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Yellow fever in Brazil: Reflections on vaccine safety and effectiveness

Simone Rodrigues da Silva Araújo[1], Ludmilla Pinto Guiotti Cintra Abreu[2], Ronaldo Gonçalves Abreu[3], Jardel Robert Henning Rodrigues de Magalhães[4], Maurício de Oliveira Chaves[5], Euzilene Felisberto Chaves[6], Maria Lúcia de Farias[7], Shairlon Luca dos Santos[8].

ABSTRACT

Yellow fever, caused by Flavivirus genus viruses, is endemic in tropical regions of Africa and South America, primarily transmitted by mosquitoes. It manifests in two cycles: sylvatic, involving transmission from infected monkeys via mosquitoes like Haemagogus or Sabethes, and urban, where Aedes aegypti mosquitoes transmit it directly between humans. Early detection of its nonspecific symptoms is crucial, as they resemble other febrile conditions. Clinically, it progresses through fever, remission marked by albuminuria, and a toxemic phase with hemorrhagic manifestations and acute liver failure. Diagnosis is challenging due to varied symptom presentation. About 50% of patients have nonspecific symptoms, 20% develop mild ones, and 30% face fulminant forms. No specific treatment exists, so focus is on vaccination, early detection, monitoring, and supportive care. Given its threat to Brazilian public health, a review analyzed the yellow fever vaccine's safety and effectiveness. This narrative review method compiles literature to present findings clearly and inclusively.

Keywords: Yellow fever, Effectiveness, Vaccine.

INTRODUCTION

Yellow fever is a disease caused by viruses of the genus *Flavivirus*, and is recognized as an endemic arbovirus in the tropical regions of Africa and South America. The individual becomes infected sporadically when bitten by mosquitoes, mainly of the genera *Haemagogus* or *Sabethes*, previously infected from monkeys carrying the virus (sylvatic cycle). In addition, human-to-human transmission (urban cycle) is also described. In this case, through *Aedes aegypti mosquitoes* (BRASIL, 2020).

It is a severe hemorrhagic disease, therefore, it requires early recognition of signs and symptoms, which are often nonspecific and may mimic other acute febrile syndromes. Clinically, it is characterized by three phases: 1) period of infection, characterized by fever; 2) period of remission, marked by albuminuria; and 3) toxemic period, with the presence of hemorrhagic manifestations and acute liver failure, evidenced by jaundice and hepatic encephalopathy (WHO, 2022).

[1] University of Rio Verde (UniRV)
[2] University of Brasília (UnB)
[3] University of Brasília (UnB)
[4] Institute of Strategic Health Management of the Federal District (IGESDF)
[5] Department of Health of the Federal District (SES)
[6] Catholic University of Brasilia (UCB)
[7] Federal Senate
[8] Federal Senate

However, approximately 50% of patients present nonspecific symptoms, 20% develop few symptoms, and 30% progress to fulminant forms. There is still no specific treatment for this disease. Because of this, vaccination, early detection of suspected or confirmed cases, monitoring of vital signs, and life support measures remain the recommended strategies (WHO, 2022).

In this sense, considering that this disease constitutes a serious threat to Brazilian public health, this narrative review is justified, whose objective was to analyze and review the main available articles on the safety and effectiveness of the yellow fever vaccine.

MATERIALS AND METHODS

This is a narrative review of the literature. In this methodological procedure, it is common to approach the subjects in topics in a broader way, as well as to compile contents from different works, presenting them to the reader in a clear and comprehensive way (RIBEIRO, 2014).

LITERATURE REVIEW

YELLOW FEVER DISEASE

Yellow fever was considered one of the worst diseases during the 18th and 19th centuries. With the advent of campaigns to eliminate the mosquito vector *Aedes aegypti* at the beginning of the twentieth century, urban yellow fever was eradicated from many countries, including Brazil. Thus, in 1942, the last outbreak of urban yellow fever was recorded in the state of Acre (SILVA et al., 2020).

From 2016 to 2018, Brazil experienced a major outbreak of sylvatic yellow fever. As a result, 2,251 cases were reported and 772 deaths were recorded, with most of the occurrences in the state of Minas Gerais, in the southeastern region of the country. In view of this, there is no doubt that this is a major public health problem (BRASIL, 2020).

After the bite, the virus infects dendritic cells and multiplies, reaches the bloodstream and mainly reaches the liver. Thus, in humans, it is considered a viscerotropic disease. In addition, it can be less frequent and may affect the kidneys, spleen, lymph nodes, and heart (DOUAM; PLOSS, 2018).

In this context, a study conducted in Brazil in 2020 analyzed the clinical presentations and liver biopsies of individuals with yellow fever who were considered for liver transplantation during the 2018 outbreak. The authors concluded that this disease frequently induces liver failure, being characterized by massive hepatocellular damage and the presence of steatosis (LEMOS et al., 2020).

With regard to epidemiology, the most affected patients are generally young males who carry out agricultural and timber extraction activities, which they enter the forest without having been vaccinated. However, a high number of tourists, women and children have been affected (ILACQUA et al., 2021). It

is a disease of immediate compulsory notification and vaccine-preventable by the yellow fever vaccine (BRASIL, 2023; BRAZIL, 2024).

THE VACCINE

The yellow fever vaccine used in Brazil is produced by the Institute of Technology in Immunobiologicals (Bio-Manguinhos), of the Oswaldo Cruz Foundation (Fiocruz), from live attenuated viruses of the 17DD substrain, which are cultured in chicken embryos (BRASIL, 2017). It is considered one of the safest and most effective immunobiologicals. Thus, it is the most effective measure for the prevention of the disease, since it is capable of providing protection against all circulating genotypes (KLITTING et al., 2018).

From this perspective, it has immunogenicity of 90% to 98%. Therefore, the presence of 17DD virus was observed in the urine of individuals within 25 days after vaccination. In addition, genomic load values ranged from $3x10^1$ to 5x105. This demonstrates viral persistence, with values close to those found in serum during the acute phase of the disease, as well as evidence of the effectiveness of this immunobiological (VOLKOV et al., 2020).

During the outbreak from 2016 to 2018, a study pointed out that the viral load can be used to project the mortality of patients with yellow fever, when the values are higher than 5.1 log10 copies/ml (KALLAS et al., 2019). Recently, the RNA of the sylvatic yellow fever virus was detected in the cerebrospinal fluid of a three-year-old child, vaccinated at nine months of age, with severe meningitis, which progressed to death (MARINHO et al., 2019).

A Brazilian study, which involved 824 children aged nine months to twelve years, found that the proportion of seropositivity decreases with the time of application of the vaccine. During the periods evaluated, it was found that immunity was 86.7% in the newly vaccinated, with 59% and 42.2%, respectively, in the immunized subgroups between 31-72 months and 73-100 months (NORONHA et al., 2019).

The Collaborative Group for Studies on Yellow Fever Vaccines analyzed the immune status of individuals who were immunized with two or more doses. Those who had one dose of the vaccine for more than ten years were 69% seropositive before receiving the second dose and 100% after revaccination. Nevertheless, immunity showed a decline according to the time interval between the first and second dose, with 90% within five years and 86% from six years onwards (COLLABORATIVE GROUP FOR STUDIES ON YELLOW FEVER VACCINES, 2019).

Currently, the vaccination schedule comprises one dose at nine months and a booster dose at four years of age. It is administered subcutaneously, in a volume of 0.5 ml. After the application of the vaccine,

protective antibodies appear between the seventh and tenth day. Therefore, immunization should take place ten days before entering a risk zone for this disease (BRASIL, 2024).

The 17DD vaccine has been widely used since the late 1930s, with rare cases of serious adverse reactions. However, some adverse events have been reported, the most common of which are: hypersensitivity, malaise, headache, muscle aches and low-grade fever. These occur between 2 and 5%, are evident around the fifth to tenth day after vaccination, last one to two days and regress without sequelae (POSSAS et al., 2018).

A retrospective, observational, cross-sectional study conducted by reviewing the medical records of patients with psoriasis who were vaccinated against yellow fever concluded that adverse events were mild and rare. Therefore, there was no record of severe manifestation, hospitalization or death. There was also no change in the clinical course of the underlying disease regardless of the treatment instituted, i.e., with or without immunosuppressive drugs (BARROS et al., 2019).

A retrospective cohort study, developed in the United States, with data from 263,979 patients between 2004 and 2019, observed that less than 1% of this sample had conditions predisposing to immunosuppression. In addition, four non-fatal cases of neurotropic diseases associated with the yellow fever vaccine (YEL-AND) and none viscerotropic (YEL-AVD) were identified, which led to the conclusion that the risk of developing these diseases post-vaccination remains rare (LEDLIE et al., 2022). However, the literature converges that the notification rate for both YEL-AND and YEL-AVD increases in people aged sixty years or older (FLETCHER et al., 2020; LINDSEY et al., 2016).

FINAL THOUGHTS

Yellow fever is an infectious disease, transmitted by arthropod vectors in both wild and urban areas, and is caused by a virus of the genus *Flavivirus*. It is a disease that was responsible for a large number of deaths between the eighteenth century and the beginning of the twentieth century, evidencing a major Brazilian public health problem.

From this study, it was possible to identify that the yellow fever vaccine is safe, highly immunogenic and effective, since it is capable of inducing the formation of long-lasting protective antibodies. Because of this, it is the most effective means to prevent and control this disease, since in addition to interrupting the transmission cycle, it provides individual and collective protection to the population, as it creates an immunity barrier, blocks the geographic spread of the disease and prevents epidemics.

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