

Yellow fever

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SUMMARY

The yellow fever (YF) virus is a *Flavivirus*, transmitted by *Haemagogus*, *Sabethes* or *Aedes aegypti* mosquitoes. The disease is endemic in forest areas in Africa and Latin America leading to epizootics in monkeys that constitute the reservoir of the disease. There are two forms of YF: sylvatic, transmitted accidentally when approaching the forests, and urban, which can be perpetuated by *Aedes aegypti*. In Brazil, the last case of urban YF occurred in 1942. Since then, there has been an expansion of transmission areas from the North and Midwest regions to the South and Southeast. In 2017, the country faced an important outbreak of the disease mainly in the states of Minas Gerais, Espírito Santo and Rio de Janeiro. In 2018, its reach extended from Minas Gerais toward São Paulo. Yellow fever has an incubation period of 3 to 6 days and sudden onset of symptoms with high fever, myalgia, headache, nausea/vomiting and increased transaminases. The disease ranges from asymptomatic to severe forms. The most serious forms occur in around 15% of those infected, with high lethality rates. These forms lead to renal, hepatic and neurological impairment, and bleeding episodes. Treatment of mild and moderate forms is symptomatic, while severe and malignant forms depend on intensive care. Prevention is achieved by administering the vaccine, which is an effective (immunogenicity at 90-98%) and safe (0.4 severe events per 100,000 doses) measure. In 2018, the first transplants in the world due to YF were performed. There is also an attempt to evaluate the use of active drugs against the virus in order to reduce disease severity.

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INTRODUCTION

Yellow fever is a non-contagious infectious disease caused by an arbovirus (arthropod-borne virus) belonging to the *Flaviviridae* family. The disease is endemic only in the tropical forests of the African continent and Latin America, with the possibility of determining urban cycles (Figures 1 and 2). The vectors of the sylvatic form in Brazil are *Haemagogus* or *Sabethes* mosquitoes that live and feed on the treetops. Urban YF is associated with the participation of the vector *Aedes aegypti*, present in several Brazilian cities.¹

According to the World Health Organization (WHO), the estimated number of severe cases in both continents is 84,000-170,000, with approximately 29,000-60,000 deaths annually.²

Yellow fever was an unknown disease until the discovery of the Americas. It probably originated in Africa and

was possibly introduced to the American continent by ships carrying slaves and the vector *Aedes aegypti*. The first epidemic was reported in the American continent, where it is possible to characterize with greater certainty the infection by yellow fever, occurred in the Yucatán peninsula in 1648.^{3,4}

In the US, an epidemic in Philadelphia in 1793 decimated about 10% of the population.² In 1881, Cuban epidemiologist Carlos Finlay associated the transmission of the disease with mosquito bites. In 1900, physician Walter Reed proved this association and carried out effective measures to control the transmission by mosquitoes in the American territory.

In Brazil, the descriptions of epidemics of yellow fever date back to the 17th century; since then, we have found several reports of seasonal activity of the disease in many localities throughout the country. Yellow fever, which was



FIGURE 1 Yellow fever vaccine recommendations in the Americas.¹

¹Current as of September 2016. This map, which aligns with recommendations also published by the World Health Organization (WHO), is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

²Yellow fever (YF) vaccination is generally not recommended in areas where there is low potential for YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status).

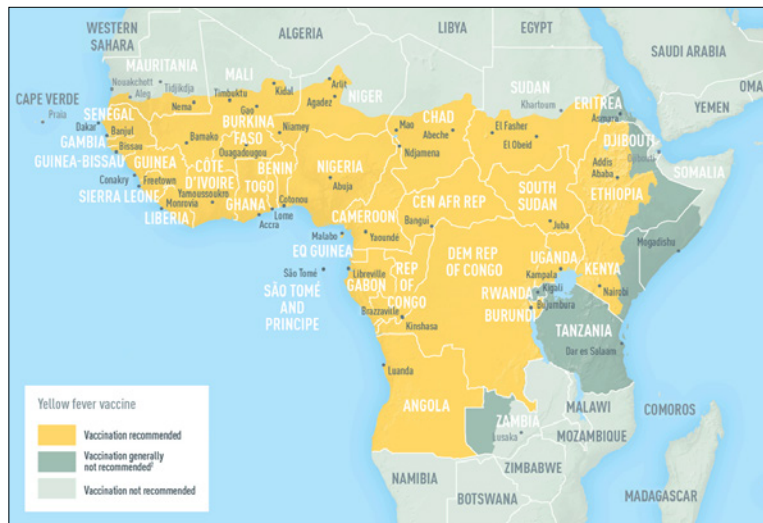


FIGURE 2 Yellow fever vaccine recommendations in Africa.¹

¹Current as of September 2016. This map, which aligns with recommendations also published by the World Health Organization (WHO), is an updated version of the 2010 map created by the Informal WHO Working Group on the Geographic Risk of Yellow Fever.

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considered an important public health problem in Rio de Janeiro, was a challenge tackled by Oswaldo Cruz, who in 1903 was the general director of Public Health and adopted measures similar to those of the Cuban model in the fight against *Aedes aegypti*, known at the time as *Stegomyia fasciata*. In 1907, after great efforts, the endemic in the city of Rio de Janeiro was considered controlled.⁵

The last cases of urban yellow fever in Brazil occurred in the city of Sena Madureira, state of Acre, in 1942. Since then, all reported cases are due to the accidental infection of humans when entering or approaching forest areas where the virus circulates (wild cycle). In cycles of approximately 5 to 10 years, it is possible to observe the intensification of cases in primates (epizootics) leading to a greater chance of human infection. Over the years, epizootic areas have spread to the mid-south of the country and more recently to the southeast, near densely populated areas, which increases the risk of urban reintroduction of the disease.

Recent epidemics such as those reported in Angola and the Democratic Republic of Congo between 2015 and 2016 remind us of the significant risk of local outbreaks progressing when control measures are not readily taken.

ETIOLOGICAL AGENT

The yellow fever virus is an RNA virus of the genus *Flavivirus* and family *Flaviviridae*. The virus was isolated in 1927 by Adrian Stokes of a patient from Ghana, known as Asibi. Other viruses from the same family that affect humans include: Dengue, West Nile virus, Rocio and St. Louis encephalitis. There are genotype differences among strains found on the African and South American continent.⁴

EPIDEMIOLOGY

Yellow fever is a disease with compulsory notification, even on simple suspicion of the disease. About 80% of the cases are in males, predominantly in the age group of 15-35 years, which reflects a higher degree of exposure to forests.

The most common period of the disease occurs between the months of December and May, characterized by higher rainfall volume in Brazil. Currently, transmission to humans is linked to the wild cycle, which has monkeys as reservoir and mosquitoes of the genera *Haemagogus* (*Haemagogus janthinomys* and *Haemagogus leucocelaenus*) and *Sabethes* (*Sabethes chloropterus* and *Sabethes albiprivus*) as vectors. The most susceptible animals are howler monkeys, capuchin monkeys and the common marmoset. Transmission to humans is incidental, occurring most of times when people enter a forest area for extraction or recreation activities. Epizootics occur cyclically and periods of epidemiological silence probably coincide with a decrease in the number of susceptible primates.

The urban cycle involves infected humans and the *Aedes aegypti* vector. There have been no urban cases in the Americas since 1954, but it is still very common in African countries. An intermediate cycle was described in areas of transition to forest in Africa (savannah), with participation of monkeys, vector *Aedes* spp and humans.

In Brazil, after the eradication of the *Aedes aegypti* mosquito in 1954, the sylvatic transmission area of the virus predominantly covered the legal Amazon region (Figure 3). Over the years, the transition area has also moved to the Midwest and Southeastern states such as São Paulo, Minas Gerais and Rio de Janeiro, as well as the southern states of Paraná, Santa Catarina and Rio Grande do Sul.

In December 2016, the Brazilian Ministry of Health reported cases of sylvatic yellow fever in the state of Minas Gerais, with rapid expansion in the first six months of the outbreak to the states of Espírito Santo, São Paulo, Bahia and Rio de Janeiro. In the first half of 2017, there were 3,564 suspected cases of sylvatic yellow fever. Of these, 777 (21.8%) were confirmed, 2,270 (63.7%) ruled out, 213 (6.0%) were still being investigated, and 304 (8.5%) were considered inconclusive.

After the Brazilian Ministry of Health declared the end of the transmission of new cases on September 6th, 2017 new autochthonous cases began to be notified as of epidemiological week number 38/2017 in the state of São Paulo (Figures 3, 4 and 5).

According to official CVE-SP (Center for Surveillance and Epidemiology – São Paulo) data, from January 2017 to February 14th, 2018 there have been 183 confirmed autochthonous cases, with 64 deaths, resulting in a mortality rate of 35%. The majority of cases occur in males (83.1%) and the median age is 43 years (2-89 years). Many cases are still being investigated.⁶ New cases have also been confirmed in Minas Gerais (77) and Rio de Janeiro (27).

INCUBATION PERIOD

The mean time between being bitten by the infected mosquito and the onset of the first symptoms is 3-6 days^{2,7,8} and may reach 10-15 days.⁸

CLINICAL MANIFESTATION

Half of those infected are estimated to be asymptomatic.⁸

Yellow fever is described as a biphasic disease:⁷

- Viremic phase: high fever, with a mean duration of three days,⁹ myalgia, headache, lack of appetite and nausea. Mostly, these symptoms subside within 2 to 4 days, characterizing mild and moderate cases, which are estimated to account for 20-30% of infected patients.⁸
- Toxemic phase: takes place in approximately 15% of patients^{2,7,10} and begins after a period of clinical improve-

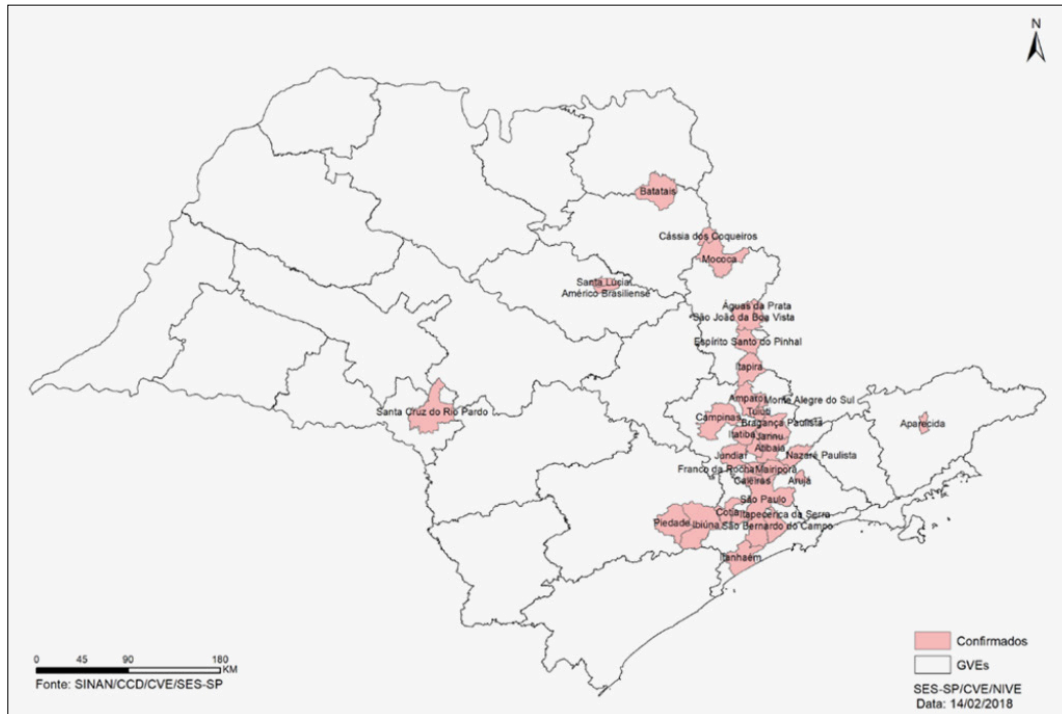


FIGURE 3 Distribution of autochthonous yellow fever cases by municipality (origin of infection). State of São Paulo, 2017-2018.

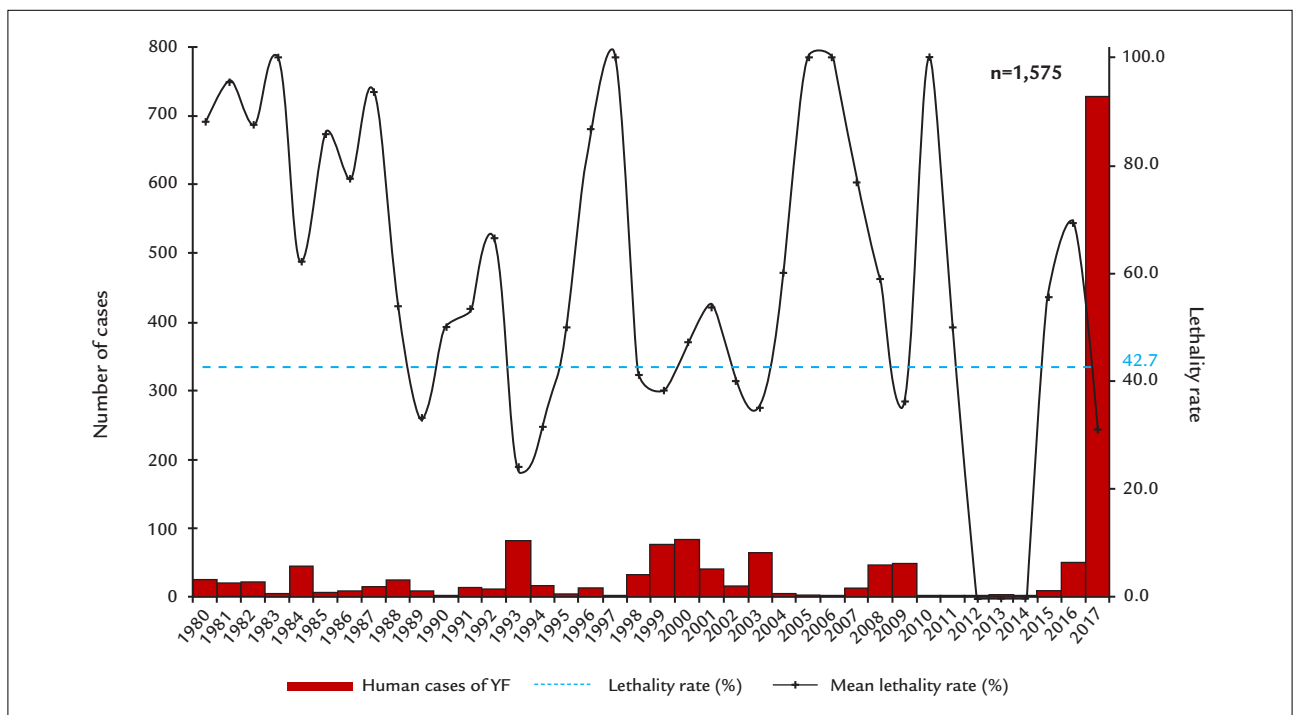


FIGURE 4 Historical series of the number of confirmed human cases of YF and lethality according to the year of onset of symptoms, Brazil, from 1980 to June 2017.

Source: Sinan; GT-Arbo/UVTV/CGDT/DEVIT/SVS/MS

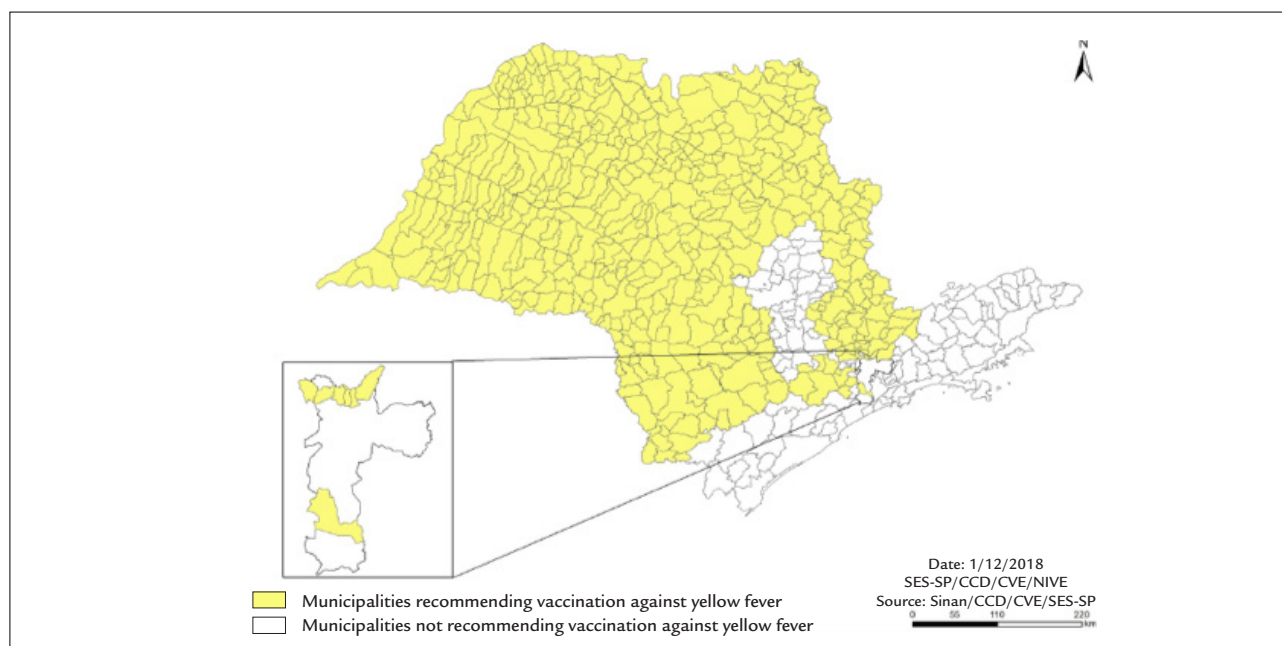


FIGURE 5 Municipalities in the state of São Paulo and Administrative Districts of the capital currently recommending vaccination against yellow fever. State of São Paulo, 2018.

ment that follows the first phase, lasting 24 hours on average.⁹ It is characterized by recrudescence of high fever, chills, worsening of headache and myalgia, and involvement of various organs and systems. It is in this second phase that, later on, icteric discoloration of the skin that characterizes the disease develops. There may be bleeding, kidney dysfunction with oliguria,¹¹ as well as cardiovascular dysfunction and neurological impairment with seizures.^{7,8,10} Often, the unusual pairing of fever with bradycardia (Faget sign) is observed.⁸⁻¹⁰ Up to half of these patients progress to death in 10 to 14 days, and the rest recover without significant sequelae.^{7,8}

During the outbreak in São Paulo, some patients who progressed to severe disease (mainly elderly) did not develop fever at any time (personal observation of the authors).

It should be noted that the notification must be made on suspicion, as it is COMPULSORY and IMMEDIATE, and must be informed by telephone, fax or e-mail to the local responsible agency.⁸

LABORATORY CHANGES

The main changes are listed below.

Leukopenia is characteristic (leukocytes between 1,500 and 2,500 cells/mL, plus relative neutropenia⁹) both in the early and late phases; however, leukocytosis is sometimes seen in a later period.¹⁰ C-reactive protein is generally low, even in patients who progress to death. Hyper-

bilirubinemia usually occurs more intensely at the end of the first week, and appears after an increase in transaminases. The observed levels of AST and ALT in severe cases are often above 5,000 IU/L, sometimes reaching more than 20,000 IU/L, levels rarely seen in other causes of hepatitis. AST values are usually higher than ALT values. Both creatinine and urea levels rise frequently and their worsening correlates with deterioration of the patient's condition.

CLASSIFICATION

The clinical picture can be classified as mild, moderate, severe or malignant.⁸ In mild and moderate forms, the symptoms and laboratory changes are less intense, with mild thrombocytopenia and moderate increase in transaminases. In this form, there is usually no increase in bilirubin. Severe disease, on the other hand, leads to intense thrombocytopenia and increased transaminases, in addition to increased creatinine. Malignant yellow fever is that in which disseminated intravascular coagulation is observed with fibrinogen consumption and accumulation of D-dimer, in addition to the previous alterations.⁸

TREATMENT

To date, there is no specific antiviral against yellow fever.

In mild cases (Table 1), outpatient follow-up with daily visits can be implemented, provided that there is quick access to health services and someone at home who can observe the patient. It is important to alert patients

with suspected yellow fever that there may be a rapid worsening of the condition. In such cases, only symptomatic medications with no potential action on the liver, such as dipyron (avoiding NSAIDs and paracetamol, due to the risk of hepatotoxicity), and adequate hydration (60 mL/kg/day) are recommended.⁸

Other patients (moderately severe and severe cases) should be hospitalized. For patients hospitalized in infirmary wards, the following is recommended: thorough control of diuresis, with an ideal flow of > 1mL/kg/h, with clinical reassessments at least every 4 hours; and daily laboratory tests or if there is any sign of clinical worsening.⁴ In this case, it is important to keep the patient euvoletic. If there is any sign of dehydration, it is recommended to initiate intravenous fluid replacement with 0.9% saline boluses of 10 mL/kg in the first hour, with subsequent reassessment of vital signs and diuresis and, if necessary, maintenance with 30 mL/kg/day or a sufficient volume of fluids to maintain adequate diuresis.⁸

Patients with the malignant form may progress with a need for endotracheal intubation and protective mechanical ventilation due to upper gastrointestinal bleeding, lowered level of consciousness or respiratory failure. Dialysis is often necessary. Use of routine gastric protectors and transfusion of fresh frozen plasma (10 mg/kg) in cases of bleeding or intense coagulopathy is also recommended.⁸

DIAGNOSIS

Clinically, it is difficult to differentiate it from other viral diseases in the initial phase, and yellow fever should be considered in all cases with compatible clinical manifestations, even if mild, and positive epidemiology (having visited a risk area within 15 days prior to the onset of symptoms without being previously vaccinated, or having been vaccinated within less than 30 days⁸).

Yet, in patients who evolve more severely, some clinical and laboratory characteristics lead us to suspect more readily of yellow fever, such as a rapid increase (in a matter of 2-3 days) of the transaminases to very high levels, with a predominance of AST compared to ALT,^{8,11} which is the opposite of that seen in classical viral hepatitis, perhaps reflecting skeletal and myocardial muscle cell involvement.¹¹ As observed in the São Paulo outbreak, laboratory worsening tends to precede clinical worsening.

Confirmation of the diagnosis is made using a method of molecular amplification of the virus in the blood (highly sensitive and specific method, which may even allow to differentiate the sylvatic virus from the vaccine strain¹¹), which classically occurs up to the fifth day of the disease.⁸ It should be noted, however, that, in some patients, viremia seems to persist longer, sometimes until after the 10th day.

As of day 5, serology (detection of IgM and IgG, specific for yellow fever) is recommended.⁸ Serology, how-

TABLE 1 Classification table according to clinical picture, expected laboratory changes and treatment for cases of suspected or confirmed yellow fever.

Classification	Symptoms	Laboratory changes	Treatment
Mild	Fever Myalgia Headache Lack of appetite Bradycardia	Leukopenia AST and ALT < 2x the normal limit Normal platelets	Dipyron Oral fluid therapy (ORT) 60 mL/kg/day Daily outpatient visits
Moderate	The previous ones, plus: Abdominal pain Vomit Mild jaundice	Leukopenia Mild low platelet count AST and ALT < 10x Bilirubin < 5x	Admission into infirmary ward Control of diuresis IV fluids, if necessary Clinical reassessment each 4 h Daily laboratory analyses
Severe/malignant	The above, plus: Intense abdominal pain Frequent vomiting Jaundice Bleeding Organ and system failure (oliguria, AKF, lowered level of consciousness)	Leukopenia Severely low platelet count AST and ALT > 10x Increased bilirubin Increased PT/aPTT Depressed fibrinogen levels Increased D-dimer Increased urea and creatinine Hypoglycemia	ICU admission Hydration and euvoemia Hemodialysis Endotracheal intubation Transfusion of blood products, if necessary

AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time; ICU: intensive care unit; IV: intravenous.

ever, can cross-react with other flaviviruses, such as dengue virus^{10,11} or simply indicate a response to recent vaccination for yellow fever. In case of death, the diagnosis can be confirmed in several tissues in up to 24 hours;⁸ or by immunohistochemistry.^{8,10}

TREATMENT PERSPECTIVES

This year at Hospital das Clínicas da FMUSP, the first YF-related liver transplant was performed, followed by four more in patients with malignant yellow fever who progressed to complete liver failure. At this point, the role of liver transplantation in treating severe forms of yellow fever, or the correct timing for this, has not yet been established. Criteria such as hepatic encephalopathy and factor V < 20 or 30% (if the patient is younger or older than 30 years, respectively) for indication of transplantation is currently being discussed.

Clinical and laboratory research is underway for antiviral testing against yellow fever virus, such as sofosbuvir (now used for treatment of hepatitis C).¹²

DIFFERENTIAL DIAGNOSIS

Leptospirosis (of all, the disease most similar to yellow fever⁹), malaria, dengue, mononucleosis, influenza, viral hepatitis, rickettsiosis, Zika (in mild early phases), chikungunya, sepsis and typhoid fever.¹

FOLLOW-UP

The Brazilian Ministry of Health recommends hospital discharge based on the following criteria: patient afebrile for > 24 hours with at least 10 days of illness or afebrile for > 3 days, regardless of disease duration, in both cases with progressive improvement of transaminases and platelets.⁸

Convalescence, with prolonged asthenia, may last up to 8 weeks, with transaminase oscillations (ALT prevailing at this stage) and even transient increases in bilirubin. There is no need for future vaccination, as the patient is considered protected.⁸

YELLOW FEVER VACCINE

Prevention is based on the use of attenuated live virus vaccine from strain 17D, developed in 1937 by Max Theiler, a virologist who received the Nobel Prize in Medicine in 1951. The vaccine is considered safe (1,255 severe adverse events for 333 million doses applied¹³) and highly effective (immunogenicity between 90% and 98% after day 10⁸). Since 2013, the WHO has reviewed the need to repeat additional doses every 10 years.¹⁴ Currently, only a single dose is indicated throughout life. In immunocompromised populations such as people living with HIV/AIDS, women vaccinated while pregnant and children under 5 years of age, there may be changes in the recommendations in the near future. However, the main contraindication is related to the use of immunosuppressive drugs at the time of vaccination or weeks before receiving the vaccine (Table 2).

During the 2015 and 2016 epidemic in Angola and the Federative Republic of Congo, the fractional dose of the vaccine was chosen to protect large numbers of people, with a good response to restrain the epidemic.¹⁵

This strategy was also adopted in 2018 for the vaccination of part of the population in the states of São Paulo, Rio de Janeiro and Bahia. Studies suggest that the use of fractionated doses (1/5 of the usual dose) leads to the production of neutralizing antibodies at levels equivalent to that of the conventional dose.¹⁵ The durability of this pro-

TABLE 2 Vaccine recommendation by the Brazilian Ministry of Health.⁸

Recommended	Contraindicated	With caution ^{***}
People residing or traveling to areas with vaccine recommendation*	Cancer patients on chemotherapy or radiotherapy Immunosuppressive or immunomodulating drugs Steroids, depending on dose and length of use ^{**}	Those aged > 60 years who have never been vaccinated Pregnant or lactating women with infants < 6 months Breastfeeding women should stop breastfeeding for 10 days after vaccination
AND	Patients who underwent bone marrow or solid organ transplantation < 2 years	HIV+ patients with CD4 > 350 cells/mm ³ (require more attention if CD4 between 200 and 350 cells/mm ³)
Age > 9 months and < 60 years	Previous thymus disease (myasthenia gravis, thymoma) Systemic lupus erythematosus	Autoimmune diseases
AND	Rheumatoid arthritis Primary immunodeficiencies	Hematologic diseases
No contraindications	Advanced HIV infection (CD4 < 200 cells/mm ³) Infants under 6 months of age Individuals with a history of anaphylactic reaction related to substances present in the vaccine	Patients who underwent bone marrow transplantation > 2 years, stable, with no graft versus host disease (GVHD)

*List of Brazilian municipalities with vaccine recommendation:

<<http://portal.arquivos2.saude.gov.br/images/listavacinacaofa.pdf>>.

**Equivalent to 20 mg or more of prednisone for > 14 days; or pulse therapy.

***Cases where the administration of the vaccine is conditional on individual medical risk-benefit assessment.

tection is not certain. In a Bio-Manguinhos/Fiocruz study, the fractional dose vaccine continued to provide protection after 8 years. Those vaccinated with the fractionated dose do not receive an international yellow fever vaccination certificate and, therefore, if a certificate is necessary, they must request the standard dose.

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