We report three cases of yellow fever (YF) in a family traveling from the city of Sao Paulo, Brazil (without previous vaccination) to an endemic area, acquiring the disease and presenting mild-to-moderate symptoms. Despite posing the intermittent risk of YF in endemic areas, it also alerts to the threat of introduction and spread of YF in the urban cycle, when infected travelers return to non-endemic areas where potential vectors are highly prevalent.

Yellow Fever (YF) is a zoonotic disease caused by YF virus, the prototype virus of the family Flaviviridae (genus Flavivirus). The disease is distinguished by two transmission cycles: sylvatic, transmitted among wild nonhuman primates by the Haemagogus janthinomys and Sabethes chloropterus mosquitoes; and urban, transmitted to humans from infected Aedes aegypti. The clinical presentation ranges from nonspecific illness to fatal hemorrhagic fever. Approximately 90% of cases are asymptomatic or mild. Among the remaining 10% (severe cases), the mortality rate is 50%. The incubation period varies from 3 to 6 days, and symptom onset is typically abrupt, with fever, chills, malaise, headache, lower back pain, and myalgia. In 15% to 25% of cases, the presentation includes fever, vomiting, jaundice, renal failure, and hemorrhagic diathesis. Viremia peaks 1 to 3 days after symptom onset and is of longer duration among nonsurvivors. IgM antibodies appear during the first week of illness, by the end of which neutralizing antibodies (and T cell responses) clear the virus. In humans, the disease is preventable through vaccination. A single dose of the 17D vaccine protects for 10 years or longer.

The risk of YF in travelers to endemic areas is difficult to ascertain, since it is influenced by various factors: immunization status, occupational and recreational activities while traveling, duration of travel and of exposure, geographic location, season, and local rate of virus transmission. Approximately 200,000 cases occur annually: 90% in Africa and 10% in the tropical regions of South America. Between 1990 and 2006, there were 478 confirmed cases in Brazil, with 202 deaths. In the first 4 months of 2008, there were 41 confirmed cases and 21 deaths (mortality rate 42.2%–51%). Most cases (90%) were in unvaccinated travelers or in those who had ignored vaccination status and 10% had nine or more years without boosters.

Although reported cases of human disease are the principal guide to the level of YF transmission, under-reporting can occur due to asymptomatic infection, limitations of passive surveillance, and a lack of diagnostic capability. The risks of YF disease and death are approximately 10 times lower in South America than in Africa (1:20,000 for disease and 1:100,000 for death for a 2-wk rural journey), although the risks vary by specific location, season, and the immunization of the local population. There have been few reported cases of YF acquired by travelers. In the last 30 years, there have been only 10 such reports, 9 of which were related to unvaccinated travelers to endemic regions. Of the four travelers contracting YF in South America, three were infected in Brazil (in the state of Amazonas) and one was infected in southeastern Venezuela. However, since the majority of the population living in the endemic region is immunized, most cases in South America are the result of unvaccinated tourists and migrant workers moving from non-endemic coastal regions to the interior. We report cases of YF in three family members that traveled to an endemic area. The samples were tested using the IgM antibodies capture enzyme-linked immunosorbent...
assay (MAC-ELISA). All three presented signs of and positive serology for YF (MAC-ELISA). They had not used repellents or mosquito nets and had been exposed to floodwater and to mosquito bites while trekking through an endemic area of YF. None of the three had ever been vaccinated against YF (Table 1).

Case report

Case 1 (index case)

A 49-year-old female was admitted to the hospital in the city of Sao Paulo, a non-endemic area of YF, after acute onset of fever, myalgia, arthralgia, retro-orbital pain, and headache. She had never been vaccinated against YF. In the initial physical examination, she was alert but presented headache, together with myalgia in the lower limbs. Her temperature was 39°C. Jaundice was not noted, and the lungs were clear to auscultation. She reported that, 5 days prior to symptom onset, she had been exposed to floodwater and mosquito bites while trekking through an endemic area of YF—the zone surrounding the rural township of Agua Clara (20°26′53″S; 52°52′41″W; population, approximately 13,000), located in the state of Mato Grosso do Sul, in central-west Brazil. She had not used any form of insect bite protection. Her medical history was unremarkable.

Initial laboratory test results were as follows: leukocyte count, 2,910/mm³ (34% neutrophils, 56% lymphocytes, and 10% monocytes); hematocrit, 39%; platelet count, 89,000/mm³; blood urea nitrogen, 32 mg/dL (normal 10–50 mg/dL); serum creatinine, 0.9 mg/dL (normal 0.7–1.5 mg/dL); and total bilirubin, 0.8 mg/dL (normal 0.2–1.2 mg/dL). Levels of alanine aminotransferase and aspartate aminotransferase were markedly high (320 and 780 U/L, respectively). The patient was hospitalized for 6 days. Serological tests were negative for all hepatitis viruses. Although two MAC-ELISA tests for dengue were negative, another for YF was positive. At 6 days after discharge, the patient reported to the Travel Medicine Outpatient Clinic of the Emílio Ribas Infectious Diseases Institute. At that time, she was feeling well, and the laboratory findings were normal.

Case 2

A 65-year-old male was contacted by epidemiological surveillance after his wife (the index case) was hospitalized. He was referred to the Travel Medicine Outpatient Clinic. The patient had not been vaccinated against YF, and he reported having mild symptoms (fever and headache for less than 1 day) during the trip. He stated that he had been to the same places during the same period as had the index case. He had not used any form of insect repellent. Laboratory test results were unremarkable. The MAC-ELISA for dengue was negative, whereas that for YF was positive. The patient had a history of controlled hypertension.

Case 3

A 69-year-old female was contacted by epidemiological surveillance after her daughter (the index case) was hospitalized. She was referred to the Travel Medicine Outpatient Clinic. The patient had not been vaccinated against YF, and she had traveled to the same locale as had the index case. Beginning 2 days after arrival at their destination, the patient presented mild symptoms, including headache as well as vomiting (on 1 d only). She had not used any form of insect repellent. Laboratory test results were unremarkable. She had a history of diabetes mellitus. The MAC-ELISA results were negative for dengue but positive for YF.

Discussion

Since YF is a preventable disease, individuals exposed to endemic areas should be vaccinated, unless vaccination is contraindicated. The cases presented were in residents of the city of Sao Paulo, a non-endemic area for YF, who were not vaccinated against YF and did not seek medical counseling prior to traveling to an endemic area of YF.

Concerning the YF transmission risk, four areas are recognized in Brazil: endemic (viral circulation, infected mosquitoes, human cases, and epizootic in monkeys); transitional (sporadic viral circulation, with sporadic outbreaks in humans, and epizootic); potential risk (without circulating virus but presenting environmental conditions conducive to transmission); and transmission-free. The majority of the population in Brazil lives in transmission-free areas. The YF vaccine is not included in the routine vaccination schedule in transmission-free areas such as the city of Sao Paulo, and its inclusion in an expanded program of immunization poses a great challenge for public health officials in Brazil, since reports of serious adverse events associated with the vaccine have been increasing and have caused alarm.

Epidemiological surveillance plays an important and crucial role in identifying endemic and epidemic diseases. In the cases reported here, the Epidemiological Surveillance Center, a division of the Sao Paulo State Department of Health, contacted the family of the index case. Two affected family members were immediately identified and referred to the Travel Medicine Outpatient Clinic. Laboratory test results were unremarkable, and the family members were feeling well, although they had experienced nonspecific symptoms consistent with mild YF infection. The MAC-ELISA was positive for YF, indicating recent infection.

Although the case fatality ratio for YF is very high in Brazil, our index case experienced only moderately severe disease and recovered well after hospitalization. The clinical presentation of YF ranges from asymptomatic to mild infection in 90% of the infected people. However, asymptomatic individuals and those with mild forms of the disease present viremia for 3 to 6 days and therefore could represent a source of YF.
transmission. This could lead to an urban cycle of transmission, in which sylvatic strains are introduced into non-endemic areas by travelers returning from endemic areas. It is of note that, in the first quarter of 2008, the YF mortality rate was significantly higher in Brazil than in Paraguay or Argentina. There are many factors involved in the epidemiologic profile of each country, among which is the definition of a case. Although many oligosymptomatic cases were reported in those countries, only patients living in or coming from endemic areas and presenting acute fever with jaundice or hemorrhagic symptoms would meet the criteria to be considered suspected cases.

Historically, the areas of YF virus circulation in Brazil were restricted to the Amazon Basin and central-west states. In the last 7 years, the resurgence of sylvatic transmission has been described outside this area, and this has increased the risk for national and international travelers, especially those who have not been vaccinated. Although YF is rare among international travelers, it continues to pose a significant risk to individuals traveling within Brazil, many of whom live in non-endemic areas, are not routinely vaccinated, and are not aware of the risks when they decide to enter endemic zones.12

The Travel Medicine Outpatient Clinic plays an important role by providing specific information about endemic and epidemic diseases, as well as recommending vaccination when indicated. In addition, the spread of YF in Brazil presents an ongoing risk of reintroduction of the virus into the densely populated coastal areas. Continued surveillance and control are critical measures in order to limit the impact of YF. Although YF cannot be eradicated as a zoonosis, reduction of the human disease is achievable through programs of specific prevention and control.

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Declaration of Interests

The authors state they have no conflicts of interest.

References
