

## Controversies in the expansion of areas with routine yellow fever vaccination in Brazil

Controvérsias sobre a ampliação das áreas com vacinação de rotina contra a febre amarela no Brasil

Controversias sobre la ampliación de las áreas con vacunación rutinaria contra la fiebre amarilla en Brasil

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### Abstract

*Yellow fever is a potentially severe viral disease transmitted by mosquitos of the genera Haemagogus, Aedes, and Sabethes. Vaccination is the most important measure for prevention and control of the disease. This article analyzes the immunization guidelines in Brazil based on epidemiology of the disease in recent decades. Considering the ease of human movement into areas at risk of transmission and the tendency for these areas to expand, in time the entire country will probably need to adopt routine vaccination. However, in the decision on expanding the target population for vaccination, vaccine safety issues have been emphasized. We present a risk-benefit analysis of vaccination and strategies for controlling the disease and preventing its urbanization in regions where the vaccine is still not recommended. We conclude that inclusion of the yellow fever vaccine on the childhood immunization schedule is a proactive, easily operationalized strategy as a response to the increase in the number of cases of sylvatic yellow fever in Brazil, and an attempt at preventing re-urbanization of the disease.*

*Yellow Fever Vaccine; Yellow Fever; Immunization Programs*

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## Introduction

### Yellow fever: the disease

Yellow fever is an acute febrile infectious disease caused by a virus of the Flaviviridae family (genus *Flavivirus*), transmitted by mosquitos of the genera *Haemagogus*, *Aedes*, and *Sabethes*. The disease displays considerable clinical variability, and approximately 10% of infections involve severe manifestations. The predominance of mild or asymptomatic forms hinders detection and probably leads to underreporting<sup>1,2</sup>. In Brazil, average yellow fever case-fatality is around 50% but has reached 100% in certain periods of the historical series, suggesting preferential detection of severe cases<sup>3</sup>.

Due to the clinical severity of yellow fever and the potential for its spread to urban areas with high infestation rates with the mosquito *Aedes aegypti*, yellow fever is one of the most epidemiologically relevant arbovirus infections. There is no specific treatment for the disease, and vaccination is the most important measure for its prevention and control in humans<sup>4,5</sup>. Yellow fever vaccination is required by the International Health Regulations for travelers to or from endemic areas<sup>5</sup>. Even so, in 2016, a predominantly urban yellow fever epidemic with transmission by *Ae. aegypti* occurred in Angola, with 4,306 suspected cases (884 laboratory-confirmed cases with 121 deaths), spreading to the Democratic Republic of the Congo, where there were 2,987 suspected cases (81 confirmed cases, with 16 deaths). Propagation of the disease across several provinces and the exhaustion of the emergency vaccine stockpile available for mass vaccination campaigns facilitated spread of the disease to countries like China, Kenya, and Uganda, posing a risk to global health security<sup>6,7</sup>. Beginning in 2010, the disease expanded from West Africa to central and eastern regions of the continent, where mass vaccination campaigns for prevention had not been held previously. The situation with yellow fever in Angola, with its national and international expansion, highlighted the need for proactive prevention measures in the countries of Central and East Africa. According to a recommendation by the World Health Organization (WHO) Emergency Committee, Brazil requires the International Certificate of Vaccination or Prophylaxis (ICVP), temporary and limited to travelers coming from or in transit to Angola and the Democratic Republic of the Congo<sup>8</sup>. Thus, in addition to vaccination campaigns in countries with reported cases, short-term intensification of control measures in vulnerable regions is necessary to avoid spread of the disease and interrupt viral circulation. However, the limited global vaccine supply in emergency situations like this has been a major obstacle to effective control of the disease<sup>9</sup>.

In the past, yellow fever was one of Brazil's main public health problems, but it was controlled with the elimination of urban transmission in 1942. Still, due to the impossibility of eradicating sylvatic yellow fever (since it is a zoonosis of wild animals), plus the wide dispersion of *Ae. aegypti* in Brazilian cities, the re-urbanization of yellow fever is a constant threat in Brazil<sup>10</sup>.

The aim of this article is to analyze the current guidelines and possibilities for adjustments to the vaccination program in Brazilian territory, considering the trends in the national and international yellow fever epidemiological profile in recent decades. The problem is complex and has sparked legitimate demands by professional associations<sup>11</sup> and lay sectors of society such as political parties<sup>12</sup>, signaling the need for a more-depth approach to key technical aspects. The study thus sought to update the debates organized by the Brazilian Ministry of Health<sup>13</sup> in light of the evolution in the epidemiological situation in the last decade, and particularly in 2017.

### Yellow fever vaccine

The currently available yellow fever vaccines are attenuated live virus vaccines<sup>14,15</sup>, having been produced since 1937 in Brazil, which has the largest of the world's four vaccine manufacturers. Mass use of the vaccine began at a time when there was no requirement of proof of efficacy and safety by national regulatory authorities. Since the serological correlate of protection in human beings is unknown, post-vaccination seropositivity and yellow fever control in the Americas and Africa are considered indicators of vaccination effectiveness. In fact, the number of cases has remained relatively low in areas with high vaccination coverage, and the outbreaks in areas where vaccination was not recommended have been controlled with vaccination campaigns. Seroconversion by vaccination is

95-100% in adults, and the occurrence of cases in vaccinated individuals is considered rare<sup>9,16</sup>, even though the information on vaccination history in adults has limitations.

### **Safety of yellow fever vaccine**

Yellow fever vaccine is generally well-tolerated and is rarely associated with serious adverse events<sup>3,17</sup>. Some 2 to 5% of vaccinated individuals can present headache, myalgia, fever, and other mild and nonspecific symptoms between the 5<sup>th</sup> and 10<sup>th</sup> day after vaccination. Pain, redness, and induration at the injection site are usually mild or moderate and disappear in a few days<sup>4,18,19,20,21</sup>.

Acute viscerotropic disease is a rare complication related to dissemination of the vaccine virus to various organs, with shock, pleural and abdominal effusion, multiple organ failure, and high case-fatality<sup>22</sup>. No significant mutations were detected in the vaccine virus isolated from viscerotropic cases, which appear to be determined by individual patient factors that are still poorly understood<sup>23</sup>. Age over 60 years, history of thymectomy, and autoimmune diseases are some of the factors implicated in the etiology of this adverse event. Acute viscerotropic disease has also occurred after administration of sub-strain 17D vaccines used in other countries<sup>15</sup>. In the United States, in 2007-2013, the rate was 0.3 per 100,000 doses distributed (as informed by manufacturers)<sup>24</sup>.

Yellow fever vaccine presents a minimal degree of neurological virulence, manifested as rare cases of post-vaccination meningoencephalitis, principally in infants in the first months of life. Since the vaccine has been contraindicated in infants less than 6 months of age, the neurological manifestations have become even rarer, generally with favorable evolution and without sequelae. In Brazil, from 2007 to 2012, the overall rate of adverse neurological events after primary yellow fever vaccination (sub-strain 17DD) was 0.20 per 100,000 doses administered, with a higher rate in the 5 to 9 year age bracket and a lower rate in children 1 to 4 years of age (0.83 and 0.09 cases per 100,000 doses administered, respectively)<sup>25</sup>. In the United States, in 2007-2013, the overall rate of these events was 0.8 per 100,000, with a peak in the 60-69-year age bracket (2.5 per 100,000)<sup>24</sup>.

Hypersensitivity reactions can occur in the first 2 hours after vaccination (eruptions, urticaria, and bronchospasm) and are extremely rare. They are attributed to proteins of the egg or other components of the vaccine, like gelatin, kanamycin, and erythromycin. Multiple and severe adverse events involving bacterial contamination can also occur rarely and generally result from technical errors in handling and administering the vaccine (Instituto de Tecnologia em Imunobiológicos, Fundação Oswaldo Cruz. Vacina contra febre amarela. [http://www.anvisa.gov.br/datavisa/fila\\_bula/frmVisualizarBula.asp?pNuTransacao=14091032016&pIdAnexo=3189203](http://www.anvisa.gov.br/datavisa/fila_bula/frmVisualizarBula.asp?pNuTransacao=14091032016&pIdAnexo=3189203), accessed on 15/Mar/2017).

The reported risk estimates show striking differences, perhaps reflecting the data's limitations more than actual variations in the events' frequency. The number of doses administered during the period and the region where the cases occurred is subject to information errors. Case detection is also subject to variations in the sensitivity of surveillance in different contexts. If regular, passive surveillance tends to underestimate, heightened surveillance in campaigns can overestimate the frequency of events. The working definition of serious adverse events faces the challenge of considering the availability of human and laboratory resources to characterize and differentiate events of interest and attribute causality<sup>26</sup>. Thus, estimates in Brazil indicated a risk per 100,000 doses administered of 0.8 for anaphylaxis, 0.25 to 0.8 for neurotropic disease, and 0.25 to 0.4 for viscerotropic disease<sup>27</sup>. But after the vaccination campaigns in São Paulo and Rio Grande do Sul in 2009, the serious adverse event rates were higher: 0.31 and 0.11 per 100,000 doses, respectively. In Rio Grande do Sul the rate of neurological events (aseptic meningitis and Guillain-Barré syndrome) was 1.1 per 100,000 doses<sup>28</sup>. Also in Rio Grande do Sul, two cases were confirmed of meningitis due to vaccine virus acquired through human breast milk<sup>29</sup>.

The reasons for the emergence of acute viscerotropic disease (AVD) only five decades after continuous use of the vaccine are subject to speculation. Cases of AVD in the past may have been diagnosed as yellow fever, since the clinical picture is similar, while association with the vaccine may not have been suspected in endemic regions. The technology for differential diagnosis by isolation and genotyping of the vaccine virus, even in developed countries, only became available and accessible in recent decades. In Brazil, the expansion of vaccination occurred in regions much better equipped for clinical investigation of these cases, with more sensitive surveillance and more resources to investi-

gate the association with the vaccine. Even in the states of Southeast, South, and Central Brazil, where yellow fever vaccination was already being done in selected areas, a major share of cases of AVD were detected after vaccination campaigns, suggesting that structured and more heightened surveillance systems for adverse events may partially explain the peak in AVD beginning in the 2000s.

Even with serious and rare adverse events, the risk-benefit margin of vaccination has been considered highly favorable in endemic areas and in other situations of yellow fever risk<sup>30,31</sup>.

### **WHO guidelines for use of the vaccine**

Yellow fever vaccine is used to protect residents and travelers in endemic and epidemic areas, and to prevent international spread of the disease. In endemic areas, the inclusion of yellow fever vaccination in the basic immunization schedule, preferably between 9 and 12 months of age, is considered more cost-effective than vaccination campaigns. For all these indications, in 2013 the World Health Organization, after a discussion on the duration of immunity to yellow fever, began to recommend a single dose of the vaccine to confer lifelong protection, without a booster dose<sup>27</sup>, although granting that infants and HIV-positive individuals may require a booster. The Advisory Committee for Immunization Practices of the Centers for Disease Control and Prevention (ACIP/CDC) also considers a single dose of yellow fever vaccine sufficient for long-term protection and adequate for the vast majority of travelers. However, it recommends additional doses of the vaccine for laboratory professionals that handle wild virus, travelers to areas with outbreaks, and travelers staying for long periods in endemic areas<sup>16</sup>.

Yellow fever vaccine is contraindicated in infants less than 6 months of age and is only recommended from 6 to 8 months of age during epidemics, when the risk of infection with the yellow fever virus is high. Other contraindications to yellow fever vaccine are severe hypersensitivity to egg components, severe congenital or acquired immunodeficiency, and breastfeeding. Pregnant women and elderly individuals should have the risk-benefit margin of primary vaccination assessed individually<sup>27</sup>.

According to the WHO, ACIP/CDC, and Brazilian National Immunization Program, yellow fever vaccine can be administered simultaneously with other vaccines or four weeks apart from the administration of subsequent vaccines, with the exception of oral polio vaccine, which can be administered at any time in relation to yellow fever vaccine<sup>27,32</sup>. The Brazilian National Immunization Program considered the evidence that immunogenicity in infants, which is already lower than in adults, is affected by the combined administration of live attenuated vaccines for measles, mumps, and rubella<sup>33</sup>, and recommends that these vaccines be administered with a minimum interval of 30 days. The recommendation is waived to accommodate epidemic situations and difficulties in access to vaccination services, and does not apply to booster doses or to adults, in whom the immune response is more intense and presumably less susceptible to interference<sup>34</sup>.

### **Yellow fever vaccination in Brazil**

Priorities for yellow fever control in Brazil include: (i) routine vaccination in primary care for 100% of the population residing in areas where vaccination is recommended, starting at 9 months of age; (ii) timely vaccination (at least 10 days in advance) of travelers to such areas or those with a public health emergency of national concern, with individual evaluation of yellow fever risk at the destination and of the risks of post-vaccination adverse events; (iii) monitor vaccination coverage in all the municipalities; (iv) investigate post-vaccination adverse events; (v) conduct surveillance of suspected yellow fever cases and epizootics, with capture of vectors and primates in the investigation of human cases and epizootics and monitoring of viral circulation in the area<sup>3</sup>. Regular vaccination is complemented by mass immunization campaigns, including infants from six to nine months of age, to contain outbreaks. Special attention is required for the minimum 30-day interval between the yellow fever vaccine and the triple viral vaccine (measles- mumps-rubella) for children under 2 years of age, both in routine vaccination and in immunization campaigns<sup>34</sup>. Entomological surveillance with isolation of the yellow fever virus in vectors has been recommended as a complementary surveillance strategy for human cases and epizootics (passive surveillance), and for monitoring sentinel and vulnerable areas,

with early detection of viral circulation to support planning of prevention and control measures and the occurrence of human cases (enhanced surveillance).

Due to the epidemic and epizootics in Minas Gerais State in 2017, areas with temporary recommendation of vaccination were designated in neighboring municipalities in the States of Espírito Santo, Bahia, and Rio de Janeiro, with priority for rural areas. The strategy aimed to create a blocking immunization ring, anticipating the eventual expansion of virus transmission, and assumed that there was no evidence of yellow fever transmission by the urban vector. Enhanced surveillance was also recommended, including a change in the working definition of suspected case, also considering the seasonal increase in the circulation of travelers and tourists. In the State of Rio de Janeiro, in March 2017, based on the identification of five cases of sylvatic yellow fever (including one death) in a municipality in the Coastal Lowlands (*Baixada Litorânea*), vaccination was expanded to a total of 64 municipalities (data as of March 17, 2017), including the northern, northwestern, mountainous, and lakes regions of the state, with plans to include the capital and metropolitan area by the end of that same month<sup>35</sup>. As of this article's submission, 23 cases of sylvatic yellow fever had been reported, with 8 deaths from the disease<sup>36</sup>.

Yellow fever vaccination in Brazil began in 1937 and began to be applied in vaccination campaigns every 5 years in the endemic area by mobile vaccination teams<sup>10</sup>. In 1999, the vaccine was incorporated into the childhood immunization schedule starting at 6 months of age for residents in the Legal Amazonia and Central region, and starting at 9 months for those residing in the so-called "transition area", in addition to travelers to all these regions<sup>37</sup>.

Beginning in 2001, with the expansion of viral circulation outside the Amazon Region, the vaccination area was also expanded in the Central, South, and Southeast regions of Brazil, where yellow fever vaccine began to be administered to the resident population and unvaccinated visitors<sup>10</sup>. A similar situation occurred again in 2008 and 2009 with the expansion of routine vaccination to 271 municipalities in Rio Grande do Sul State, 44 in São Paulo, 11 in Santa Catarina, and 4 in Paraná, reaching some 8,500,000 inhabitants<sup>3</sup>.

A household survey to evaluate yellow fever vaccine coverage in children 18 to 30 months of age in the year 2006 in 15 cities in the area recommended for vaccination showed that 79% had documented vaccination at 12 months, 86% at 18 months, and 91% at any time prior to the survey<sup>38</sup>. However, the Ministry of Health, considering the number of doses administered and number of live births, estimated vaccination coverage at 65.3% for all the areas recommended for vaccination from 2003 to 2013, considered low for areas at risk of yellow fever transmission. Yellow fever vaccine coverage varied widely between regions of the country, falling to below 60% in various areas with risk of transmission of the disease<sup>39</sup>. The discrepancy in the survey's data in state capitals may indicate imprecision in records on the doses administered and lower coverage outside of large cities. More recent data from the Brazilian Ministry of Health, from 2005 to 2015, show the heterogeneity of vaccination coverage rates between municipalities in areas recommended for vaccination, with low coverages in areas with evidence of viral circulation, which can translate as increased vulnerability in the population<sup>40</sup>. In fact, the 2017 epidemic in Minas Gerais showed low vaccination coverage rates in rural populations with favorable conditions for sylvatic cycle viral circulation.

### **Situation with yellow fever in Brazil: human cases and epizootics**

Since the reemergence of yellow fever virus in the Central, Southeast, and South of Brazil in 2008 and 2009, a public health emergency of national concern was announced and measures were stepped up in the surveillance and monitoring of human cases and epizootics of yellow fever in Brazil. From 2012 to 2013, 125 cases of epizootics were reported in non-human primates, with the highest frequency in the Central, followed by the Southeast and South regions. The most heavily affected non-human primates genera were *Callithrix* (67.4%) and *Alouatta* (16.3%), following by *Pithecia* and *Saguinus* (3.3% each), *Cebus* and *Leontopithecus* (2.2% each), and *Aotus*, *Ateles*, *Sapajus*, *Papio*, and *Callicebus* (1.1% each). Various species of these genera are common in Brazil's urban areas. During this same period, 279 suspected cases of yellow fever in humans were reported, with confirmation of two cases in unvaccinated individuals in Amazonas. The areas with active transmission were limited to portions of Amazonas and Roraima, and close to pockets with vaccination coverage below 60%, where prevention and control

were intensified<sup>39</sup>. Starting in July 2014, there was an increase in reports of confirmed yellow fever epizootics associated partly with the occurrence of human cases<sup>41</sup>.

From July 2014 to December 2016, also considered a period of reemergence of yellow fever virus outside the Amazon Region, 15 human cases of yellow fever were confirmed, presumably infected in Goiás, Pará, Mato Grosso do Sul, São Paulo, and Amazonas. During the same period, 49 yellow fever epizootics in non-human primates were confirmed in São Paulo, Goiás, Distrito Federal, Tocantins, Minas Gerais, and Pará. Most of the events were initially recorded in the Central Region, where the virus reemerged beginning in July 2014 and transmission spread towards the South and Southeast (Minas Gerais)<sup>42</sup>.

An epidemic beginning in December 2016 had reached 1,561 notifications (including 264 suspected deaths) in 188 municipalities in eight states of Brazil by March 2017. With 448 cases (144 deaths) confirmed in four states (77% in Minas Gerais), it is already considered the largest yellow fever epidemic in recent decades. In the month of March, the state of Rio de Janeiro joined the statistics, with the confirmation of five cases (one death) of sylvatic yellow fever in residents of the rural area of a municipality in the Coastal Lowlands (*Baixas Litorâneas*) region. The five patients had no history of having traveled to areas with proven circulation of the virus<sup>43</sup>.

As of March 2017 there was no evidence of transmission by *Ae. aegypti*, and the demographic profile is consistent with outbreaks of sylvatic yellow fever (83.5% in men, 93.3% over 20 years of age), suggesting exposure during outdoor work activities<sup>44</sup>.

From December 2016 to February 2017, 1,228 epizootics in non-human primates were reported to the Brazilian Ministry of Health, of which 386 were confirmed for yellow fever in three states, based on the laboratory criterion or epidemiological link to epizootics in non-human primates or confirmed human cases in affected areas (municipalities with evidence of viral circulation) and expanded areas (municipalities bordering on affected municipalities).

### **Risk of re-urbanization of yellow fever in Brazil**

The historical records on yellow fever in the Americas indicate that it was an essentially urban disease, and that sylvatic transmission was only recognized in the 1930s<sup>45</sup>. In Brazil, the campaigns to control *Ae. aegypti* in the early 20<sup>th</sup> century, and later mass vaccination, allowed the eradication of urban yellow fever. Isolated cases and outbreaks occurred periodically, especially in the rainy season with high vector density, with peaks every 7 to 10 years<sup>13</sup>. The low incidence until 2016 was attributed to vaccination of residents and visitors to transmission areas for the disease. The epidemic in 2017 revealed the weakness of the control program that left a sizable contingent of vulnerable individuals in areas with epizootics.

The reintroduction and spread of *Ae. aegypti* in Brazil in the 1980s in cities in regions without recommendation for routine vaccination (whose population is susceptible to yellow fever) creates considerable potential for re-urbanization of the disease<sup>46</sup>. Estimates of the risk of re-urbanization are limited by uncertainties on relevant factors, such as the probability of a susceptible individual being infected in the sylvatic cycle and of being exposed during the viremic period to a competent urban vector<sup>47</sup>. Considering the high infestation rates with *Ae. aegypti*, the fact that its vectorial capacity has already been proven experimentally<sup>48,49</sup>, population density, and low vaccination coverage rates, even in areas recommended for vaccination in many regions of Brazil, the risk of re-urbanization should not be ignored. Some specialists believe that yellow fever urbanization requires much higher household infestation rates with *Ae. aegypti* (28% in Angola in 2016<sup>50</sup>) than in Brazilian cities (< 8%)<sup>51</sup>, under the effect of programs to fight dengue and more recently Chikungunya and Zika. Apparently there are other determinants, still poorly understood, since urban transmission has not occurred. Biological, environmental, and behavioral factors have fed hypotheses on the absence of yellow fever in countries of Southeast Asia, despite intense infestation with *Ae. aegypti*<sup>47,48</sup>. Meanwhile, the Brazilian epidemic in 2017 reaffirms the threat, given the proximity of cases to urban areas. Heightened surveillance of epizootics also allowed detecting infected monkeys in the urban area of Belo Horizonte (Minas Gerais State)<sup>52</sup>, highlighting the threat in urban national parks in other metropolitan areas.

Given the risk of re-urbanization of yellow fever in Brazil, the expansion of vaccination to the urban population has been considered by health administrators and specialists. Prata<sup>46</sup> contends that

the best strategy for yellow fever control is vaccination of the country's entire population, with the inclusion of yellow fever vaccine in all health units. The issue is still controversial, and the discussion has appeared repeatedly during the outbreaks in the last 20 years. Some experts contend that the discussion of recommendation of the vaccine for the entire country should only be done after the outbreak is over, since it requires intense mobilization of resources for the population at immediate risk of the disease<sup>53</sup>.

### **Strategies for yellow fever control in Brazil**

Strategies for yellow fever control in Brazil are based essentially on vaccination in regions of the country in which the surveillance of human cases and epizootics indicates viral circulation. Complementarily, the existence of populations of susceptible primate species and sylvatic vectors with the potential to sustain viral circulation contribute to the demarcation of areas for vaccination to block outbreaks and to anticipate vaccination in vulnerable populations<sup>3</sup>. In the absence of evidence of transmission by an urban vector, the approach has been targeted to sylvatic transmission, the control of which is essential to avoid re-urbanization.

The occurrence of human cases and epizootics of yellow fever in non-human primates continues to require southward and eastward expansion of the area recommended for vaccination, conducted in the last 15 years. If the outbreaks of sylvatic transmission in regions without recommendation of vaccination show the unpredictability of epizootics, the occurrence of human cases in areas in which the vaccine is recommended shows the difficulties of vaccination programs in reaching susceptible individuals that visit or reside in areas with known or presumed risk. The evaluation of risk of infection poses a considerable challenge due to the limitations of surveillance data on epizootics and the scarcity of human cases in areas where vaccination is already done. Due to the distorted perception of risk, the guidelines may be ignored, which explains the occurrence of cases in ecotourists, migrants, and residents in areas with a consolidated vaccination program. The isolated cases and outbreaks refuel the fear of re-urbanization, since the urban vector has been active in large numbers of municipalities in all of Brazil's major geographic regions.

Given the expansion of the area at risk of yellow fever in Brazil in the last 15 years, the inclusion of yellow fever vaccine in the country's routine immunization has been a recurrent issue. Considering the increased risk of adverse events during vaccination campaigns to block outbreaks<sup>13</sup>, the risk-benefit ratio of expanding the routine vaccination area may represent an advantage over preventive vaccination campaigns. There is also evidence that routine yellow fever vaccination is more effective for reducing cases and deaths, with a greater cost-effectiveness margin compared to the emergency control of outbreaks<sup>27</sup>.

Due to the controversy generated by the risks of serious adverse events, future expansion of yellow fever vaccination to include the entire population will have to begin in states with viral circulation, some of which already vaccinate part of their population. Stepwise implementation considers the availability of vaccine for the huge population in areas currently without recommendation of vaccination. The introduction of yellow fever vaccine in the routine immunization schedule in children less one year of age, as already done in a large number vaccination services in Brazil, could be a strategy. The advantages of this approach include the difficulty in demarcating the area of circulation of the virus, despite its obvious geographic expansion in recent decades; operational ease and the perspective of broad vaccination coverage already achieved with other vaccines using the existing network of services; familiarity of vaccination services with the vaccine would increase the capacity to respond to a public health emergency of national concern with campaigns (there would be less need for extra vaccines); greater predictability of the demand for the vaccine, with better organization of vaccination activities and better planning of vaccine production; relatively low incidence of post-vaccination adverse events considering the total number of doses administered in the country; rarity of severe adverse events in areas where the vaccine is administered routinely; and lower risk of severe adverse events in children less than 4 years of age. According to the arguments against: (1) although the risk is very low for viscerotropic disease and neurotropic disease in infants, it would have more serious implications in areas without evidence of viral circulation; (2) vaccination would begin in an age group with lower risk of the disease; (3) the time to reach adequate vaccination coverage in all the

age groups would be too long; and (4) there would be a need for epidemiological and environmental studies to define the risk for each area in Brazil's territory prior to expansion of the vaccination area<sup>13</sup>. The conservative position has prevailed thus far, to expand the area recommended for vaccination to include regions with risk detected by the appearance of cases. The epidemic in 2017 indicates that this approach needs to be revised, and that it will be.

## Discussion

The rapid and uncontrolled spread of *Ae. aegypti* throughout Brazil, creating favorable conditions for dengue, Chikungunya, and Zika epidemics, has been considered further proof of the threat of re-urbanization of yellow fever, since studies have demonstrated the vector's competence for yellow fever virus transmission<sup>47,48</sup>. Analyses by Massad et al.<sup>54</sup> showed a large contingent of individuals not vaccinated for yellow fever and living in areas infested with *Ae. aegypti* in the State of São Paulo (until the year 2001) and thus with the potential for re-urbanization of yellow fever. This probably failed to occur due to the vaccination coverage rates reached in most of the endemic areas<sup>38</sup>, which kept the incidence of the disease low, and because the epizootics occurred in areas with low population density. However, the areas recommended for vaccination and with evidence of transmission in humans or in non-human primates are now closer to urban areas. The epidemic in 2017 revealed the insufficient coverage rates in the State of Minas Gerais, where 249 cases had been confirmed, nearly all of which in unvaccinated adults. The occurrence of an epidemic in a state where yellow fever vaccination has already been part of the basic immunization schedule for nearly two decades exposes the difficulties in reaching the adult population, especially in rural areas, outside of epidemic periods.

The presence of primate species involved in the sylvatic cycle of yellow fever and inhabiting areas without recommendation for vaccination, or with low vaccination coverage, creates risk of exposure to the wild virus during recreational activities in parks, for example. In fact, heightened surveillance of epizootics detected infected non-human primates in Greater Metropolitan Belo Horizonte and led to the closing of municipal and state parks in Minas Gerais. In the future, it may lead to the indication of regular vaccination in states in the Northeast and Southeast of Brazil that are not currently included on the routine immunization schedule, besides further accelerating expansion of the area with recommendation of yellow fever vaccination.

The occurrence of serious post-vaccination adverse events has inhibited the expansion of vaccination to the entire population, although routine regular vaccination of infants has occurred, and surveillance of adverse events (already consolidated) has not produced observations that question the recommendation. Meanwhile, vaccination campaigns in 2000 and 2008 in South and Southeast Brazil, in response to outbreaks in areas previously considered free of the virus, led to a rush on health services, even in state capitals far from where the outbreaks took place, with serious adverse events occurring at higher rates than observed in routine immunization activities. This may have resulted from heightened surveillance of adverse events during campaigns, with higher sensitivity (and possibly lower specificity) for the identification and notification of such events. In addition, mass vaccination of adults may reach individuals that are more vulnerable to adverse events and that do not present any of the known contraindications to the vaccine (such as autoimmune diseases and breastfeeding, which did not involve restrictions on vaccination). The mobilization for campaigns could also force immunization services to the limit of their capacities, especially in areas where the yellow fever vaccine is not on the basic immunization schedule, thereby increasing the likelihood of operational failures.

Currently, the recommendation to vaccinate residents of non-endemic areas that travel to endemic areas, and the ease of individuals' movement between regions for work or leisure, already involves vaccinating a large number of individuals. The area with recommendation of the vaccine cannot shrink, that is, it does not appear possible to remove the recommendation of vaccinating (except perhaps in areas with temporary recommendation). On the contrary, the area has grown steadily, tending to extend vaccination to the entire Brazilian population. This expansion has been reactive, responding to outbreaks, with the onus of fatal cases of the disease, an overload on immunization services that are unfamiliar with the yellow fever vaccine, and shortages of the vaccine. The current situation of



internal and external expansion of the disease in Africa is an example of how controlling the disease depends on the availability of the yellow fever vaccine, especially when emergency strategies are prioritized, like vaccination campaigns responding to already established outbreaks.

## Conclusion

Having characterized the need and timeliness of introduction of yellow fever vaccination in routine immunization in regions where it is currently only done for travelers, it is necessary to deal with the risks in relation to the presumed benefits. Considering the safety of vaccinating infants, done for decades in large areas of Brazil, introduction of the vaccination in the basic childhood immunization schedule in other areas of the country can be the initial stage in a proactive strategy with better acceptance by the public and a lower additional burden for immunization services in the public health system, as compared to vaccination campaigns. After consolidating this stage and evaluating its impact, the vaccine would then be offered to other groups when they appear for other vaccines, like the TD (tetanus-diphtheria) booster, for example. Meanwhile, the occurrence of serious post-vaccination adverse events, even without proof of causality and rarer than in campaigns, would have a much greater impact in regions without reports of the disease. The size of the epidemic in 2017 may reduce the resistance and hesitation of many specialists in relation to universal yellow fever vaccination and facilitate adherence by the population to an injectable vaccine in an immunization schedule that is already quite full. The epidemics and epizootics in recent decades indicate the need for revision of the risk-benefit ratio of “preemptive” vaccination. In a sense, areas with temporary recommendation that are anticipating the occurrence of epizootics and cases in humans are already a step ahead in relation to the prevailing guidelines, which provide for gradual expansion in response to outbreaks and epizootics.

The epidemic that was under way during the preparation of this article produced new data for the analysis of mid- and long-term strategies to avoid future epidemics in areas currently without recommendation of vaccination, and worse yet, involving the urban vector.

## Contributors

T. G. Noronha and L. A. B. Camacho participated in the article's conception, design, and elaboration.

## Conflict of interests

T. G. Noronha works in Institute of Technology in Immunobiology (Bio-Manguinhos), the technical unit of Oswaldo Cruz Foundation (Fiocruz) that produces yellow fever vaccine.

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## Resumo

*Febre amarela é uma doença viral potencialmente grave, transmitida por mosquitos Haemagogus, Aedes e Sabethes. A vacinação é a medida mais importante para a sua prevenção e controle. Neste artigo, analisamos as recomendações de vacinação no Brasil, segundo a epidemiologia da doença nas últimas décadas. Considerando a facilidade de deslocamentos de suscetíveis para áreas de risco, e sua tendência de expansão, é provável que eventualmente todo o país tenha de adotar a vacinação rotineira. Porém, no processo decisório de ampliação da população candidata à vacinação, questões relacionadas à segurança vacinal têm sido destacadas. Apresentamos uma análise dos riscos e benefícios da vacinação e das estratégias para o controle da doença e prevenção da sua urbanização nas regiões onde a vacina ainda não é recomendada. Concluímos que a introdução da vacina contra a febre amarela no calendário de vacinação das crianças é uma estratégia proativa, de mais fácil operacionalização, como resposta ao aumento do número de casos de febre amarela silvestre no Brasil e tentativa de prevenção da reurbanização da doença.*

*Vacina Contra Febre Amarela; Febre Amarela; Programas de Imunização*

## Resumen

*La fiebre amarilla es una enfermedad viral, potencialmente grave, transmitida por mosquitos Haemagogus, Aedes y Sabethes. La vacunación es la medida más importante para su prevención y control. En este artículo, analizamos las recomendaciones de vacunación en Brasil, según la epidemiología de la enfermedad en las últimas décadas. Considerando la facilidad de los desplazamientos de personas susceptibles hacia zonas de riesgo, y la tendencia de expansión de esta enfermedad, es probable que eventualmente todo el país tenga de adoptar la vacunación rutinaria. No obstante, en el proceso de decisión para la ampliación de la población candidata a la vacunación, se han destacado cuestiones relacionadas con la seguridad de la vacunación. Presentamos un análisis de los riesgos y beneficios de la vacunación y de las estrategias para el control de la enfermedad y prevención de su urbanización en las regiones donde la vacuna todavía no está recomendada. Concluimos que la introducción de la vacuna contra la fiebre amarilla en el calendario de vacunación de los niños es una estrategia proactiva, de más fácil operacionalización, como respuesta al aumento del número de casos de fiebre amarilla silvestre en Brasil, así como una tentativa de prevención frente a la reurbanización de la enfermedad.*

*Vacuna Contra la Fiebre Amarilla; Fiebre Amarilla; Programas de Inmunización*

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