



## Editorial

## Yellow fever in Brazil: Epidemiological aspects and implications for travelers



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The current epidemiological situation of yellow fever (YF) in Brazil constitutes a public health emergency, due to the potential threat of the re-urbanization of YF in this country. The last report of transmission of urban YF in Brazil was described in 1942, in the state of Acre in the northern region of the country. Since then, wild, non-urban transmission has come to predominate with cyclical outbreak records at regular intervals of five to seven years as observed up to 1997 [1].

As of 1998, there has been a change in this cyclical pattern. Yellow fever showed a strong seasonal trend, with 93% of the cases identified between December and May. This trend was observed both in the Brazilian Amazon and in other regions of the country, when YF started to occur as sporadic cases and occasional epidemics, displaying an irregular periodicity of the disease [1,2].

Although the irregular periodicity of YF is not fully understood, climatic factors such as elevation of temperature and rainfall, high vector density and primary hosts, presence of susceptibility, low vaccine coverage, emergence of new virus strains are all possible factors that favor transmission and re-emergence of the virus in the country, in addition to the endemic areas [2].

Several aspects may have an impact on the risk of re-urbanization of YF in Brazil, including the fact that the majority of Brazilian cities have geographical boundaries of forest areas very close to the urban perimeter (for example, Mairiporã, a municipality very close to the city of São Paulo with a focus of the largest number of cases in this epidemic) [3] and with significant infestation of *Aedes aegypti*, the main vector of the urban cycle.

In addition, in 2017, for the first time YF was detected in *A. albopictus* mosquitoes in Brazil, in rural areas of Minas Gerais state, indicating that this species of mosquito is susceptible to YF both in forest environments and in peri-urban areas. This finding may mean establishing an intermediate (rural) cycle of YF in the Americas, similar to what occurs in Africa [Vasconcelos, unpublished, 2018].

Another aspect that impacts on the risk of re-urbanization of the disease is the increase in the practice of ecological tourism and wild life

tourism observed in the last decades that increasingly attracts domestic and international tourists to these activities in the affected areas. Unvaccinated individuals, including travelers, who enter these areas, are at risk of contracting YF and develop, and may, when they return with viremia to the urban areas infested by *A. aegypti*, be sources of YF dissemination in Brazilian cities as well as other cities infested with the vector.

Moreover, and in addition to the possibility of re-urbanization of YF infection the low coverage rates of YF vaccination observed locally and in tourists visiting the newly infected areas are a matter of concern. According to official data from the National Immunization Program, during the period from January 2005 to December 2014, 57.6 million doses of the YF vaccine were administered in the Brazilian population, corresponding to a vaccination coverage of 65.2% of the targeting population [3]. No data about vaccination coverage of travelers visiting infected areas on Brazil is available, but it is presumed to be low. The lack of awareness on the new YF risk areas by the international travel medicine advisors as well as by the travelers is another critical factor for prevention failure. Due to rapidly evolving YF epidemiology, travel medicine recommendations need constant updating so that visitors to at-risk areas are vaccinated against YF.

Since 2017, Brazil has been facing one of the most serious outbreaks of YF in recent decades. Minas Gerais, Espírito Santo, Rio de Janeiro and São Paulo were the most affected states by this outbreak. Official data from the Ministry of Health of Brazil recorded 6565 reported cases (till May 8, 2018), with 1257 cases and 394 deaths confirmed of the disease (case fatality rate of 31%), 1499 cases remain under investigation and 3809 were discarded. All confirmed cases of the disease were acquired by transmission involving the wild cycle of YF, not being evidenced yet *A. aegypti* infected with the yellow fever virus in the searches performed by entomological surveillance mosquitoes.

There have been 7410 cases of non-human primates (epizootics) notified to the Ministry of Health: 738 confirmed, 2225 under investigation, 2544 undetermined and 1903 discarded. Most of the

confirmed human cases were reported in the Southeast region of Brazil (99.9%) [4].

The inadequate vaccine coverage among adults of yellow fever in the affected regions is one of the determining factors for the expressive epidemic of YF in Brazil. The density and mobility of nonhuman primates (NHPs), and intense human mobility in the viremic phase in mosquitoes infested areas add up to other factors that may contribute to the expansion of the YF virus in Brazil, particularly its dissemination to the Atlantic coast, as observed in the current epidemic. Some concerns remain unanswered: How to predict spatiotemporal dynamics, and the emergence and reemergence of wild yellow fever? What are the relative weights of ecological (adaptation) and evolutionary (natural selection) phenomena in the appearance of wild yellow fever?

In order to control the current epidemic of wild yellow fever and prevent the re-urbanization of YF in the country, the Ministry of Health released 20 million doses of the vaccine to municipalities of São Paulo, Rio de Janeiro and Bahia. Considering the large population that lives in these states and the stocks of vaccines, for the first time Brazil adopted the fractional-dose of YF vaccine from 0.5 mL to 0.1 mL, multiplying by 4–5 times the number of people vaccinated. This was a pragmatic decision in the face of the vaccine shortage in the world [6].

This measure was also supported by scientific evidence showing the fractional-dose of YF vaccine, a measure adopted at the time of the epidemic in the Congo's capital, in 2016, which resulted in the cessation of disease transmission [6,7]. The exact duration of the immunity conferred by the fractional vaccine is unknown, and may reach up to eight years according to some authors. According to the World Health Organization, the fractional dose of the yellow fever vaccine could be used in response to an emergency situation when the current vaccine supply was insufficient [7], but it is not suitable for travelers [8].

A Yellow Fever Vaccination Campaign is underway in the states of Bahia, São Paulo and Rio de Janeiro. The target is to reach vaccine coverage of 95% of the eligible population, about 22.7 million people. A total of 21,817,990 cumulative doses and the Campaign were administered in the states of Rio de Janeiro, Bahia and São Paulo. Vaccination coverage in these states corresponds to 69.45%, 55.03% and 57.07%, respectively [5]. Therefore, vaccination coverage persists as one of the greatest challenges for YF control in the affected areas.

In order to face the challenge of YF control, from the intense circulation of the virus in populated areas and expansion to new regions, the Ministry of Health of Brazil recently announced the gradual expansion of YF vaccine in the routine vaccination calendar in all Brazilian states, with the aim of anticipating protection against the disease for the entire population. This measure had been advocated by specialists for more than 10 years, and can be seen as one of the lessons learned in the current epidemiological scenario of YF experienced in Brazil [9].

The population of travelers can be sentinel to introduce new pathogens with serious repercussions in public health in a region, country or even continent [10]. The current epidemic of YF in Brazil has also affected travelers. This was observed in the report of more than ten cases of YF infections, including fatal cases in Chilean and Argentinean travelers who traveled to Ilha Grande, in the state of Rio de Janeiro [11–13]. Current epidemics in Brazil have resulted in exportation of cases to other countries in the Americas, but also to Europe countries such as France, Switzerland, Romania and Germany [12–14]. For additional considerations, a recently published study found that countries such as China, India, Mexico, Peru and the United States of America had the highest volumes of travellers arriving from yellow fever-endemic

areas and the largest populations living in cities suitable for yellow fever transmission [15].

Finally, we urge all medical and travel health professionals to be on alert to guide national and international travelers to Brazil [12–14], especially from border areas and close neighboring countries in the Americas. It is important that these professionals have the understanding that in the current context, there is no definitive recommendation on the YF vaccine, and for this reason the traveler's health care services must be up-to-date and in line with constantly evolving recommendations and the changing YF epidemiology. Another aspect to be considered at this moment is that probably the decision of the Brazilian government to gradually increase yellow fever vaccination coverage throughout Brazil and this may impact on the recommendations of public health institutions worldwide regarding recommendations for YF vaccination for travelers to Brazil [11–13].

### Conflicts of interest

Opinions expressed in this editorial are not the position of GSK, but of A. Lepetic and the rest of the authors.

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