

Risk of re-emergence of urban yellow fever in Brazil

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Yellow fever (YF) is an acute infectious, febrile, communicable disease of short duration (12 days at the most) and of variable seriousness. It is caused by an arbovirus of the *Flavivirus* genus and the *Flaviviridae* family. The disease is endemic and enzootic in diverse tropical regions of the Americas and Africa. It is responsible for periodic outbreaks of variable magnitude.¹ Its more severe form is characterized clinically by manifestations of liver and kidney failure which may lead to death. There is no specific aetiological treatment for YF. Vaccination is the most important measure for preventing the disease.¹

From an exclusively epidemiological point of view, two transmission cycles can be differentiated: urban and sylvatic. In both cycles the disease is the same with regard to its aetiological, clinical, immunological and physiopathological aspects. In the urban cycle the disease is anthroponotic whereby animal reservoirs are not of epidemiological importance. *Aedes aegypti* is its main vector, both in South America and in Africa. Despite being susceptible to infection with the YF virus in laboratory conditions, infected *Aedes albopictus* have never been found in natural settings. In the sylvatic cycle, YF is a zoonosis transmitted, on the Americas, by mosquitoes of two genera, *Haemagogus* (*H. janthinomys* and *H. albomaculatus*) and *Sabethes* (*S. chloproteros*), whereby the main source of infection are non-human primates, especially monkeys of the *Allouata*, *Cebus*, *Atelles* and *Callithrix* genera.²

There have been no records of the urban cycle of YF in Brazil since 1942. The last three cases were reported in the town of Sena Madureira in the state of Acre. The last big epidemic occurred in Rio de Janeiro in 1928 and 1929, when 738 cases and 478 deaths

were recorded.³ In the Caribbean the last epidemic was recorded in Trinidad and Tobago in 1954 which, in addition to human suffering and the direct costs of caring for the ill, also caused severe economic harm related to decline in tourism and overseas trade. An outbreak of the urban form of the disease was recorded in Paraguay in 2008.⁴

Urban YF transmission continues to occur in Africa. In Angola, where YF is endemic, in December 2015 the first case of urban YF was reported since 1988, when 37 cases and 14 deaths were recorded. Local transmission in Luanda has led to more than six million people being vaccinated in the province. The epidemic has spread to other large urban centres of that country.⁵ Between December 2015 and June 2016, almost 18 million doses of yellow fever vaccine were distributed for use in emergency campaigns in Angola, the Democratic Republic of the Congo and Uganda.⁵

In Africa the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization reviewed existing evidence and concluded that using one fifth of the normal dose of vaccine continues to offer protection against the disease for at least 12 months and possibly for longer. This split dose may be a safe and efficacious option for mass vaccination campaigns and to control urban outbreaks in situations of vaccine shortage.⁵

Nevertheless, since 2010 YF has spread from West Africa to Central and East Africa where vaccination campaigns had not been held. The outbreak in Angola underscores the need to reinforce assessment of risks and vaccination in Central and East Africa.⁵

In Brazil the re-emergence of YF outside the Amazon Region with effect from the year 2000 has rekindled the

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concerns of health authorities regarding the expansion of the areas of virus circulation documented during the preceding decade. The areas affected most recently in the country's Southeastern and Southern regions are close to large densely populated urban centres the inhabitants of which, for the most part, had not been vaccinated against YF. In many large urban centres in these regions, *Aedes aegypti* infestation is propitious to the occurrence of successive periods of high levels of dengue fever.⁶

The increase in the number of sylvatic YF cases, high density of *Aedes aegypti* infestation and low vaccination coverage are factors favouring the risk of re-emergence of urban YF in Brazil. On the other hand, the maintenance of low density *Aedes aegypti* infestation and high vaccination coverage in endemic areas, together with the short period of YF viraemia (transmissibility) in relation to that of dengue, are factors that hinder the re-emergence of the urban transmission of YF in Brazil.

Since December 2016 Brazil has been experiencing one of the largest outbreaks of sylvatic YF in its history, with occurrence in states in the Southeast region, mainly in Minas Gerais and Espírito Santo, but also in Rio de Janeiro and São Paulo.

Between 2000 and 2012, 326 YF cases and 156 deaths were confirmed in Brazil, with average fatality of 47.8%.⁷ Between December 2016 and the second fortnight of March 2017, 448 cases and 144 deaths were confirmed in the country as a whole. The state of Minas Gerais recorded 349 confirmed cases and 118 deaths, exceeding the numbers for the period 2000 to 2012, when 101 cases and 41 deaths were confirmed in that state. The states of Espírito Santo and Rio de Janeiro, which until then were not considered to be endemic areas, recorded 93 confirmed cases and 22 deaths, and 3 confirmed cases and 1 death, respectively, between December 2016 and March 2017.

Expanding coverage of the area where vaccination against YF is recommended in Brazil is still a controversial subject. Those in favour of expanding the current area base their opinion on the detection of sylvatic transmission of YF in regions infected with *Aedes aegypti*, but which have not had autochthonous cases of sylvatic transmission for many years, such as the states of Bahia, São Paulo (2000) and Minas Gerais (2001). In 2001, in the west of the state of Rio Grande do Sul, YF virus circulation was recorded with laboratory confirmed deaths of monkeys. In this region there had also been

no records of epizootic YF for more than 20 years. Undoubtedly, the areas of risk of occurrence of sylvatic YF are expanding in Brazil.²

Prior to the current outbreak, immunization against the disease was recommended for the Brazilian states of Acre, Amapá, Amazonas, Goiás, Maranhão, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Pará, Rondônia, Roraima and Tocantins, as well as the Federal District and some areas of the states of Bahia, Paraná, Piauí, Rio Grande do Sul, Santa Catarina and São Paulo. Vaccination of international travellers was recommended in the state of Espírito Santo in March 2017. In April 2017, WHO included 88 new Brazilian municipalities as areas for which YF vaccination is recommended for international travellers. These areas include the cities of Rio de Janeiro/RJ, Niterói/RJ, Salvador/BA and the urban area of Campinas/SP.⁸

The sylvatic YF epidemic that has been affecting the Brazilian states of Minas Gerais, Espírito Santo, Rio de Janeiro and São Paulo since December 2016, as well as the occurrence of deaths of monkeys with laboratory confirmed infection with YF virus in other states, have given rise once more to discussion about the need to adopt measures to reduce the risk of reurbanization of the disease. Controlling *Aedes aegypti* infestation, maintaining high vaccination coverage in recommended areas and including this vaccine on the child vaccination calendar nationwide are important measures for reducing the risk of reurbanization of the disease.

With regard to preventing reurbanization of the disease, universal vaccination of the Brazilian population has been questioned in terms of risk/benefit, in view of the following aspects: (i) scarcity of yellow fever vaccine to immunize the entire population of large metropolitan areas in Brazil; (ii) the occurrence of some serious and even fatal, although rare, adverse vaccination events; and (iii) the existence of population groups for whom vaccination is contraindicated – immunosuppressed persons, people being treated for cancer, people allergic to the components of the vaccine (egg proteins, for instance), pregnant women (except those assessed as being at high risk of infection and situations for which there is express health authority recommendation) and people aged 60 or over who can only be vaccinated following careful medical assessment.⁸ However, extending vaccination coverage to all Brazilian children – a population group considered to be easy to access, with the possibility of adequate assessment of any contraindications, without

reports of significant adverse vaccination events and with vaccine availability – currently appears to be one of the most accepted measures, providing gradual protection to the entire Brazilian population.

In April 2017 the Ministry of Health adopted a single vaccine dose against YF for all areas in the country where vaccination is recommended, in compliance with WHO guidelines. The Ministry of Health has also announced the preparation of health services for the possibility of splitting vaccine doses with the aim of containing the

disease in the metropolitan regions where it needs to be blocked. Since then, people who have already had one dose of vaccine will no longer need new doses against YF for the rest of their lives.⁹

Another measure to be considered at this time is the implantation of mobile vaccination units, especially in municipalities in areas where there is sylvatic transmission of the disease, in order to achieve greater vaccination coverage among rural populations more vulnerable to infection.

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