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Perspective

Yellow Fever — Once Again on the Radar Screen in the Americas

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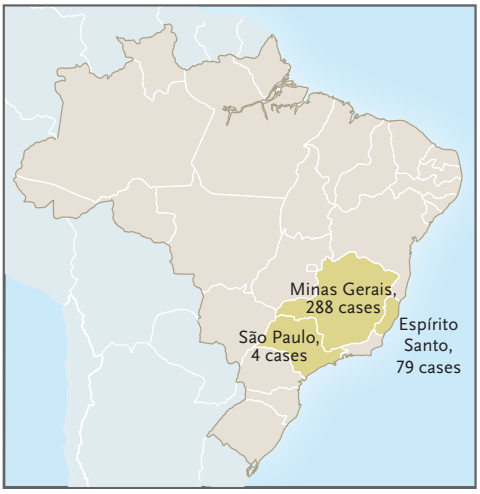
Four arthropod-borne viruses (arboviruses) have recently emerged or reemerged in the Americas, spreading rapidly through populations that had not previously been exposed to them and causing substantial morbidity and mortality.[1] The first was dengue, which reemerged to cause widespread disease predominantly in South America and the Caribbean in the 1990s. This epidemic was followed by West Nile virus in 1999, which has since become endemic in the continental United States, and chikungunya in 2013, which continues to cause disease, predominantly in the Caribbean and South America. Most recently, Zika virus emerged in Brazil in 2015 and spread through infected travelers to more than 60 countries and territories in the Americas, including the United States.

Over the past several weeks, a fifth arbovirus, yellow fever virus, has broken out in Brazil, with the majority of the infections occurring in rural areas of the country. These are referred to as sylvatic, or jungle, cases, since the typical transmission cycle occurs between forest mosquitoes and forest-dwelling nonhuman primates, with humans serving only as incidental hosts. In this ongoing outbreak, health authorities have reported 234 confirmed infections and 80 confirmed deaths as of February 2017.[2] Confirmed infections have occurred in the Brazilian states of Minas Gerais, Espírito Santo, and São Paulo (see map), and hundreds of additional cases remain under investigation. The high number of cases is out of proportion to the number reported in a typical year in these areas.

Although there is currently no evidence that human-to-human transmission through *Aedes aegypti* mosquitoes (urban transmission) has occurred, the outbreak is affecting areas in close proximity to major urban centers where yellow fever vaccine is not routinely administered. This proximity raises concern that, for the first time in decades, urban transmission of yellow fever will occur in Brazil.

As we have seen with dengue, chikungunya, and Zika, *A. aegypti*–mediated arbovirus epidemics can move rapidly through populations with little preexisting immunity and spread more broadly owing to human travel. Although it is highly unlikely that we will see yellow fever outbreaks in the continental United States, where mosquito density is low and risk of exposure is limited, it is possible that travel-related cases of yellow fever could occur, with brief periods of local transmission in warmer regions such as the Gulf Coast states, where *A. aegypti* mosquitoes are prevalent.

It is also conceivable that yellow fever outbreaks may occur in



Confirmed Cases of Yellow Fever in the Current Outbreak.

Data are from the Brazilian Ministry of Health.

the U.S. territories, just as the recent Zika epidemic reached Puerto Rico, causing a significant outbreak there and leading to thousands of travel-related cases and more than 250 locally transmitted cases in the continental United States. In an era of frequent international travel, any marked increase in domestic cases in Brazil raises the possibility of travel-related cases and local transmission in regions where yellow fever is not endemic. In light of the serious nature of this historically devastating disease, public health awareness and preparedness are critical, even for individual cases.

Yellow fever most likely originated in Africa and was imported into the Americas in the 1600s.[3] It claimed hundreds of thousands of lives in the 18th and 19th centuries. The Philadelphia yellow fever epidemic of 1793, for example, killed approximately 10% of the city's population and prompted the federal government to flee the city. In 1881, Cuban epidemiologist Carlos Finlay proposed that yellow fever was a mosquito-borne infection. The U.S. Army physician Walter Reed and a Yellow Fever Commission verified that fact in 1900. Subsequently, mosquito-control efforts and better sanitation practices virtually eliminated yellow fever from the United States and other nonendemic areas of the Americas, although sporadic outbreaks of varying magnitude continued to occur in tropical regions where the disease was endemic.[4]

In 1937, virologist Max Theiler developed a live attenuated yellow fever vaccine that is still in use today and that provides lifetime immunity in up to 99% of vaccinees, according to the World Health Organization (WHO). Extensive vaccination campaigns combined with effective vector-control strategies have significantly reduced the number of yellow fever cases worldwide. However, localized outbreaks continue to occur in parts of Africa and Central and South America, resulting in an estimated 84,000 to 170,000 severe cases and 29,000 to 60,000 related deaths per year, according to the WHO.

Beginning in December 2015, a large urban outbreak of yellow fever occurred in Angola and subsequently spread to the Democratic Republic of Congo, causing 961 confirmed cases and 137 deaths. In addition, cases related to travel from those countries were noted in nonendemic areas such as China, raising concern about international spread of disease. During the outbreak, the world's emergency vaccine stockpile reserved for epidemic response was exhausted, prompting health authorities to immunize inhabitants of some areas using one fifth of the standard dose in order to extend the vaccine supply.[5] Since vaccination is the mainstay of epidemic response, the limited number of stockpiled vaccine doses and the long time needed to produce additional vaccine made this outbreak difficult to control. To prevent a similar occurrence in Brazil or in future yellow fever outbreaks, early identification of cases and rapid implementation of public health management and prevention strategies, such as mosquito control and appropriate vaccination, are critical.

Early recognition may be difficult in countries such as the United States, where most physicians have never seen a case of yellow fever and know little about the clinical manifestations. Typically, yellow fever is suspected on the basis of clinical presentation and confirmed later, since definitive diagnosis requires testing available only in specialized laboratories. The clinical illness manifests in three stages: infection, remission, and intoxication.[3] During the infection stage, patients present after a 3-to-6-day incubation period with a nonspecific febrile illness that is difficult to distinguish from other flulike diseases. High fevers associated with bradycardia, leukopenia, and transaminase elevations may provide a clue to the diagnosis, and patients will be viremic during this period.

This initial stage is followed by a period of remission, when clinical improvement occurs and most patients fully recover. However, 15 to 20% of patients have progression to the intoxication stage, in which symptoms recur after 24 to 48 hours.[3] This stage is characterized by high fevers, hemorrhagic manifestations, severe hepatic dysfunction and jaundice (hence the name "yellow fever"), renal failure, cardiovascular abnormalities, central nervous system dysfunction, and shock. Anti-

bodies may be detected during this stage; however, viremia has usually resolved. Case-fatality rates range from 20 to 60% in patients in whom severe disease develops, and treatment is supportive, since no antiviral therapies are currently available.[3,4]

Yellow fever is the most severe arbovirus ever to circulate in the Americas, and although vaccination campaigns and vector-control efforts have eliminated it from many areas, sylvatic transmission cycles continue to occur in endemic tropical regions. The most recent outbreak in Brazil highlights this phenomenon. If the current outbreak leads to urban spread through *A. aegypti* mosquitoes, clinicians should adopt a high index of suspicion for yellow fever, particularly in travelers returning from affected regions. As with all potentially reemerging infectious diseases, public health awareness and preparedness are essential to prevent a resurgence of this historical threat.

Disclosure forms provided by the authors are available at NEJM.org.

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1. Fauci AS, Morens DM. Zika virus in the Americas — yet another arbovirus threat. N Engl J Med 2016;374:601-4.
2. Brazilian Ministry of Health. Surveillance update. February 2017 (http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/noticias-svs/27602-ministerio-da-saude-atualiza-casos-notificados-de-febre-amarela-no-pais-2).
3. Gardner CL, Ryman KD. Yellow fever: a reemerging threat. Clin Lab Med 2010;30:237-60.
4. Monath TP, Vasconcelos PF. Yellow fever. J Clin Virol 2015;64:160-73.
5. Wu JT, Peak CM, Leung GM, Lipsitch M. Fractional dosing of yellow fever vaccine to extend supply: a modelling study. Lancet 2016;388:2904-11.

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