17D vaccine is well tolerated. In practice, a small proportion of subjects complain of injection site pain, inflammation, fever, mild headache, myalgia, and malaise. In clinical trials in which the subjects were directly questioned, local and systemic adverse events have been reported by ∼25% of vaccine recipients during the first 3–7 days after inoculation [3, 16, 19, 21], but these events are mild and do not interfere with normal activities. Mild systemic reactions are probably mediated by cytokines. In persons who are vaccinated for the first time, mild viremia, not exceeding 10^2 pfu/mL, occurs for 1–3 days between the third and seventh day after vaccination and is associated with elevations of IFN-α, TNF-α, and markers of T cell activation (i.e., neopterin and β2 microglobulin) [27–30]. Revaccination results in no viremia and a lower incidence of adverse reactions [16, 28, 30], because the vaccine inoculum is neutralized by preformed antibody.

Serious and severe adverse reactions are extremely rare. These fall into 3 major categories: (1) hypersensitivity reactions, (2) encephalitis caused by neuroinvasion of the 17D virus, and (3) pansystemic infection, including hepatitis, which is similar to wild-type YF.

**Hypersensitivity reactions.** YF 17D vaccine is an extract of embryonated chicken eggs, and it is contraindicated for persons with a clear history of egg allergy (i.e., oral intolerance). In persons without egg allergy, systemic allergic reactions (e.g., anaphylaxis and urticaria) occur at an incidence of 1 case per 58,000–131,000 persons vaccinated [31], and the reactions may be caused by sensitivity to the hydrolyzed porcine gelatin used to stabilize the vaccine.

**Postvaccinal encephalitis.** Although up to 400 million persons have received YF 17D vaccine, there have been only 21 patients with postvaccinal encephalitis described in the literature, of whom 20 recovered without sequelae and 1 died [6]. Unpublished postmarketing surveillance of adverse events confirms that encephalitis is very rare, occurring at a rate of <1 case per million doses. Because postmarketing surveillance is passive, the true incidence may be higher. Postvaccinal encephalitis occurs principally in very young infants. Eighteen of the 21 published cases of postvaccinal encephalitis occurred in children, of whom 16 were infants of ≤7 months of age. Virus recovered from the brain of the single patient to have died contained 2 amino acid changes in the envelope glycoprotein gene and had increased neurovirulence in animals [32], which suggests that mutation of the vaccine virus during replication in the patient was responsible for the event.

**Fever, jaundice, and multiple-organ failure associated with YF vaccination.** Ten cases (8 of which were fatal) of a syndrome resembling wild-type YF associated with YF 17D vaccination have recently been described. Of the 10 cases, 7 have been reported in the literature [33–35], 6 occurred in persons immunized for travel, and 4 occurred in persons living in a region of endemicity. Four cases in the United States occurred in elderly patients, had a diversified and complex clinical presentation, and were labeled “multi-organ failure,” which reflects the uncertainty regarding the role of YF17D in direct viral injury. In contrast, extensive virological evidence in the cases that occurred in Brazil and Australia support the conclusion that an overwhelming infection with 17D virus was responsible.

These adverse events were characterized by rapid onset of fever and malaise within 3–5 days after vaccination; jaundice, oliguria, cardiovascular instability, and hemorrhage; and midzonal necrosis of the liver noted at autopsy [34, 35]. Large amounts of YF viral antigen were found in the liver and in other affected organs. Similar cases have undoubtedly occurred throughout the history of use of YF 17D vaccines, but they were missed or misdiagnosed.

The actual incidence of the syndrome is unknown. Estimates from a retrospective review of events passively reported to the Vaccine Adverse Events Reporting System (VAERS) in the United States during 1990–1998 suggest a reported rate of 1 case per 400,000 persons [33], but the true incidence will remain uncertain until prospective surveillance is applied to large

### Table 1. Reported cases of yellow fever in travelers, 1970–2000.

<table>
<thead>
<tr>
<th>Date of diagnosis</th>
<th>Age in years, sex</th>
<th>Vaccination status</th>
<th>Place of residence</th>
<th>Place of exposure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 1979</td>
<td>42, M</td>
<td>Not vaccinated</td>
<td>France</td>
<td>Senegal</td>
<td>Died</td>
<td>[12]</td>
</tr>
<tr>
<td>October 1979</td>
<td>25, M</td>
<td>Not vaccinated</td>
<td>France</td>
<td>Senegal</td>
<td>Died</td>
<td>[12]</td>
</tr>
<tr>
<td>October 1987</td>
<td>37, F</td>
<td>Vaccinated</td>
<td>Spain</td>
<td>Niger, Mali, Burkina Faso, Mauritania</td>
<td>Survived</td>
<td>[14]</td>
</tr>
<tr>
<td>August 1996</td>
<td>42, M</td>
<td>Not vaccinated</td>
<td>United States</td>
<td>Brazil</td>
<td>Died</td>
<td>[10, 11]</td>
</tr>
<tr>
<td>August 1999</td>
<td>40, M</td>
<td>Not vaccinated</td>
<td>Germany</td>
<td>Ivory Coast</td>
<td>Died</td>
<td>[15]</td>
</tr>
<tr>
<td>September 1999</td>
<td>48, M</td>
<td>Not vaccinated</td>
<td>United States</td>
<td>Venezuela</td>
<td>Died</td>
<td>[15]</td>
</tr>
</tbody>
</table>
populations undergoing primary vaccination. Since the syndrome was first described in 1996, ~190 million doses of YF vaccine have been distributed, and there have been 10 reported cases of this syndrome. The syndrome can probably occur only in patients who have undergone primary vaccination. Some of the patients from the United States developed very high titers of YF antibody, suggesting either prior exposure to a heterologous flavivirus or a response to abnormally high levels of YF 17D replication and antigen expression.

The syndrome is apparently not caused by mutations in the virus, but rather by the unusual susceptibility of the individual host. The virus strains recovered from patients with fatal cases failed to show mutations that could explain the unusual clinical presentation [35, 36]. The host factors for increased susceptibility are not yet identifiable. A genetic basis is likely, on the basis of observations of mice showing genetic control of susceptibility to flaviruses [37].

Retrospective analysis of VAERS data in the United States revealed a higher incidence of severe adverse reactions in elderly persons: persons aged >75 years had a risk 12 times higher than that for young adults, which suggests that waning immi-

nity with age may play a role [38]. However, elderly subjects who developed multiple-organ system failure in the study had robust immune responses to YF17D virus [35]. Although the 4 deaths in Brazil that occurred during 1999–2001 were in children and young adults, any predilection for severe reactions in the elderly population (observed in the United States) would not be apparent in Brazil, because older persons have been vaccinated in the past. In summary, no clearly identifiable risk factors related to age and immunological competence can be formulated at the present time.

Although there are no definitive data, it is likely that the vaccine may induce a milder form of hepatic injury without overt clinical signs. In a recent Phase III trial of 2 YF 17D vaccines manufactured in the United Kingdom and the United States (Arilvax [Evans Vaccines] and YF-Vax [Aventis-Pasteur], respectively), elevations in alanine and aspartate amino-transferase levels were noted in 3.5% of the subjects in both treatment groups 10 days after vaccination, with resolution thereafter [16]. Without a placebo group, it is uncertain whether the chemical hepatic dysfunction was caused by vaccine. If so, subclinical hepatic dysfunction is probably inconsequential, because persons who survive severe hepatitis due to wild-type YF have complete healing of the liver without postnecrotic cirrhosis.

Patients with an undiagnosed febrile illness that occurs within 10 days after vaccination should be investigated, and those with elevated liver enzyme levels should be hospitalized for observation. The examination should include collection of serial samples for quantitative viremia and antibody studies, preservation of frozen buffy coat cells for future genetic studies, reporting of the event to the VAERS (toll-free number, 1-800-822-7967), and consultation with the CDC (Division of Vector-Borne Infectious Diseases in Fort Collins, Colorado, 303-221-6400; CDC Division of Quarantine in Atlanta, 404-417-8000) [39].

**PRECAUTIONS FOR THE USE OF YF 17D VACCINE**

Physicians faced with questions about allergy, immunosuppression, or other contraindications to YF vaccination should carefully consider the true risk of exposure on the basis of the regions to be visited. Unvaccinated subjects should be advised not to travel to a region affected by a YF epidemic or to very high-risk areas, such as rural West Africa or the Amazon forest.

**Young age.** Because of the increased risk of postvaccinal encephalitis, YF vaccine is not recommended for infants aged <9 months (or <6 months during epidemics), and vaccination is absolutely contraindicated for infants aged ≤4 months.

**Egg intolerance.** Travelers with a history of egg allergy should undergo skin testing, proceeding from a scratch test to intradermal inoculation with increasing concentrations of the vaccine, as described in the vaccine package insert (YF-Vax; Aventis Pasteur) [40]. For patients who have a positive test result, the full dose should not be administered and a neutralization test should be performed >14 days later to determine whether seroconversion caused by the skin-test dose occurred. (For antibody testing, contact the Director of Laboratories, State Health Department, who may refer the request to the CDC, Fort Collins, CO.) Determination of neutralizing antibodies is the only useful test for immunity, and other less specific, less sensitive, or nonbiological assays (e.g., ELISA, hemagglutination-inhibition, and immunofluorescence) should not be used [41]. If seroconversion does not occur, desensitization before vaccination may be considered (as described in the product label), or, alternatively, personal protection against mosquito bites or avoidance of travel may be recommended.

**Immunosuppression and malignancy.** On theoretical grounds, persons with immunodeficiency due to malignancy, HIV/AIDS, or receipt of immunosuppressive therapies should not be vaccinated, because prolonged viremia may increase the risk of neuroinvasion and encephalitis, and unrestrained virus replication could enhance damage to the liver and other visceral organs. However, there are no reports of adverse events in immunosuppressed individuals. No adverse events occurred in a small study of HIV-infected children with low CD4+ cell counts; however, such patients may not have been immunized effectively [42]. Asymptomatic HIV-infected travelers with CD4+ cell counts of ≥200 cells/mm³ who require vaccination for travel should be immunized. If possible, tests should be performed to determine whether they have developed neutralizing antibodies. Similar considerations apply to persons...
taking high-dose corticosteroids or antineoplastic drugs. Recommendations of the Immunization Practices Advisory Committee (ACIP) [43] specify that intra-articular or bursal treatment with corticosteroids, short-term treatment (i.e., for <2 weeks), or systemic doses of ≤10 mg of prednisone or the equivalent are not significantly immunosuppressive and do not constitute a contraindication to vaccination.

Recently we had the opportunity to assist in the treatment of a patient with chronic lymphatic leukemia for whom active vaccination was contraindicated. Commercial lots of intravenous immunoglobulin (IVIG) contain high titers of YF neutralizing antibody [44], because 5%–10% of adult male donors in the United States were vaccinated during military service. The protective level of YF neutralizing antibody is accepted as a log neutralization index of 0.7 [45]. The patient with chronic lymphatic leukemia was treated with IVIG that had an log neutralization index of 3.0 to achieve a high initial passive titer and a protective level of antibody throughout several weeks of travel (R. McMullen, T. P. Monath, R. Nichols; unpublished data).

**Pregnancy.** The safety of YF vaccination during pregnancy has not been established, and the vaccine should be given only if travel to an area of endemicity is unavoidable and if there is a high risk of exposure. Congenital infection of the fetus with YF 17D appears to occur at a low rate (probably 1%–2%) and has not been clearly associated with fetal abnormalities [4]. In a case-control study of YF 17D vaccination of women in the early stages of pregnancy, the relative risk of spontaneous abortion was 2.3, but this study lacked statistical power [46]. Pregnant women who have received the vaccine should be reassured that there is no risk to themselves and very low risk to the fetus. These women should be observed until parturition, and if fetal abnormality is noted, a cord blood sample should be obtained for IgM testing to determine whether congenital infection had occurred. Of interest, the immune response to YF vaccination during pregnancy is impaired, and revaccination is indicated after parturition [47]. If vaccination during pregnancy is required because of a high risk of exposure during travel, it is advisable to measure neutralizing antibodies 14 days after inoculation. If the patient is seronegative, revaccination should be considered.

**RISKS AND BENEFITS**

Until the reports of multiple-organ system failure in 1996, YF 17D was widely accepted as an innocuous vaccine, with very rare complications that occur principally in persons with identifiable risk factors [2, 6]. The new serious adverse events that have occurred in persons without risk factors (except possibly advanced age) mandate closer attention to the risk-benefit
Figure 3. Comparison of models for yellow fever (YF) vaccine coverage of persons traveling to countries where YF is endemic. Variables in the model are shown in the inset key. Five parameters were varied in the model. These variables, in left to right order in the inset, were vaccine waste (0% or 1%), the proportion of travelers who were revaccinated at the recommended 10-year interval (0% or 5%), the proportion of travelers who had already been vaccinated (0%, 5%, or 10%), and the proportion of travelers at risk of acquiring YF by virtue of travel to regions where YF is endemic in countries that have zones both inside and outside the region of endemicity (33% or 100%).

equation. Until the incidence of the syndrome is quantified, it will be difficult to make clear recommendations. The estimated incidence of 1 case per 400,000 persons vaccinated [33], if accurate, may be compared with the 1 case per 750,000 risk of vaccine-associated paralytic poliomyelitis in primary vaccine recipients. Serious adverse event rates of this order of magnitude are high enough to restrict vaccination to persons who are truly at risk of exposure. As described in the section Risk of Acquiring YF during Travel, our conclusion is that the risk of wild-type YF exceeds the risk of vaccination for persons traveling to rural areas in the zone of endemicity, to inland towns and cities, or to urban areas sustaining YF outbreaks. The low incidence of recognized YF cases in travelers (table 1), despite a low vaccination coverage (discussed in the section Vaccine Coverage, below) suggests, however, that the overall risk of YF exposure may be overestimated. If there are 3 million unvaccinated travelers to regions of endemicity (as suggested in the section Vaccine Coverage, below), and the risk of death due to YF is 1 death per 10,000 infections, one would expect 300 deaths per year, whereas only 2 cases per year have been reported.

The problem is that there is no way to accurately assess the specific level of risk to the individual traveler, and the vagaries of YF virus activity in tropical jungles and forests defy prediction. The traveler and his or her physician will generally wish to accept a defined risk of adverse events due to vaccination rather than experience the fear and uncertainty associated with possible acquisition of a fatal illness during travel. However, unnecessary vaccination for travel to regions where YF is not endemic but that are within the zone of endemicity, such as coastal South America, should clearly now be avoided.

MEANS OF PREVENTING YF OTHER THAN VACCINE

Travelers who must enter areas of possible YF activity without the benefit of vaccination should take precautions against exposure to vector mosquitoes. These vectors are principally daytime biters. The use of protective clothing and repellents applied to exposed skin and to thin clothing that is penetrable by mosquito mouthparts can reduce the risk of exposure. In rural wooded areas and in moist savanna regions of Africa, use of these measures should be a continuous ritual. Indoor living spaces should be sprayed with pyrethrin insecticides, and care should be taken to treat secluded spaces, such as closets.

LOCATION OF VACCINATION CENTERS IN THE UNITED STATES

YF vaccine is available only at certified vaccination centers. The certification of YF vaccination centers is a responsibility that has been delegated to state health departments by CDC since 1977. In the United States, 3110 centers were available to the general public as of June 2001 (figure 2). These centers are concentrated in large metropolitan service areas. On a state-by-state basis, there is little variation in the density of centers. On average, each state has 1 certified center per 100,000 population, with a range of 1 center per 500,000 population in Tennessee to 1 center per 20,000 population in Alaska. Elsewhere, we have expressed concern that the urban distribution of centers represents an possible barrier to immunization in rural areas where driving distances to centers are long [48].

VACCINE COVERAGE

Although the number of persons traveling from the United States to areas where YF is endemic may be as high as 3 million, only 150,000–300,000 civilian travelers are vaccinated annually. A recent attempt to estimate vaccination coverage used a mathematical model based on the number of annual US arrivals to countries where YF is endemic (published by the World Tourism Organization) and on the number of doses of YF vaccine doses sold to civilians in 1992–1998. Several assumptions were made in developing the model that limit the conclusions until they can be independently verified. We assumed, in each year, that a constant 99% of vaccine sold was administered to individuals traveling to a country in trop-
tical South America or Africa where YF is endemic (we assumed 1% waste, either caused by the clinic refrigerator or because of administration of vaccine to persons traveling outside the countries where YF is endemic), and that 5% of the persons traveling to countries where YF is endemic had been immunized within the past 10 years. We calculated the size of the at-risk target population as follows: (1) with 33% risk, assuming that only 1 of every 3 travelers to countries of endemicity would go to a rural area of the country, and (2) with 100% risk, assuming all travelers to countries where YF is endemic are potentially at risk. Vaccination coverage for the 2 models is shown in figure 3. If only 1 in 3 travelers to countries where YF is endemic are considered, the coverage rate decreased steadily, from 64% in 1992 to 31% in 1998. If all travelers to countries where YF is endemic are considered, coverage decreased from 21% in 1992 to 10% in 1998. In both scenarios, the coverage decreases by >50% during the 7 years, largely because the rate of increase in travel to countries where YF is endemic vastly outstrips the amount of vaccine being given. The 2 recently imported cases of YF into the United States in 1996 and 1999 highlight the underuse of YF vaccine.

BARRIERS TO VACCINATION OF TRAVELERS

Traditional barriers to vaccination, such as cost and access, are unlikely to explain the suspected underuse of YF vaccine among travelers. The cost of the vaccine (approximately $50 for a single-dose vial in the United States) is modest compared with the other costs associated with travel. Lack of awareness about YF among providers and travelers is common, especially during periods of epidemiologic silence, and it is probably the most important factor. Providers are often confused by the difference between a “recommendation” for vaccination, which is designed to protect the individual traveler, and the political “entry requirements” for proof of YF vaccination, which are designed to protect a host country from importation of the virus. This confusion results in both overvaccination and undertreatment. Disease risks associated with travel are not advertised by countries wishing to attract tourists, and travel agents are not motivated to disseminate information regarding health risk. Finally, periodic fluctuations in vaccine supply and distribution may contribute to undertreatment.

RISK OF URBANIZATION

Unimmunized travelers represent the means by which YF may be introduced to receptve regions of the world. YF is currently not present in the United States, Central America (west of the Panama Canal), Mexico, the Caribbean, Australia, the Middle East, southern and northern Africa, or Asia. Countries in these regions are infested with A. aegypti and are susceptible to the introduction and spread of YF.

Virus is present in the blood during the incubation period and early stage of illness at levels capable of infecting blood-feeding A. aegypti. The recent appearance of West Nile virus in North America, which was possibly introduced by a viremic human, and of dengue in Hawaii illustrate the potential for the reemergence of urban YF, and the movement of YF-infected travelers is documented by recent imported cases (table 1). It is likely that secondary spread of YF virus in the United States would be identified rapidly, because of the dramatic clinical presentation of typical cases, and that it would be contained by vaccination and vector control. However, because full-blown cases of YF occur in only ~1 of 7 persons infected with the virus [9], virus amplification would occur before detection.

Introduction and spread of YF in other areas of the world (India and Asia, in particular) has long been considered a significant threat. Logistical barriers are breaking down as air travel increases and areas of Africa and South America where YF is endemic become less remote. Cross-protective immunity to dengue appears to be a barrier to YF in these regions [6, 49]. Time will tell whether YF will recur outside of its present boundaries, but steps to mitigate this risk should be a goal of public health programs. One specific area of concern is the worldwide shortage of YF vaccine and barriers to use of vaccine that is manufactured elsewhere and not regulated by national health control authorities. In the event of an epidemic, the amount of vaccine required might exceed the national supply. Importation of vaccine from other manufacturers might be delayed, and such vaccine would be considered an investigational product, requiring delivery under a clinical protocol requiring informed consent. On a worldwide basis, there is currently a shortage of YF vaccine, such that regional needs are not being met.

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