doi: http://dx.doi.org/10.11606/issn.1679-9836.v97i4p407-414

Yellow Fever: a review and the current epidemiological situation in Brazil

Febre Amarela: revisão e situação epidemiológica atual no Brasil

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Ribeiro Junior MAF, Feng CYD, Nguyen ATM, Rodrigues VC, Bechara GEK, Moura RR. *Yellow Fever: a review and the current epidemiological situation in Brazil* / Febre Amarela: revisão e situação epidemiológica atual no Brasil. Rev Med (São Paulo). 2018 jul.-ago.,;97(4):407-14.

ABSTRACT: Since January 2017, there have been at least 1563 suspected cases of Yellow Fever, 629 confirmed cases and 232 confirmed deaths. Yellow fever is a viral hemorrhagic disease endemic to the tropical parts of Africa and South America. At the present time, it has presented a significant increase in its incidence in Brazil, with important repercussions and impacts on the public health. This review paper outlines the causes of yellow fever, as well as the disease epidemiology, progression, diagnosis, treatment and prevention. We conclude by reporting on the current epidemic in Brazil and future directions for research. *Method:* Data from Pubmed, SciELO, Medline and government sources concerning Yellow Fever were used, dating from 2002 to 2018. In the collection of the data the following descriptors were used: Yellow-fever, Aedes, Arbovirus and Flavivirus.

Keywords: Yellow fever; Flavivirus; Flavivirus infections; Aedes; Hemorrhage.

RESUMO: Desde Janeiro de 2017, foram reportados 1563 casos suspeitos de Febre Amarela, sendo confirmados 629 casos, dos quais foram confirmadas 232 mortes devido a doença. A Febre Amarela é uma doença febril hemorrágica, sendo endêmica de regiões tropicais da África e América do Sul. Nos dias atuais, tem apresentado aumento significativo em sua incidência no Brasil, com repercussões e impactos importantes na saúde pública do país. Neste artigo são descritas as causas de Febre Amarela, bem como sua epidemiologia, progressão, os métodos diagnósticos, tratamento e prevenção da doença, de forma a promover atualização epidemiológica e direcionar futuras pesquisas na área. *Método:* Foram utilizados dados do Pubmed, SciELO, Medline e de fontes governamentais, referentes a Febre Amarela, que datam de 2002 à 2018. Na coleta do dados foram utilizados os seguintes descritores: Febre Amarela, Aedes, Arbovírus, Flavivirus.

Descritores: Febre amarela; Flavivirus; Infecções por arbovírus; Aedes; Hemorragia.

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INTRODUCTION

Epidemiology

Yellow fever is a mosquito-borne viral disease that is endemic to the tropical parts of Africa and South America. The viral hemorrhagic fever (VHF) is caused by approximately 70 positive single-stranded RNA viruses belonging to the *Flaviviridae family*. The yellow fever virus (YFV) are small (40 to 60nm), enveloped and icosahedral in shaped[1,2]. It is the E glycoprotein on the surface of the virus that is responsible for virion attachment, assembly, fusion and immunogenicity[2].

Yellow fever continues to affect 180,000 people with roughly 78,000 deaths annually[3]. Approximately 1 billion people among 46 countries live within areas considered to be at risk for infection by YFV[3]. In South America, Argentina, Bolivia, Brazil, Colombia, Ecuador, Guyana, French Guyana, Paraguay, Peru, Suriname, Trinidad and Tobago and Venezuela are areas at risk of yellow fever[2]. Figure 1 provides a detailed look at the areas at risk for yellow fever in Brazil as of January 2017.

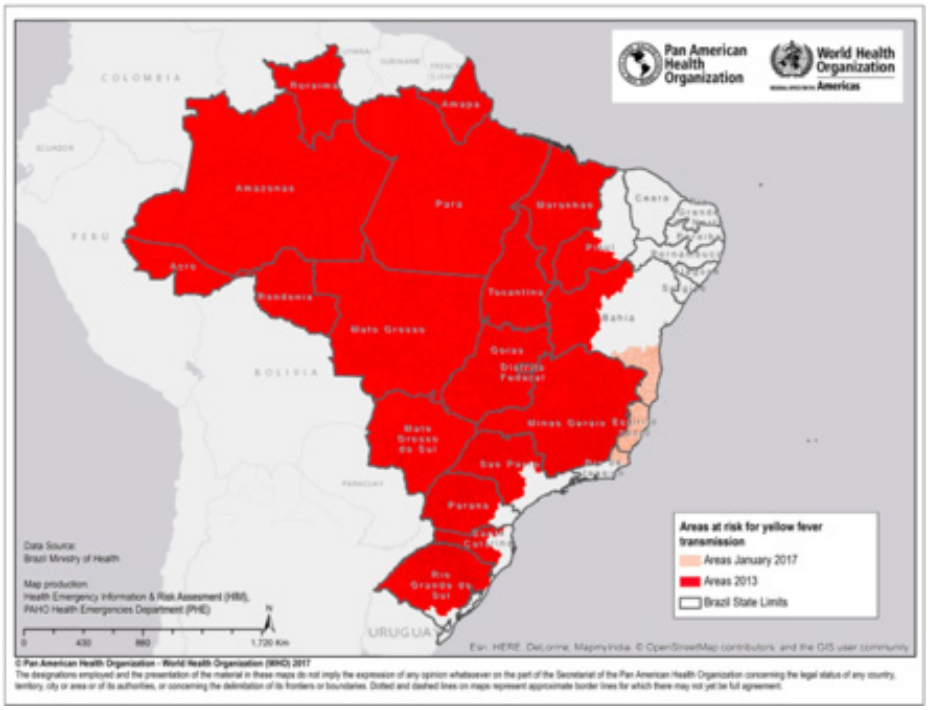

Figure 1. Areas at risk for yellow fever in Brazil. Accessed from Pan American Health Organization (PAHO)[5]

There are three cycles in the spread of yellow fever to humans; the sylvatic (jungle), intermediate and urban cycles. In the jungles of South America and Africa, the sylvatic phase involves the spread of YFV between non-human primates by several mosquito species (e.g. Haemogogus genera)[1,2]. Humans working in these jungle areas can be infected with the virus and allows the virus to move into the intermediate cycle. This phase occurs when the virus enters towns and villages bordering jungle areas. Here YFV is spread by infected, semidomestic species of mosquitos that feed on both monkey and human hosts. The urban cycle starts when YFV is introduced into areas of high population density. This phase is responsible for human epidemics of yellow fever; worse epidemics are linked to high-density populations with a significant number of unvaccinated people, as well as prolonged rainfall and temperature increases[1,2,4]. Transmission between humans occurs via inoculation by the Ae aegypti mosquito and it is not contagious between humans[2].

METHOD

This review was sourced from articles available from Pubmed, SciELO and Medline. Official data was obtained from government sources. The dating of the data ranged from 2002 to 2018.

Pathogenesis and clinical manifestations

Severe VHF has a fatality rate of 20-50% and is typically characterized by viremia, fever, liver dysfunction, renal damage, myocardial injury, hemorrhage and shock[2]. YFV causes these diseases by direct or indirect attack on the microvasculature, leading to increased vascular permeability and local hemorrhage[6]. The timeline of disease progression is as follows.

Period of infection

When an infected female mosquito is blood feeding, it inoculates roughly 1000 to 100,000 virus particles into the

host's skin. At the site of inoculation, the virus replicates in the dendritic cells of the epidermis and spreads to the regional lymph nodes via lymphatic channels. From here, the virus can reach other organs via the lymphatic and circulatory systems[7].

There is an incubation period of 3-6 days before the symptoms abruptly appear. Typically, the patient is febrile and experiences nausea, vomiting, malaise, myalgia, irritability and dizziness[8]. In severe cases, patients may also display Faget Sign, whereby there is an increase in temperature while pulse rate decreases[2]. During this period, the viral load is high enough to infect biting mosquitos, leading to further spread between humans.

Period of remission

Patients with mild disease typically recover without lasting complications; those with more severe disease can then enter a "period of remission", where the fever and other symptoms subside rapidly for 24 hours. There is clearance of the virus from the patient's circulation and patients have another chance of resolving the infection without any permanent sequelae[2].

Period of intoxication

In approximately 20% of patients, the illness progresses to a more severe form, (period of intoxication)[2]. Patients report high fevers, abdominal pain, dehydration, prostration and vomiting. There are also symptoms according to the organ involved. In yellow fever, the liver is the primary target of the YFV[2].

With liver dysfunction, a patient may develop coagulopathies that produce severe hemorrhage manifesting as petechiae, ecchymosis, epistaxis and hematemesis (gastrointestinal hemorrhage that is vomited up). Severe liver damage may also manifest in the patient as jaundice. On gross pathological examination of the liver, the lobular markings are destroyed, the liver size is normal or enlarged and appears icteric. Councilman bodies are hallmarks of fatal yellow fever infection[2].

Renal failure and albuminuria has also been reported during the period of intoxication. On gross pathological examination there are enlarged, edematous kidneys with signs of acute tubular necrosis[2].

Central nervous system symptoms may then occur during this stage of the disease as well and symptoms include seizures, coma and finally death roughly 8-10 days after infection[2,9].

Diagnosis

A presumptive diagnosis of yellow fever is often based on the patient's clinical features, places and dates of travel (if the patient is from a non-endemic region), activities, and epidemiologic history of the location where the presumed infection occurred[10].

However, yellow fever is difficult to diagnose, especially during the early stages because in approximately 90% of cases, the clinical condition is asymptomatic or oligosymptomatic[11].

The clinical spectrum of yellow fever can range from asymptomatic infections to severe and fatal conditions as described previously. It is important to highlight that the disease expression is independent of the transmission context, whether urban or wild[13].

Timely diagnosis is essential for the management of yellow fever outbreak, as it allows public health workers to effectively prioritize vulnerable locations and populations and provide vaccination and vector control measures if deemed necessary[14]. The disease can be detected using serology; viral genome by polymerase chain reaction (PCR) in serum; virus isolation; or histopathology and immunocytochemistry[15]. However, these tests require highly trained laboratory staff and specialized equipment and materials, which may be a problem for some under-resourced areas[12]. Laboratory diagnosis can be divided into specific and non-specific:

Specific laboratory diagnosis

Laboratory investigations are important and involve isolating the flavivirus in VERO cells or C6/36 clone. The virus is identified by complement fixation tests and indirect immunofluorescence, in addition to PCR[11].

The diagnosis can be confirmed by detection of viral antigens and viral RNA, as well as serology with IgM capture in enzymatic assay in paired sera. A four-fold or greater increase in antibody levels measured by IgM ELISA or by hemagglutination inhibition test in paired sera indicates an acute or recent flavivirus infection in unvaccinated people[11,16]. In fatal cases, specific antigens are detected by immunohistochemistry in tissues, which should be collected within the first eight hours after death. The collected specimen should then be sent to the reference laboratories specific to where the cases occurred[11].

The serology may have two samples. The first sample should be collected after the fifth day of symptoms and a second collected within 14 to 21 days of the initial collection.

Test results are normally available 4 to 14 days after receiving the specimen. Reporting times for test results may be longer during summer months when domestic arbovirus activity increases. Receipt of a hard copy of the results takes at least 2 weeks after testing is completed[10].

Non-specific laboratory diagnosis

Leukopenia, lymphocytosis and marked thrombocytopenia are observed in the severe forms of yellow fever, without direct correlation with levels and bleeding. In asymptomatic and oligosymptomatic cases, blood count may be normal[11]. In severe cases, there may be marked leukocytosis, significantly high aminotransferases and change in coagulation factors, mainly prothrombin,

factor VIII and thromboplastin[11,16]. Both creatinine and urea levels can rise and their worsening correlates with deterioration of patient's condition[17]. Urinalysis can show bilirubinuria, hematuria, and marked proteinuria, with values above 500 mg/100 mL of urine[11].

Differential diagnoses

During epidemic outbreaks, it is relatively easy to diagnose yellow fever, since the existence of previous cases during the period increases clinical suspicion. During periods of no epidemic outbreaks, diagnosis can be problematic. Thus, a syndromic approach to diagnosis is often used[11]. Infectious diseases that should be included in the differential diagnoses include malaria, viral hepatitis, typhoid, hemorrhagic dengue and septicemia. Among non-infectious causes, idiopathic thrombocytopenic purpura and poisoning, including venomous snake bites that produce hemorrhaging should be ruled out[7,11].

The clinical history, epidemiological antecedents and early performance of laboratory exams are the main methods of diagnosis in the majority of yellow fever cases.

Management and treatment

Care for the patient with yellow fever is mainly supportive as there is no specific antiviral therapy currently available[15]. Patients may benefit from intensive care but despite the assistance of modern hospitals the case fatality rate among patients with yellow fever remains 35%, suggesting that intensive care makes little difference to outcome of this disease[18,19].

Nowadays, it is recommended that the patient should be managed in an intensive care unit (ICU) and closely monitored for disseminated intravascular coagulation (DIC), hemorrhage, kidney, and liver dysfunction. Coagulopathy is managed with fresh frozen plasma, and renal failure may require dialysis[20].

According to an article publish in 2018 by Song et al.[21], one way to approach a patient with liver dysfunction is a liver transplantation (LT). For the first time, a LT was performed to treat a patient with severe YF. This new approach, although it may represent a paradigm shift in the management, LT could improve survival of some patients who would certainly otherwise die[21].

In past years, research has been conducted on the use of passive antibodies, interferons, immunomodulators and other drugs like tiazofurin, orotidine 5-monophosphate decarboxylase inhibitors, isoquinolone alkaloid drugs, 6-azauridine and related compounds, triaryl pyrazoline and iminocyclitol compounds with a deoxynojirimycin[22]. In the case of interferon and passive administration of antibodies, this approach may prevent disease only if given in a very short window after infection[23]. Research on the treatments mentioned did not demonstrate effectiveness on humans[19].

In studies in nonhuman primates, ribavirin treatment was not effective in prolonging survival. However, in an animal model, ribavirin initiated at a high loading dose (80 mg/kg) followed by daily doses of 40 mg/kg and started up to 120 hours after infection showed reduced mortality and hepatocellular dysfunction in hamsters[23].

According to Freitas et al.[24], another drug that has been shown efficacy as treatment for YF is Sofosbuvir. Other Flaviviruses, such Zika (ZIKV) and dengue (DENV) viruses, are susceptible to Sofosbuvir, a clinically approved drug against hepatitis C virus (HCV). Moreover, sofosbuvir has a safety record on critically ill hepatic patients, making it an attractive option. Their data show that YFV RNA polymerase uses conserved amino acid resides for nucleotide binding to dock sofosbuvir. This drug inhibited YFV replication in different lineages of human hepatoma cells, Huh-7 and HepG2, with EC50 value of 4.8 μM. Sofosbuvir protected YFV-infected neonatal Swiss mice from mortality and weight loss. Their pre-clinical results indicate that sofosbuvir could represent an option against YFV[24].

Prevention strategies and their effectiveness

The live, attenuated yellow fever vaccine was developed in 1936 and although there are two main substrates that are used in commercial manufacturing (17D and 17DD), there appears to be no major differences in safety or immunogenicity between them[25]. The yellow fever vaccine provides effective immunity within 30 days for 99% of patients[15].

Vaccination given to patients aged 9 months and older is safe, affordable, and the most effective way to prevent yellow fever. World Health Organization (WHO) recommends a single dose for most travelers, but those who are pregnant during vaccination, had a stem cell transplant, plan to spend an extended period in endemic areas or work regularly in labs with yellow fever samples may consider a booster immunization[15].

In April 2013, the World Health Organization Strategic Advisory Group of Experts on Immunization concluded that a single primary dose of yellow fever vaccine is sufficient to confer sustained immunity and lifelong protection against yellow fever disease, and that a booster dose is not needed[26]. This conclusion was based on a systematic review of published studies on the duration of immunity after a single dose of yellow fever vaccine, and on data that suggest vaccine failures are extremely rare and do not increase in frequency with time since vaccination[27].

Although the effectiveness of YF vaccine in humans has not been formally tested in controlled clinical trials, several observations attest to its effectiveness. Most studies showed a consistently high immunogenic response to YF vaccine. Four studies evaluated vaccine performance in the context of mass vaccination campaigns. The seroconversion rates in these studies ranged from 89.7% to 98.2%[27]. Moreover, Tavares-Neto et al.[28] reported a seroconversion rate of 94% after a vaccination campaign in a remote region

of Brazil, which was characterized by its difficult access, minimally trained personnel, and limited resources. These findings, although not absolute, suggest that YF vaccine is effective even in precarious field conditions.

Thirteen observational studies provided immunogenicity data on 1,137 persons vaccinated more than 10 years previously. Using a random effects model, the estimated seropositivity rate for persons vaccinated more than 10 years previously was 92%. Of the 164 persons vaccinated ≥20 years previously, the estimated seropositivity rate was 80%[26].

The recommended immunizing dose of yellow fever vaccine is 1000 IU. However, doses as low as 600 IU have been shown to induce equivalent levels of neutralizing antibodies in 97% of recipients. Potency in routine vaccine batches ranges from 1995 IU to 2511886 IU, therefore administration of a fraction of the full dose could suffice to confer protection in most instances. With this dose-sparing strategy, a larger proportion of the population at risk could be vaccinated in emergency situations when vaccine supplies are insufficient. This policy is supported by two vaccine trials that demonstrated equal safety and immunological non-inferiority. Martins et al. found that de-escalation of 17DD-YF vaccine dose from 247 476 IU to 587 IU resulted in similar seroconversion rates and geometric mean titres of neutralizing antibodies in military conscripts up to 10 months after subcutaneous (SC) vaccination. Visser and Roukens[29] showed that intradermal administration of a five-fold fractional dose of 17D-204-YF vaccine was equally immunogenic compared to the SC administered standard dose 1 year later.

The vaccine is very well tolerated; in practice few patients complain of side effects. In clinical trials, where symptoms have been solicited, common adverse events include injection site pain or redness, headache, malaise, and myalgia within a few days of vaccination in approximately 20-25% of vaccines. These symptoms are mild and do not interfere with activities. Serious adverse reactions to the 17D vaccine are very rare events; they include two syndromes, known as yellow fever vaccine-associated neurotropic disease (YEL-AND) and yellow fever vaccine-associated viscerotropic disease (YEL-AVD)[7].

However, it is important to note that the vaccine is contraindicated in breastfeeding women due to the potential for transmission of vaccine virus via breastmilk. It is also contraindicated in infants under age 9 months because of the increased risk of encephalitis. Patients with a severe, life-threatening allergy to eggs, chicken protein, gelatin, or previous yellow fever vaccines should receive the vaccine. Extreme caution should be taken before administering the vaccine to patients on chemotherapy, with HIV infection, or any other condition that compromises the immune system[15].

Current situation in Brazil

Yellow fever tends to have a cyclical pattern in forested or rural areas of South America, alternating between endemic and epidemic periods every 3-7 years, reflecting the cyclical epizootics in non-human primates, such as monkeys[30,31]. The last outbreak of yellow fever in human primates in Brazil occurred between July 2016 and June 2017, resulting in 779 confirmed human cases of yellow fever and 262 deaths[32]. However, in 2008-2009, an outbreak of yellow fever reporting 56 deaths of non-human primates in southeast São Paulo, highlights the significance of surveillance and monitoring of epizootic events as an early indicator of viral circulation[43,44].

Since January 2017, there has been 629 confirmed cases of yellow fever in Brazil, including 232 confirmed deaths[45]. As reported by WHO, there has been a tripling of confirmed cases of yellow fever in Brazil, particularly in *São Paulo* and *Minas Gerais*[34]. This includes 183 confirmed cases, including 46 deaths in *São Paulo*, 157 confirmed cases, including 44 deaths in *Minas Gerais*, 68 confirmed cases, including 27 deaths in Rio de Janeiro, and 1 death in the Federal district[33]. The suspected source of infection of all these cases are from non-human primates, with 2242 suspected epizootics in non-human primates, 411 confirmed between 1 July 2017 and 8 January 2018[35]. In December 2017, infected non-human primates were reported in urban parks in Greater São Paulo, resulting in closure of several parks[36]. This poses high risks for spread of yellow fever through Greater São Paulo, particularly with road developments such as a highway traversing through the Cantareira mountain region, dense in flora and fauna and through densely populated regions of São Paulo and Guarulhos, which would facilitate avenues for the infection to spread from primates to metropolitan areas[42].

On 15 February 2018, yellow fever virus was detected in *Aedes albopictus* mosquitoes for the first time in Brazil, found in rural areas of the *Ituêta* and *Alvarenga*, of *Minas Gerais*[33]. This strongly suggests that *A. albopictus* and possibly other species of mosquitos are becoming susceptible to yellow fever in not only forested areas, but also in areas closely surrounding urban Brazilian cities, posing a risk of re-urbanization of the disease[41].

Following the recent outbreak of yellow fever in Brazil, there are major concerns of re-development of the disease in Brazil and factors that may increase risks of yellow fever resurfacing in future must be addressed. The increasing number of domestic and international tourists that visit forest areas may increase risk of transmission and dissemination of yellow fever, if these wildlife areas were to become infected. Poor vaccination coverage in areas of Brazil also leaves large populations to be susceptible to the disease, posing high threats to future outbreaks. Furthermore, the geographical proximity of forest and urban areas in areas of Brazil, as well as large populations of monkeys and other non-human primates that occupy these areas aid in viral circulation and dissemination of

yellow fever. These factors need to be addressed in order to not only control the current situation, but also prevent future outbreaks from arising[41].

Current response and management

In response to the recent surge in cases of yellow fever in Brazil, the Brazilian Ministry of Health initiated a mass vaccination campaign of both standard (0.5 mL) and fractional (0.1mL) doses, commencing in São Paulo and Rio de Janeiro from 25 January to 17 February and in Bahia from 19 February to 3 March (32). As of 15 February 2018, 3.95 million people across São Paulo and Rio de Janeiro have been vaccinated; 19.3% of the targeted total. Due to the low numbers that were vaccinated, Rio de Janeiro authorities extended the duration of its vaccination campaign and likewise, São Paulo is assessing the potential for extension of its campaign to increase numbers vaccinated[33]. The Ministry of Health aims to vaccinate 21.8 million people across the three states by the end of the vaccination campaign[34]. On 20 March 2018, vaccination campaign was expanded to a nationwide campaign, aiming to vaccinate 78 million people by 2019[43]. This decision would increase vaccination coverage in Brazil with the future challenge to potentially universalize the vaccine across not only Brazil, but to every country internationally, in order to control yellow fever. However, a major barrier to mass vaccination is the shortage of vaccines[44].

In response to recent outbreaks, WHO has also extended the geographical areas of Brazil for which yellow fever vaccinations are required for international travelers travelling to Brazil, including all of *Espirito Santo, Rio de Janeiro, São Paulo* and selected areas of *Bahia* State[37]. WHO recommendations are that all unvaccinated travelers aged between nine months and 60 years of age without contraindications should be vaccinated for yellow fever at least 10 days prior to travelling to at risk areas (Figure 2). Advice also include adopting suitable measures to avoid mosquito bites, being well-informed of symptoms and signs of yellow fever and seeking medical help when recognizing these symptoms upon return[38].

Figure 2. Expanded yellow fever vaccine recommendation areas in Brazil. Accessed from CDC[39]

Challenges and approach

Currently, of major concern to health authorities in Brazil and internationally is the large population of unvaccinated people in Brazil living in areas considered favorable for transmission of yellow fever[34]. Whilst the mass vaccination campaign launched by the Ministry of Health aims to combat this issue, the vast areas and large population that must be covered in order to ensure widespread vaccination coverage remains a great challenge. Due to limitations in availability of vaccines, Pan American

Health Organization (PAHO) in association with WHO recommends that national authorities assess vaccination coverage in at risk areas to ensure at least 95% coverage. States that are not experiencing outbreaks should not conduct vaccination campaigns, to give priority to at risk areas. Routine vaccination in children residing in non-endemic areas should also be postponed to ensure that endemic areas are prioritized[33].

A confirmed case of yellow fever in an unvaccinated returning traveler from Brazil to the Netherlands was reported on 11 January 2018[34]. This reinforces the importance of vaccination in international travelers to Brazil, as it poses the risk of disseminating yellow fever to other countries that are receptive to yellow fever, such as countries with high prevalence of mosquitoes. Consequently, a large area to target is immunization requirements for foreign travelers, with proof of yellow fever vaccination certificates required upon return from affected areas. Particularly with the Carnival occurring between 9 and 14 February in Brazil, precautions must be taken to prevent the number of unvaccinated travelers coming into Brazil for this event[39].

The approach to this recent yellow fever outbreak should be a holistic movement, involving liaison between state, national and international authorities and organizations to ensure that the outbreak is contained and morbidity and mortality is minimized. Support should be provided for the Brazilian government, in the form of yellow fever vaccine supplies, syringes and vaccination cards, as was provided in previous outbreaks by PAHO and WHO. Education remains forefront in ensuring that all key stakeholders are well-informed. In December 2017, a workshop was conducted for yellow fever control specialists based in Brasilia, organized by PAHO, the Global Outbreak Alert and Response Network (GOARN) and WHO, aiming to teach strategies for vaccination in an outbreak situation[40]. PAHO also was involved in mosquito control and identifying outbreaks in non-human primates, to allow for more targeted vaccination campaigns by identifying at risk areas.

CONCLUSION

In the context of the recent outbreak of yellow fever in Brazil, increased awareness and knowledge of the typical presentation, natural progression and prevention of the disease is essential to containing the epidemic. Further support and education for healthcare providers on the diagnosis, management of yellow fever and vaccine available can allow for better quality of care to infected individuals. An examination of current and future strategies to identify the strengths and weaknesses will be helpful in addressing current and future outbreaks.

Authors' contributions: MR was the main editor and leader of the project group. CF, AN, VR, GB and RM contributed to the research and the writing process. MB provided expert feedback and guidance to the team. All authors read and approved the final manuscript.

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Received in: June 7, 2018
Accepted on: Nov 12, 2018