Editorial

Challenges in the control and treatment of yellow fever in Brazil

Yellow fever is an acute infectious disease caused by a virus of the family Flaviviridae , transmitted by mosquitoes of the genera Haemagogus and Sabethes (wild-type yellow fever), as well as by those of the genus Aedes (urban-type yellow fever). The virus was probably brought from the African continent to the Americas in the sixteenth century, on slave ships, together with the vector of the urban form, Aedes aegypti. In the nineteenth century and early twentieth century, several yellow fever epidemics occurred in Brazil, most notably a highly lethal epidemic that occurred in the city of Rio de Janeiro. In 1901, Emílio Ribas, then Director of the São Paulo State Department of Health, wrote the first work on the subject in Brazil, entitled "The mosquito considered an agent of the spread of yellow fever", and recommended that the public "avoid allowing water to stagnate". In 1903, Oswaldo Cruz, a public health physician, was appointed director general of the National Public Health Institute (now the National Ministry of Health) and led several campaigns to eradicate Aedes aegypti in the states of Rio de Janeiro, São Paulo, and Minas Gerais.[1] At that time, yellow fever was an urban disease. Although other outbreaks followed, the campaigns of Emílio Ribas and Oswaldo Cruz, together with the development of the yellow fever vaccine in 1937, epidemics of urban yellow fever were controlled, the last case occurring in the state of Acre, Brazil, in 1942.

Over the past 20 years, several outbreaks of wild yellow fever have occurred in southern and southeastern Brazil. Municipal, state, and federal public health authorities have underestimated the magnitude of those outbreaks, which have intensified, extending to populated regions and resulting in the deaths of hundreds to thousands of monkeys. At the end of 2016, the epidemic began to intensify even further, especially in the states of Minas Gerais, São Paulo, and Rio de Janeiro. The deaths of monkeys serve as sentinel events, indicating that the virus is circulating in a given region. The objective of monitoring epizootics in nonhuman primates is to detect the circulation of the virus early in the enzootic cycle and to initiate measures for the prevention and control of yellow fever outbreaks. According to the dates and locations of the monkey deaths was constructed an epidemiological model that describes the direction, speed, and likely pathways of the spread of the disease.[2] Coming from the region known as the Triângulo Mineiro, located in the western part of the state of Minas Gerais, the virus traveled an average of 0.9 km per day towards the coast of São Paulo, carried by mosquitoes, marmosets, and black capuchin monkeys. By January 2018, the virus had moved from north to south at rates of 2.7 km per day in the warmer months and 0.5 km per day in the cooler months.[2] In the

first months of 2018, extensive efforts were made to expand vaccination in the areas designated as high-risk, where the disease is concentrated in non-human primates.

The epidemics of yellow fever are directly related to climate change and changes in social structure. High temperatures and high humidity increase the voracity of the female mosquito for blood (from monkeys and eventually from humans), in order to ensure successful oviposition. Deforestation, natural disasters, and anthropogenic disasters, resulting in population displacements to areas near forests, increase the possibility of human-mosquito contact, as do environmental imbalances.

After the infected mosquito bites, the yellow fever virus spreads to dendritic cells, to regional lymph nodes, and subsequently throughout the entire body. Entry into the cell occurs through binding of the viral E protein to the cell membrane. The E protein can be detected by monoclonal antibodies, as can nonstructural proteins such as NS1, which binds to the membrane of the infected cell. The organ most often affected by yellow fever is the liver, followed by the kidneys, spleen, heart, and brain. In severe cases, hepatic necrosis caused by coagulation is characterized by widespread destruction of hepatocytes, probably by apoptosis.[1]

The incubation period of yellow fever is 3–6 days. The majority of cases are asymptomatic or mildly symptomatic; approximately 20% evolve to the severe forms, with jaundice. Among patients with severe yellow fever, mortality ranges from 20% to 60%. Early diagnosis is quite important. Although molecular biology techniques -detection of the viral genome by polymerase chain reaction or detection of viral antigens - are feasible, they are not available in most emergency departments. From the fifth day of infection, infected individuals test positive for antibodies against the yellow fever virus, although antibody titers are less sensitive because they can cross with those against other flaviviruses and vaccine-related antibodies.

There is as yet no specific treatment for yellow fever. Patients with severe forms are admitted to the intensive care unit for monitoring, volume resuscitation, and replacement of coagulation factors, which are reduced in severe liver failure. In such cases, the treatment of last resort is liver transplantation. Recently, liver transplants have been performed in specialized liver transplantation centers in the southeastern region of Brazil, mainly in the city of São Paulo. Although the results have not yet been consolidated, those valiant efforts have undoubtedly saved many lives. Antiviral agents with anti-flavivirus activity, such as sofosbuvir, could be a therapeutic alternative for patients with yellow fever. In a recent study, Freitas et al.[3] demonstrated, in vitro, that sofosbuvir binds to conserved amino acid residues in the NS5 RNA-dependent RNA-polymerase of the yellow fever virus, inhibiting viral replication in human hepatocytes and decreasing mortality in animal models.

The yellow fever vaccine is highly effective in preventing the disease. As previously discussed, the yellow fever virus is endemic to tropical and subtropical areas of Africa, Central America, and South America. The World Health

Organization recommends administering a standard dose of the vaccine, stating that the standard dose is sufficient to ensure immunity and lifelong protection for travelers to endemic areas. In January 2018, the World Health Organization declared the state of São Paulo a high-risk area for yellow fever and recommended vaccination for all international travelers passing through the state.[4] Since January 2018, 10 travel-related cases of yellow fever, including four deaths, have been reported in international travelers returning from Brazil. None of the 10 travelers had received yellow fever vaccination.[5]

With the advance of the epidemic to areas of high population density in Brazil, a large number of doses were required and were not available in the short term. Therefore, the use of a fractional dose was adopted as an alternative means of containing the epidemic. A fractional (0.1 mL) dose of the yellow fever vaccine, corresponding to one fifth of the total dose, was used in the epidemic that occurred in Angola and the Democratic Republic of Congo in 2016. In 2018, Ahuka-Mundeke et al.[6] evaluated the immune response to that fractional dose of the vaccine in children over 2 years of age and nonpregnant adults. The authors concluded that the fractional dose was effective in inducing seroconversion in individuals who were seronegative prior to administration of the vaccine. The proportion of individuals undergoing seroconversion (98%; 95% CI: 96–99) was similar to the > 98% previously reported for those who received the full dose.[6] To date, there are no conclusive studies on the timing of immunity maintenance in individuals who took the fractional vaccine and also the immune response in children under the age of 2 years, in pregnant, immunocompromised, and elderly individuals. The incidence of serious adverse events related to the use of the fractional dose is calculated at 0.5 events per 100,000 doses, similar to that calculated for the use of the full dose.

We have learned much from the current epidemic of yellow fever. Major advances in the identification of new therapeutic alternatives and preventive measures are being evaluated. Although wild-type yellow fever can not be eradicated by immunization, because nonhuman primates serve as a natural reservoir in the forest, it will be possible to control the current outbreak with ample vaccination coverage.

Eduardo Alexandrino Servolo Medeiros, MD, PhD
Professor of Infectious Diseases, Department of Medicine, Escola Paulista de Medicina, Head of the Nosocomial Infection Control Division of the Hospital São Paulo, Universidade Federal de São Paulo; researcher for the Brazilian Council for Scientific and Technological Development (CNPq)

DOI: http://dx.doi.org/10.1590/1982-0194201800017

References

1. Figueiredo LT, Fonseca BA. Febre amarela. In: Focaccia R. Veronesi – Tratado de Infectologia. 4 a ed. São Paulo: Atheneu; 2017.
2. O alarme dos macacos. Pesquisa Fapesp. 2018; 19(263):18-23. [citado 208 Fev 10]. Disponível em: www.revistapesquisa.fapesp.br.
3. Freitas CS, Higa LM, Sacramento C, Ferreira AC, Reis PA, Delvecchio R, et al. Yellow fever virus is susceptible to sofosbuvir both in vitro and in vivo. bioRxiv [posted online 2018 Feb 15]. [cited 2018 Jun 13]. Available from: http://dx.doi.org/https://doi.org/10.1101/266361..
4. Updates on yellow fever vaccination recommendations for international travelers related to the current situation in Brazil [Internet]. Genva: WHO; 2018. [cited 2018 Feb 10]. Available from: http://www.who.int/ith/updates
5. 1: Hamer DH, Angelo K, Caumes E, van Genderen PJJ, Florescu SA, Popescu CP, Perret C, McBride A, Checkley A, Ryan J, Cetron M, Schlagenhauf P. Fatal yellow fever in travelers to Brazil, 2018. MMWR Morb Mortal Wkly Rep. 2018;23;67(11):340-341.
6. Ahuka-Mundeke S, Casey RM, Harris JB, Dixon MG, Nsele PM, Kizito GM, et al. Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak - Preliminary Report. N Engl J Med. 2018 Feb 14. doi: 10.1056/NEJMoa1710430.