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Critical aspects of yellow fever control in Brazil

ABSTRACT

This paper presents epidemiological and control characteristics of yellow fever in Brazil, taking its wild and urban transmission cycles into consideration. No urban cases have been reported in Brazil since 1942, but urban yellow fever cases were reported in Paraguay in 2008, after more than 50 years without registered cases in the Americas. The two main objectives of yellow fever control programs in Brazil are to reduce the number of wild cases and to maintain zero incidence of urban cases. Although there is a consensus regarding control measures that should be applied in areas endemic for the wild form, this is not so in relation to areas infested by *Aedes aegypti*. The arguments for and against expansion of the vaccination area are discussed. Environmental and entomological studies are needed so that areas receptive to wild-type transmission can be recognized, even if they have been silent for many years.

DESCRIPTORS: Yellow Fever, prevention & control. Yellow Fever, epidemiology.

INTRODUCTION

Yellow fever is transmitted to human beings through the bites of infected mosquitoes of the genera *Aedes*, *Haemagogus* and *Sabethes*, and it currently occurs in central African countries and several countries in South America.[1,9]

From an exclusively epidemiological point of view, an urban cycle and a wild cycle of transmission can be differentiated. Etiologically, clinically, immunologically and physiopathologically, the disease is the same. In the urban cycle, the disease is an anthroponosis, without recognized animal reservoirs of epidemiological importance. *Aedes aegypti* is its most important vector, both in South America and in Africa.[2,3] Although *Aedes albopictus* is susceptible to infection by the yellow fever virus in the laboratory, it has never been found infected in nature.

Since 1942, there have not been any recorded occurrences of the urban cycle of yellow fever in Brazil. The last three cases were notified in the municipality of Sena Madureira, Acre. The last major epidemic occurred in Rio de Janeiro in 1928 and 1929, with 738 recorded cases and 478 deaths.[a] Elsewhere in the Americas, the last epidemic was recorded in Trinidad and Tobago in 1954, which not only brought human distress and the direct expenses due to patient care but also brought large-scale economic losses relating to reductions in tourism and foreign trade.[10] In 2008, based on epidemiological data, an outbreak of the urban form of the disease was recorded in Paraguay.[b]

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Received: 9/29/2009
Approved: 12/1/2009

Article available from www.scielo.br/rsp

[a] Franco O. A história da febre amarela no Brasil. Rio de Janeiro: Superintendência de Campanhas de Saúde Pública. Brasília: Ministério da Saúde; 1976.
[b] Organizacion Panamericana de la Salud. Brote de fiebre amarilla en Paraguay. *Bol Epidemiol.* 2008;27:1.

In the wild cycle, yellow fever is a zoonosis that is transmitted in the Americas by mosquitoes of two genera: *Haemagogus* (*H. janthinomys* and *H. albomaculatus*) and S*abethes*, (*S. chloropterus*). The main source of infection is non-human primates, particularly monkeys of the genera *Allouata, Cebus, Atelles* and *Callithrix*.[2] Other mammals may act as reservoirs, such as certain marsupials and rodents.[7] Non-immune humans may become accidentally infected through penetration into enzootic areas.

In 1955, Brazil achieved the elimination of *Ae. aegypti* mosquitoes (which are also the main transmission agents for dengue), from its territory after a campaign that lasted for more than 20 years. Another 17 countries in the Americas were also successful in this endeavor, as certified by the Pan-American Health Organization.[a] However, Brazil and all these other countries subsequently suffered reinfestation. In 1967, significant reinfestations occurred in Belém, Pará, and in São Luiz, Maranhão, and these were only eliminated in 1973. However, in 1976, starting from the port of Salvador, Bahia, there was reinfestation that, unfortunately, not was not eliminated but also propagated throughout the country.[c] Currently, data from the Ministry of Health (from 2007) reveal that this mosquito is present in more than 4,000 municipalities.

Preventive vaccines against the disease exist. In Brazil, since 1937, vaccine containing attenuated virus has been used. This consists of the strain 17-DD, which comes from samples of the African Asibi strain and does not present neurotropism and viscerotropism. It is cultivated in embryonated hens' eggs. The vaccine is produced by the Bio-Manguinhos Laboratory of the *Fundação Oswaldo Cruz* (Ministry of Health), and it is very effective and relatively safe. Its protective effect starts on the tenth day after vaccination and continues for a minimum of ten years.

The contraindications for using the vaccine are the following: history of hypersensitivity to substances present in hens' eggs, age less than six months, pregnancy (except in situations of epidemiological emergency), acute infectious disease with a febrile state (higher than 38.5 ºC) and states of immunodepression.[c]

CRITICAL ASPECTS OF CONTROL

There are currently two challenges relating to yellow fever control in Brazil: 1. To reduce the incidence of wild-cycle cases of the disease, which cannot be eradicated because it is a zoonosis; and 2. To maintain zero incidence of urban-cycle cases, i.e. to prevent reurbanization of the disease. Regarding the first of these challenges, there is a consensus that vaccination is required for all people living in and visiting endemic areas, although uncertainties still exist today regarding exactly which areas these are. In relation to the second of these challenges, there is unanimity regarding the need to combat the mosquito *Ae. aegypti*,[4,6,9] but there is no consensus regarding the need to vaccinate the whole population of urban areas infested with *Ae. aegypti* and/or *Ae. albopictus*.

The fight against *Ae. aegypti* includes institutional and behavioral measures. Public authorities have the responsibility to provide adequate water supplies and regular garbage collection; to establish municipal sanitary legislation relating to used tire dumps and scrap iron yards that are exposed to rain, and to inspect compliance with the legislation; to require that sand be placed in vases in cemeteries; to clean up vacant plots of land; and to apply larvicide to water accumulations that cannot be eliminated. Among the behavioral measures, there is a need for intensive sanitary education with the aim of getting people to eliminate the mosquitoes' preferred breeding sites, for example by keeping water tanks covered, keeping backyards clean, ensuring correct drainage from the water gutters of roofs, avoiding leaving receptacles exposed such that they might accumulate water and changing the water in flowerpots and trays frequently.[8]

There is also a consensus regarding the need for effective epidemiological surveillance of suspected cases (individuals with febrile-jaundiced-hemorrhagic syndrome coming from areas endemic for wild-type yellow fever), in areas infested with *Ae. aegypti*. Moreover, there is a consensus regarding the need for sanitary surveillance at ports, airports and borders, with the purpose of requiring presentation of a valid International Vaccination Certificate, by travelers coming from areas that are endemic for the disease. Likewise, there is full agreement regarding the need to keep suspected patients in isolation during the period of viremia, in order to avoid infecting *Ae. aegypti* and/or *Ae. albopictus* mosquitoes that might be present in the area.

There is no agreement regarding vaccination of the populations living in areas infested with *Ae. aegypti* and/or *Ae. albopictus*, especially since certain very relevant recent events. People who declare that they are against geographical expansion of vaccination coverage base their view on the importance of four occurrences of death associated with the vaccine: one in Goiânia, GO, in 1999; one in Americana, SP, in March 2000;[10] one in Jaboticatubas, MG, in March 2001; and one in Três Passos, RS, in September 2001.[d] Additional

[c] Ministério da Saúde. Fundação Nacional de Saúde. Manual de vigilância epidemiológica da febre amarela [internet]. Brasília; 1999 [cited 2009 Sep 29]. Available from: http://portal.saude.gov.br/portal/arquivos/pdf/manu_feam.pdf
[d] Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação Nacional de Imunização. Unpublished data.

deaths associated with the vaccine were found in 2008 and 2009, during the intensification of vaccination in the states of São Paulo and Rio Grande do Sul. In the literature, there are reports on cases of death associated with the vaccine in the United States and Australia.[5] The factors that lead some people to present severe adverse events that are associated with the vaccine are still not fully understood. In addition to the contraindications already mentioned, there are individual immune factors that so far remain unidentified and fail to impede uncontrolled replication of the vaccine virus, thus reproducing the disease.[10] Since the vaccine is not completely harmless, indiscriminate use of the vaccine among populations in areas infested with *Ae. aegypti* and/or *Ae. albopictus* should only take place when there is a high risk of urban transmission. Improvements in epidemiological surveillance might, up to a point, enable early detection of outbreaks, thereby making it possible to rapidly institute blocking vaccination.

People who declare that they are in favor of expanding the present area of vaccination coverage base their view on the fact that wild-type yellow fever transmission was detected in regions of the states of Bahia and São Paulo in 2000, and Minas Gerais in 2001, which presented infestation with *Ae. aegypti* but had not presented autochthonous cases of the wild form for many years. Also in 2001, in the western region of Rio Grande do Sul, virus circulation was detected through the deaths of monkeys, with laboratory confirmation. In that region too, there had not been any records of epizootic yellow fever for more than 20 years. There is no doubt that the areas at risk of occurrences of wild-type yellow fever in Brazil are expanding. In 2008, in regions of the states of São Paulo and Rio Grande do Sul that had not been considered to be areas with virus circulation, deaths of non-human primates and cases and deaths among humans were recorded. These events have expanded the areas within which vaccination for people living there and travelers going there is recommended. Given the proximity of locations of human yellow fever occurrences to areas infested with *Ae. aegypti*, it is increasingly difficult to identify whether the cases recorded were transmitted by wild or urban vectors. Many researchers and healthcare professionals favor gradual expansion of the areas of vaccination coverage in Brazil, in view of the following points: 1. Recommendations for vaccination only after cases and deaths have been recorded in such areas should be avoided; 2. The risk of urban transmission of the disease needs to be reduced, given the immense dispersion of *Ae. aegypti* and *Ae. albopictus* and the recent episode that occurred in Paraguay; 3. The worldwide scarcity of vaccine that could be used for urgent vaccination of populations in large urban centers if a disease outbreak occurred, either transmitted by *Ae. aegypti*, or resulting from a wild cycle on the periphery of these centers; 4. The difficulty in achieving timely vaccination (ten days before traveling) among tourists and migrants to areas with virus circulation; 5. Occurrences of serious adverse events associated with the vaccine have mainly been registered at the time of implementing vaccination in situations when thousands of people make demands on vaccination units within a short space of time and contraindications are often not respected; 6. The risk of adverse events is often greater among people receiving the vaccine for the first time than among revaccinated individuals, and this is the situation of the vast majority of people living in areas that are not considered endemic. Initially, the vaccine should be included in the child immunization calendar throughout the country and should be applied to people living in and visitors to areas that are characterized as receptive to transmission of the wild cycle of the disease, even if these areas have been silent for many years.

Choosing only to perform blocking vaccination in emergency situations is a strategy advocated by people who are against geographical expansion of vaccination coverage. This strategy is criticized by those who advocate expansion of the coverage, on the grounds that on such occasions, mass vaccination of thousands of individuals would be required over a short space of time, and that this would result in some of the problems already cited, such as: scarcity of vaccine in unplanned situations, which was observed recently in the outbreak of urban yellow fever in Paraguay; and an exponential increase in the number of serious adverse effects associated with the vaccine, because it becomes difficult to identify and respect contraindications for vaccination. The risk of occurrence of such adverse effects is much greater among individuals receiving vaccination for the first time, which is the situation of the vast majority of people in areas that are not considered endemic.

In view of this controversy, there is a growing need to delimit the areas that are receptive towards transmission of the wild cycle of the disease, even if such areas have been silent for many years. This delimitation involves conducting environmental, entomological and animal reservoir studies. Based on evidence of receptiveness, recommendations to vaccinate in such areas would avoid the situations of public health emergency that have been experienced over the past decade, during which vaccination areas were only expanded after observing epizootic disease among monkeys or cases and deaths among humans.

In conclusion, if on the one hand there are strong arguments against the expansion of routine vaccination against yellow fever in areas in which the risk of serious events subsequent to vaccination is greater than the risk of acquiring the disease itself; on the other hand, the recent expansion of the area of wild-type yellow fever transmission and the overlapping of the presence of wild-cycle and urban-cycle vectors would speak in favor of the need to expand the vaccination coverage to

protect individuals living in or traveling to these areas. There is an urgent need for ecological and epidemiological assessments in areas that are considered non-epidemic, so that decisions can be made based on the best evidence possible. There is also a need for studies that might lead to identifying individual factors that predict occurrences of severe and lethal forms of the disease that are associated with vaccine use.

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The author declares that there are no conflicts of interest.