



# Mid-term evaluation of the Global Strategy to Eliminate Yellow Fever Epidemics (EYE)

2017–2026

How Brazil responded to an outbreak that  
changed the face of yellow fever: a case study



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## **ABBREVIATIONS AND ACRONYMS**

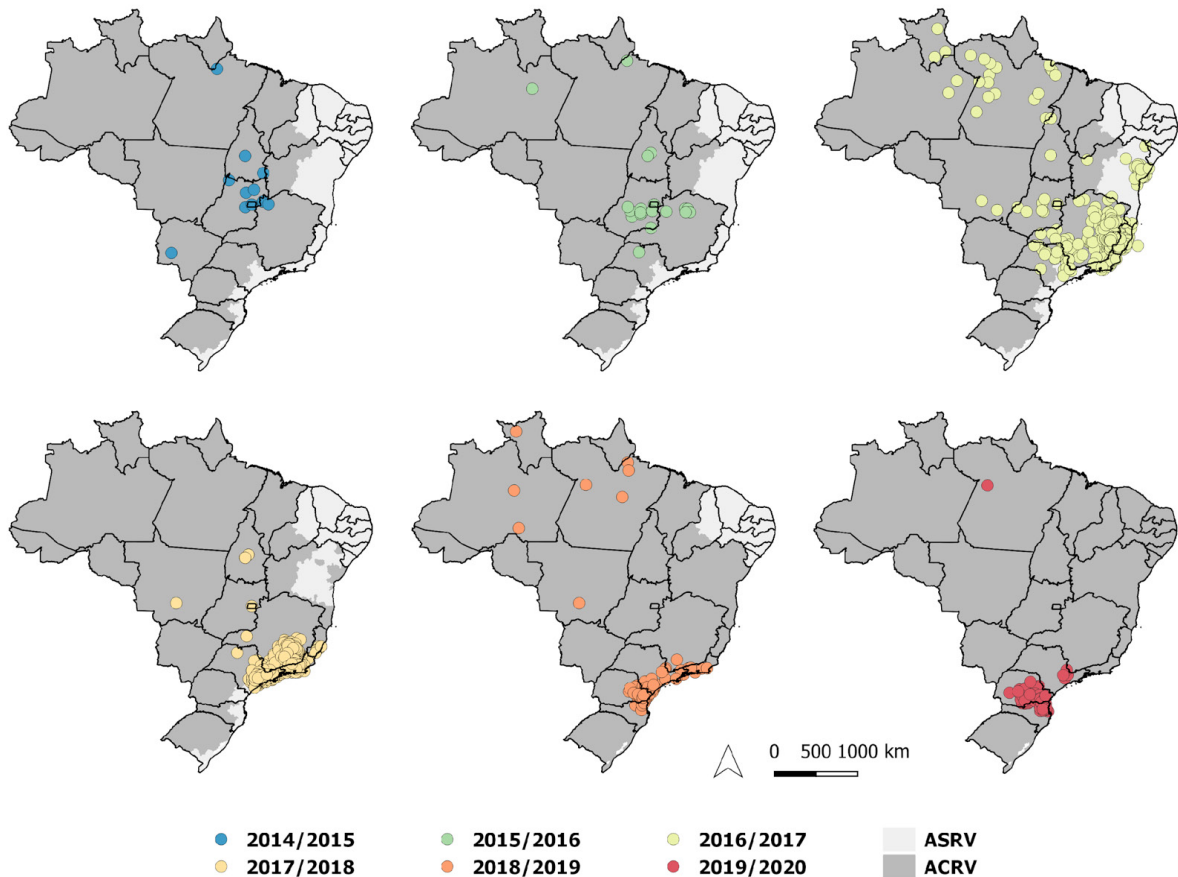
CDC	Centers for Disease Control and Prevention
EYE	The global strategy to Eliminate Yellow fever Epidemics 2017–2016
GRUMFA	Yellow fever modelling study group
ICU	Intensive care unit
MCV1	Measles containing vaccine first dose
MoH	Ministry of health
NHP	Non-human primates
PAHO	Pan American Health Organization/WHO Regional Office for the Americas
SES	Secretaria de Estado de Saúde (State Secretary of Health)
SISS-GEO	Sistema de Informação em Saúde Silvestre (sylvatic health information system)
SUS	Sistema Único de Saúde (Unified Health System)
UNICEF	United Nations Children’s Fund
WHO	World Health Organization
WUENIC	WHO and UNICEF estimates of national immunization coverage

## 1. INTRODUCTION AND CONTEXT FOR THE STUDY

### 1.1 Yellow fever epidemiology in Brazil

The urban transmission of yellow fever was interrupted in the 1940s due in part to far-reaching vector control efforts and initial mass vaccination campaigns that had begun in 1937(1).<sup>1</sup> However, yellow fever remains endemic in northern Brazil, namely in the Amazon region, where transmission is characterized as enzootic with human infection in sylvatic cycles. Yellow fever outbreaks occur seasonally with most cases reported from December to May. However, the pattern of yellow fever outbreaks has changed over the last two decades where sporadic and non-cyclical outbreaks in non-endemic regions have occurred. Several of the affected areas had traditionally not included yellow fever in their routine immunization protocols until after the observed outbreaks (Fig. 1).

Fig. 1. Timeline of detection and distribution of yellow fever cases in Brazil by municipality (human and/or epizootics)



ASRV: areas without recommended vaccination; ACRV: areas with recommended vaccination.

Source: (1)

Yellow fever virus circulation was detected outside the Amazon endemic region in 2014 in Tocantins state. After that, epizootic cases occurred in the states of Goiás, Mato Grosso do Sul and Minas Gerais. However, it was not until December 2016 that the alarm bells were finally sounded when the circulation reached Minas Gerais and the first human case was

<sup>1</sup> The last urban yellow fever epidemic in Brazil was in 1929 in Rio de Janeiro and the ultimate yellow fever urban case was in 1942 in Acre state.

detected. This human case was preceded by epizootic transmission among non-human primates (NHP) in the state. The 2016–2017 wave<sup>2</sup> spread through the Southeastern Region of Brazil including in densely populated areas resulting in an increased incidence in the neighbouring states of Espírito Santo (258 human cases and 84 deaths from 2016 to 2018) and São Paulo with cases detected in Mairiporã which is located north of the São Paulo metropolitan area (2).

From 2016 to 2019 Brazil was dealing with the most serious period of that crisis, responding to two yellow fever waves (not different outbreaks but the virus arriving in areas that had been free of yellow fever until that time) while trying to expand yellow fever programming. The continuous advance of yellow fever virus circulation sparked fears about the re-urbanization of the disease, once it reached the most populous region in the southeast of the country. The yellow fever strain, generating the first outbreak in Minas Gerais in 2016 and 2017 was the same yellow fever strain generating outbreaks in Paraná in 2018 and 2019 and reaching Rio Grande do Sul in 2021. Viral sequencing was able to determine that it was the same virus circulating in all three states. In other words, the yellow fever virus "escaped" from Amazon around 2014 and spread from Tocantins to Rio Grande do Sul up until 2021.

From 2014 to June 2020, 18 states across Brazil reported a total of 2283 human cases and 779 deaths in addition to 1810 epizootics in NHP (laboratory confirmation) (3). Those who acquired the yellow fever virus were mainly men aged 14 to 35 who engaged in work and activities in rural and sylvatic areas. They were largely unvaccinated and resided outside the recommended vaccination coverage areas. The most affected states were São Paulo state where 655 human cases and 230 deaths were reported from 2015 to 2019 and Minas Gerais with 997 human cases and 333 deaths reported from 2016 to 2018.

## **1.2 Purpose of the case study**

The mid-term evaluation of the global strategy to Eliminate Yellow fever Epidemics (EYE) 2017–2026 (4) included two country case studies (in Brazil and Ghana) with the overall purpose of providing lessons learned and documenting best practices on the implementation of various key EYE actions in different contexts.

The main objectives of the country case studies under the mid-term evaluation were to:

- document learning and best practices in the implementation of various activities in line with the components of the EYE strategy/yellow fever response;
- identify critical factors and key enablers for successful implementation of specific components of the EYE strategy;
- identify potential for scale up and replication.

The final learning themes for the two countries were agreed upon through a collaborative process involving key country-level stakeholders.

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<sup>2</sup> Note that yellow fever surveillance in Brazil is based on the concept of "monitoring period" which runs from July to June of the following year hence the periods referenced throughout this document are 2015–2017, 2017–2018 and 2018–2019.



This case study in Brazil particularly focuses on generating greater experience and best practices relating to the third strategic objective of the EYE strategy which aims to contain outbreaks rapidly. The emergence and focus of public health responses in Brazil, however, began much earlier (in the 1930s and 1940s) with efforts towards the eradication of the *Aedes aegypti* mosquitos, vectors of urban yellow fever virus, and has continued to evolve over the past eight decades. Countless efforts have been made to both understand the virus and its transmission patterns, respond to outbreaks, and integrate yellow fever vaccination into routine immunization. The most recent evolution of preparedness and outbreak yellow fever response is best understood from the response to the massive 2016–2017 yellow fever outbreak (or rather virus circulation) period and the evolution of the municipality, state and federal response. This response is marked with positive results and lessons learned implemented in the subsequent spread of the virus in similar geographical areas and ultimately the strengthening of yellow fever prevention and response.

This case study thus concentrates on critical elements of an overall learning story for Brazil in response to outbreaks in Minas Gerais, São Paulo and Rio de Janeiro in 2016–2017. These critical elements were identified, designed and implemented by key community, municipality, state and federal stakeholders with invaluable support from the Pan American Health Organization (PAHO), the Regional Office for the Americas of the World Health Organization, among other EYE partners.

The following critical elements and best practices are covered in this report:

- political will, coordination and management
- yellow fever surveillance (in São Paulo)
- outbreak response in Minas Gerais
- clinical response and management
- research informing practice
- adapting vaccination strategies and monitoring adverse effects
- vaccine supply ensured by local production
- risk analysis and data modelling.

## **2. METHODS AND APPROACH**

### **2.1 Data collection and analysis**

The case study used a mixed-methods approach combining qualitative and quantitative methods for data collection and analysis. An initial document and data review was supplemented by primary data collection, mainly through learning and dissemination sessions organized by PAHO, the Ministry of Health (MoH) in Brasilia, the state secretariats of health in Minas Gerais and São Paulo and Fiocruz/Biomanguinhos in Rio de Janeiro. These sessions took place from 26–30 September 2022 and included stakeholders from the national and state levels involved in yellow fever prevention and response. Representatives from the MoH (federal level) attended all learning and dissemination sessions in the three

states and actively participated in question-and-answer sessions that followed each session. A five-member team from PAHO also attended all sessions and were essential in sparking debate and enriching technical discussions. Overall, these sessions served as opportunities to highlight best practices, but also discuss the challenges and way forward for yellow fever response in Brazil.

The learning and dissemination session covered a broad range of topics focusing on yellow fever control strategies including:

- laboratories and surveillance – zoonotic, epidemiological, entomological;
- immunization – adverse effects, efficacy of fractional dosing, immunization protection;
- outbreak response – coordination, situation rooms, political will;
- clinical management – in times of crises and beyond;
- research – modelling; predictive studies; virus spread corridors; and
- vaccine production.

Altogether, 25 presentations were made across three states and at the federal level by individuals from the MoH, state secretariats of health departments (laboratory, immunization, veterinary services, surveillance, communication, vaccines, etc.) research institutes, universities, hospitals, the private sector, etc. Some PowerPoint® presentations are cited as source material throughout this report and in the reading list in Annex 1. Additional information on presenters and presentations can be made available on request to the WHO Evaluation Office.

Notes taken during the learning and dissemination sessions, coupled with data from the document and data review, were analysed and organized according to theme and content, and interpreted to inform findings. The best practices and learnings are presented in this report with emphasis on key enablers, critical factors, specific results and their potential for replication, scale-up and sustainability.

## **2.2 Limitations**

The country case study was restricted by time and scope and lent itself to learning and dissemination sessions (group discussions) rather than one-on-one interviews. The breadth and depth of information and exposure to critical actors in the yellow fever response ranged from entomologists, zoologists, laboratory technicians, clinical specialists to researchers and managers. They provided detailed insights into the vast and varied efforts undertaken to plan for and respond to yellow fever at municipality, state and federal levels.

## **3. FINDINGS**

The sections below set out the findings from the case study and identify areas that demonstrated good practices in the prevention and response to yellow fever from 2016 to the present.

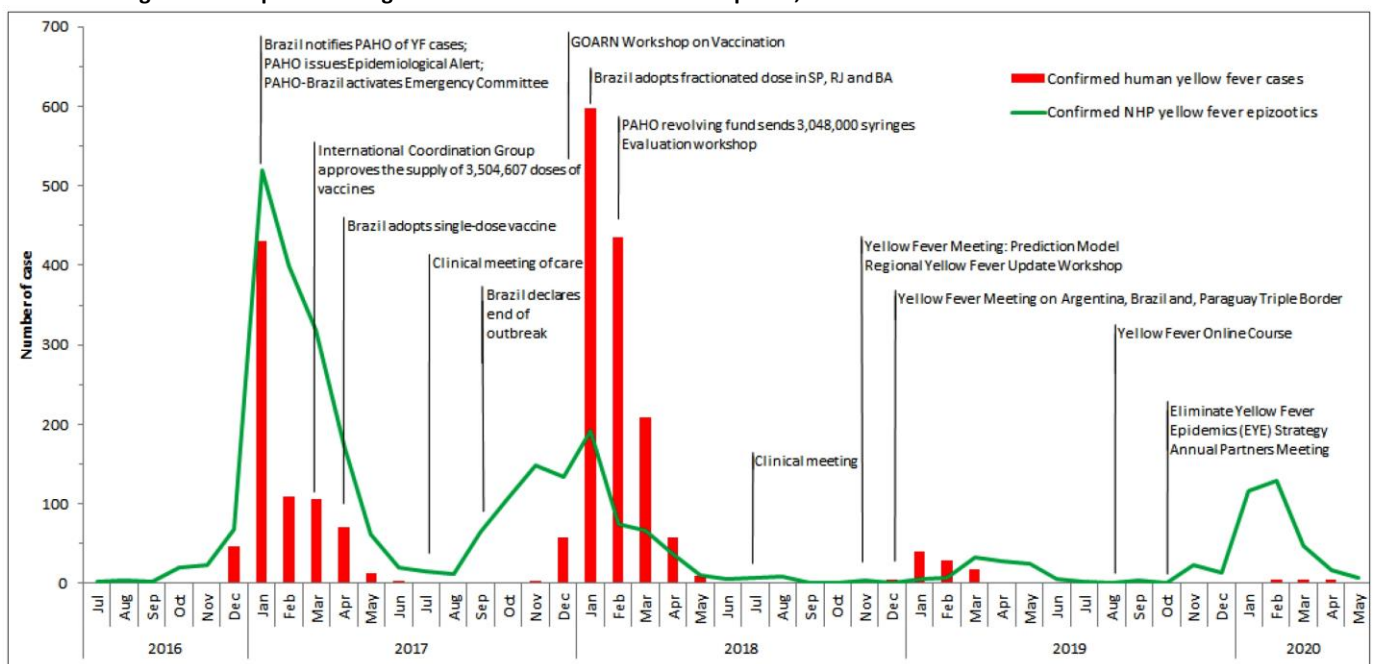
### **3.1 Overarching context**

In 2016, the largest outbreak of yellow fever in the 21st century in the Americas reached Minas Gerais. The virus circulated in the southeastern states, particularly in sylvatic environments near densely populated areas with emerging peri-urban and urban presence

and continued there until 2019, including in other areas where vaccination had not previously been recommended.

The pace of the yellow fever response was unprecedented and created long-lasting changes to the yellow fever response processes. Some of the changes were also based on several years’ experience of yellow fever surveillance and tackling previous waves of yellow fever in 2001, 2003, 2008 and 2009. Overall, these changes were critical in addressing shortcomings in entomological and epizootic surveillance systems and low vaccination coverage, which had contributed to the large outbreak. They were also critical in addressing the lack of clinical-care knowledge and management practices. Some of the critical points during the response from 2016 to 2020 are presented in Fig. 2 below while best practices are outlined in the subsequent sub-sections.

**Fig. 2. Critical points during the evolution of outbreak and response, 2016–2020**



Source: Summary of yellow fever cooperation. PowerPoint® presentation, Pan American Health Organization, n.d.

## 3.2 Best practices

### 3.2.1 Political will, coordination and management

Political will, management, coordination and an integrated approach were at the centre of the response to the yellow fever virus spread from 2016 to 2019. As one presenter said, “without integration you do not have a response”. The coordinated and integrated response was evident from the community level to the municipalities, regions and state levels where it was communicated that the response had the “full mobilization and cooperation of the State” in reference to São Paulo with the same sentiment in Minas Gerais. Governors were involved in decision-making and announced, as in the case of Minas Gerais, a public health emergency (which during the 2016–2017 outbreak was not declared by the MoH at the Federal level), thereby raising awareness of the urgency to respond to the outbreak including the critical importance of immunization. Other key players in the coordination in Minas Gerais included Secretaria de Estado de Saúde (SES) together with state secretariats for the environment, agriculture, civil defence military police, etc.

Representatives from all these secretariats attended regional seminars on the response focusing on the yellow fever situation.

**Fig. 3. Closure of São Paulo City park to combat the spread of yellow fever, September 2022**



In São Paulo, without the buy-in and support from the State Government, SES, the police, military, etc., the crucial move to close one of the biggest parks in São Paulo City (Fig. 3), for the first time in the history of the State, would not have been possible. This measure heightened public awareness of the seriousness of the outbreak and resulted in an immediate flood of citizens to vaccination centres and vaccination campaign sites.

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Platforms were also used to ensure coordination within and across states. A WhatsApp group was established early in 2017 to help coordinate the response to the epidemic in Minas Gerais. The original group members numbered around 15 people and included various key people from SES departments, coordinators from intensive care units, PAHO, etc. There were daily discussions aimed at highlighting the key activities, responses, successes, challenges, patient statistics, surveillance results, and situations in the various municipalities and regions. The group was key in ensuring a coordinated and up-to-date response in addition to providing each other with the moral support needed to keep up the momentum. It served as a platform for exchanging experience and best practices, for discussing strategies and as a resource for other states. Through the group, members were able to alert neighbouring states of the imminent arrival of the virus and communicate the lessons learned from Minas Gerais.

The state government in Minas Gerais has demonstrated significant political will to continue combating yellow fever in the years to come. Government resolutions from 2019 to 2021 demonstrated the commitment, political will and funding in advancing the fight against arboviruses (Dengue, Zika, Chikungunya and yellow fever).

This commitment included financing incentives, which complement existing efforts of surveillance, control and technical assistance for the control of arboviruses transmitted by *Aedes aegypti* in urban settings in the sum of BRL 158 million (Brazilian reais) in 2019.<sup>6</sup> This was followed by the establishment of the State Committee for Combating Arboviruses and the Regional Committees for Combatting Arboviruses in 2020. A state contingency plan was approved in 2021 and guidance provided to municipalities along with BRL 40 million as a financial incentive to municipalities to help fight arboviruses (5–8).

Political will and coordination continue to promote yellow fever programming and speak to the undisputable need to guarantee an integrated response. This integrated response includes ensuring essential elements are in place, most notably, proper surveillance and

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<sup>6</sup> BRL = 0.25764 US\$ (best rate, 1 January 2019).

laboratory capacity for mosquitoes, primates, humans as well as immunization schemes and constant communication.

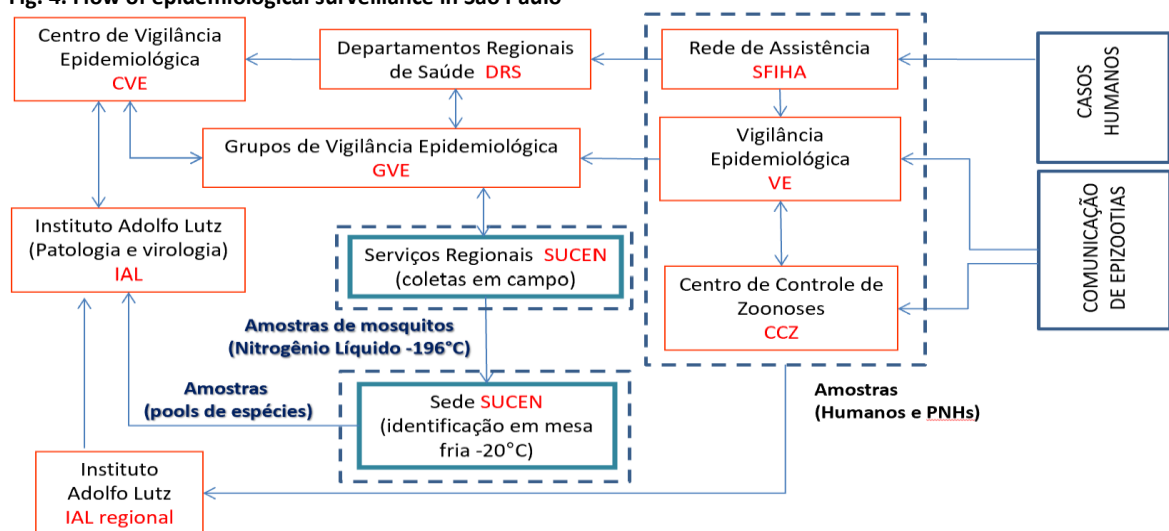
### 3.2.2 Surveillance in São Paulo

Surveillance (genomic) of human and epizootic (NHP) populations at risk of yellow fever is essential in ensuring both the rapid detection of yellow fever virus circulation and the containment of transmission to prevent humans being infected. An outbreak among NHP is a sentinel event for yellow fever virus circulation and should trigger a warning of a potential threat to humans and, ultimately, the development of methods to prevent yellow fever virus transmission. Unlike other arboviruses, yellow fever virus is dependent on epizootics to cause cases in humans. Therefore, entomological surveillance is critical to a coordinated surveillance response.

The yellow fever surveillance system was revived in 1998 with the development of an epidemiological surveillance manual that served as an official tool in the fight against yellow fever. Suspected cases were clearly defined increasing the sensitivity of surveillance and, ideally, the increase in the early detection of cases. This recognition of the importance of surveillance and reorganization was carried out simultaneously with the training of professionals from the state secretaries of health, rolled out to municipalities which resulted in the formulation of local epidemiological surveillance teams. These developments also included the decentralization of laboratory diagnostics to the public health centre laboratories in all 27 states resulting in faster detection and confirmation of yellow fever cases. One of the greatest developments was considered to be in the surveillance of epizootics in NHP which started in 1999 and resulted in the first globally distributed NPH manual produced in 2005 (9).

During the outbreaks and in the years following the outbreaks, São Paulo has developed some of the most sophisticated surveillance systems in Brazil. See below the various entities involved in human, epizootic, and entomological surveillance of yellow fever in the state. Fig. 4 illustrates the flow from the first communication of zoonotic cases (NHP) and human cases and their connectedness throughout the cycle which culminates in overreaching the epidemiological surveillance centre.

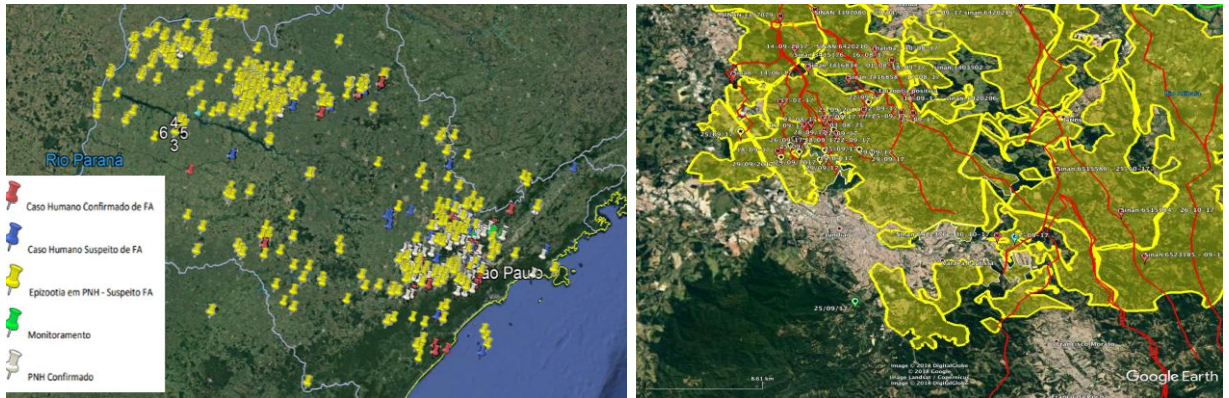
**Fig. 4. Flow of epidemiological surveillance in São Paulo**



Source: Vigilância Entomológica Febre Amarela [Yellow fever entomological surveillance], PowerPoint® presentation, São Paulo State Government, 2022 (in Portuguese).

Because of advances in and coordination of surveillance efforts in the state supported at the federal level, São Paulo is able to overlay suspected and confirmed cases of yellow fever in real time as can be seen in the map below (Fig. 5).

**Fig. 5. Surveillance of yellow fever in São Paulo, in real time, 2016–2019**



Notes: left-hand image shows red as confirmed human cases; blue as suspected human cases; yellow as suspected NHP cases, white as confirmed NHP cases.

Right-hand image shows the corridors of transmission (red lines) with the dates of identification of confirmed cases in NHP (M) and humans (yellow star).

Source: Vigilância Entomológica Febre Amarela [Yellow fever entomological surveillance], PowerPoint® presentation, São Paulo State Government, 2022 (in Portuguese).

### **NHP surveillance efforts**

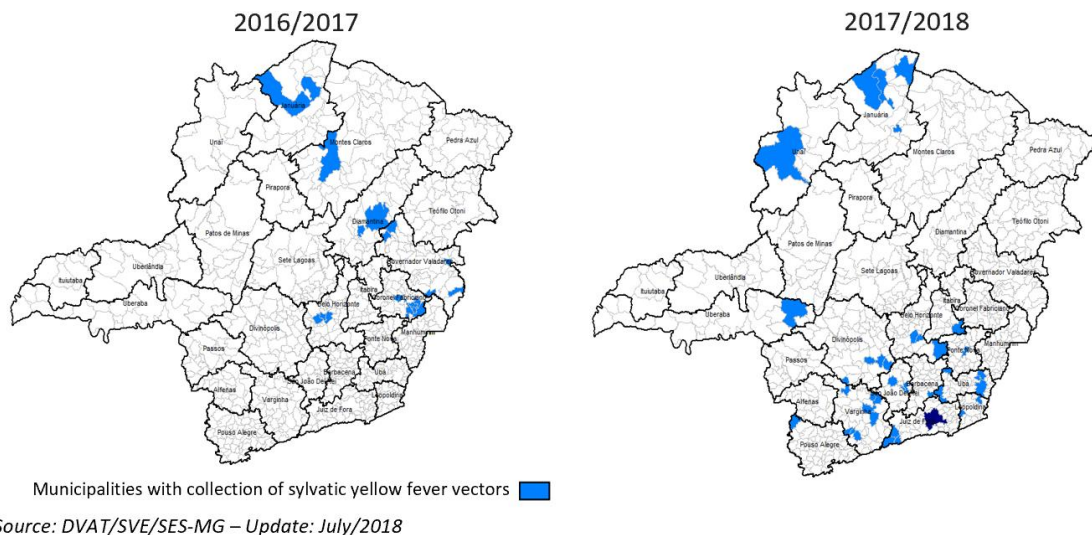
Studies of NHPs are at the forefront of surveillance work in the State of São Paulo where best practices in combining epizootic and epidemiological surveillance in the fight against yellow fever during the 2016–2019 outbreak period are notable. Rapid genomic surveillance together with epidemiological and spatial data helped guide vaccination responses during the outbreak. Various articles have been produced showing viral dissemination to new areas and genomic and epidemiological monitoring of yellow fever virus transmission potential, along with susceptibility in NHP compared to humans and the implications for surveillance. These studies were produced predominantly by on-the-ground health-care professionals and researchers from Brazilian institutions and were used to guide the response.

### **Entomological surveillance efforts**

Entomological research from 2016–2019 in São Paulo alone was carried out in 207 municipalities including 889 localities with over 1200 days of mosquito collection. Areas of monitoring activities were concentrated along the corridors of transmission in line with what zoological and epidemiological surveillance was demonstrating. Two different protocols guided collection of the mosquitoes in urban and non-urban areas.

In Minas Gerais, the number of municipalities undergoing entomological studies, and the collection of vectors for sylvatic yellow fever, increased between 2016 and 2018 (Fig. 6). This was in order to better understand the virus patterns and movement. It is important to note that all the entomological findings supported the non-existence of urban transmission, in spite of the large-scale yellow fever spread, reaching the vicinities of large urban areas such as São Paulo and Belo Horizonte.

**Fig. 6. Municipalities collecting sylvatic yellow fever vector samples, Minas Gerais**

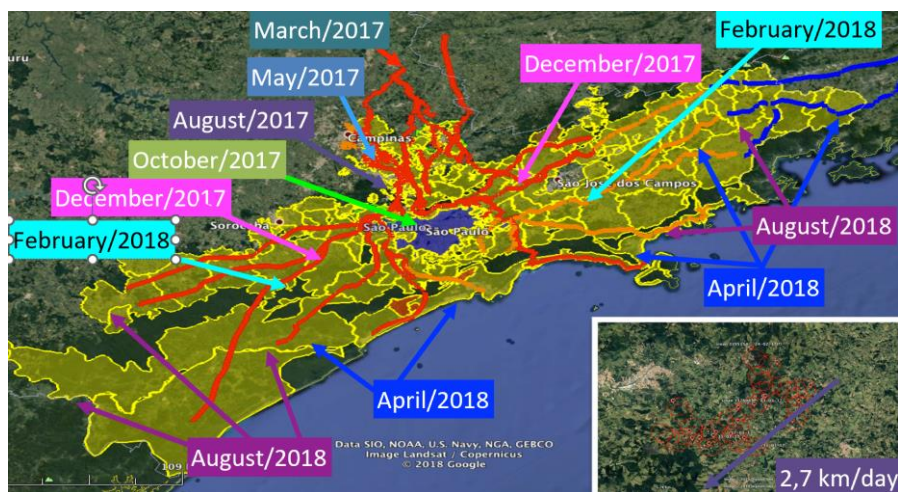


### Ecological corridors of transmission strategy

Consolidating information from zoological, epidemiological and entomological surveillance efforts, and working together in a coordinated manner with various departments within the State Secretariat of Health, São Paulo was able to map out corridors of transmission in order to identify priority areas and timing for vaccination (Fig. 7). This was essential given the speed at which the virus was travelling, determined to be 2.7 km/day based on real-time surveillance efforts, and the vast numbers of individuals who required vaccination (in large part due to non-vaccination geographical classification) coupled with forecasting and an adequate supply of vaccine which warranted a phased approach.

The conditions that decisively influenced the success of the ecological corridors of transmission strategy were: (a) the development of the strategy by the SES researchers, as no previous strategy existed; (b) the large number of NHP samples collected, allowing for the model to be "fed" with sufficient amounts of data; (c) the rapid flow of samples from the field to the laboratory; and (d) the rapid processing and dissemination of results, permitting the model to be updated with positive NHP entries in a short period of time between collection and final sample report.

**Fig. 7. Vaccination priority areas and timing overlaid on the corridors of transmission (red lines)**



Source: Pinter A. Febre Amarela Estratégia de corredores ecológicos [Yellow fever ecological corridor strategy], PowerPoint® presentation, n.d.

**SISS-GEO:** Advancing surveillance has been further supported countrywide by the Sistema de Informação em Saúde Silvestre (SISS-GEO), developed by Fiocruz, which is a technology to monitor animal populations and generate alerts about events that may have public health-related implications. Through this user-friendly platform, citizens can report animals they suspect are unwell or deceased in real time which triggers a public health investigation response. Health officials investigate the event and, where possible, collect samples to determine cause of death and its potential association with yellow fever. Every case is evaluated, and the results entered into the platform's database thereby providing feedback to the individual who registered the case.

SISS-GEO was officially adopted in 2019 and launched in the southeastern and southern states during the yellow fever virus spread. The App was shown to have:

...systematically aggregated the records of geographical coordinates, provided the opportunity to notify (in real time, for all spheres of management) and greatly increased the proportion of events with identification of the NHP involved, with validation by collaborating experts from the photographs that accompany the records in the system (10).

Currently, over 200 municipalities, states, partners and other stakeholders are using the platform. The data gathered through SISS-GEO is used in epidemiological surveillance including in risk-modelling exercises (see Section 3.2.8). SISS-GEO has demonstrated how scientific solutions can be brought to the public and used for epidemiological surveillance, including in times of crisis, at a nominal cost.

### **3.2.3 Outbreak response in Minas Gerais**

Responding to the yellow fever outbreaks in Minas Gerais was a government priority and involved coordination at the highest levels ranging from the Governor's Office and the State Secretary of Health (SES), to ministries of the environment, planning, agriculture, civil defence, military police and civil police<sup>10</sup> (see also Section 3.2.1 above). In addition, the MoH (Federal level) deployed technical teams to assist the state (including field epidemiology training programme teams), regional and municipal secretariats of health with surveillance and outbreak investigation, vector control, and coordination of vaccination campaigns and health-care services.

Speed was of the essence in the outbreak response and Minas Gerais rose to the challenge of the suspected NHP cases (2 January 2017) and notification of epizootics on 4 January 2017, by deploying a technical team to the area of circulation within two days. This was followed by the SES engaging in a video conference with the Governor of the Municipality and the confirmation of the first human cases on 9 January 2017 (see timelines below for 2017 and 2018, Fig. 8 and Fig. 9). By 13 January 2017, a Regional Decree of Public Health Emergency was declared<sup>11</sup> covering 152 municipalities (not reflected in the timeline below). Although speed was of the essence, the ability of the state to analyse NHP samples was extremely limited, at times taking up to 8 months to obtain the results, which constrained the time taken to predict the threat to human populations.

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<sup>10</sup> Avaliação de Meio Período da Estratégia de Eliminação de Epidemias de Febre Amarela (EYE) 2017–2026 [Mid-term evaluation of the yellow fever epidemic elimination strategy (EYE) 2017–2026]. PowerPoint® presentation. Directorate for Surveillance of Communicable Diseases, 2022 (in Portuguese).

<sup>11</sup> DE no. 20/2017 of 13 January 2017.



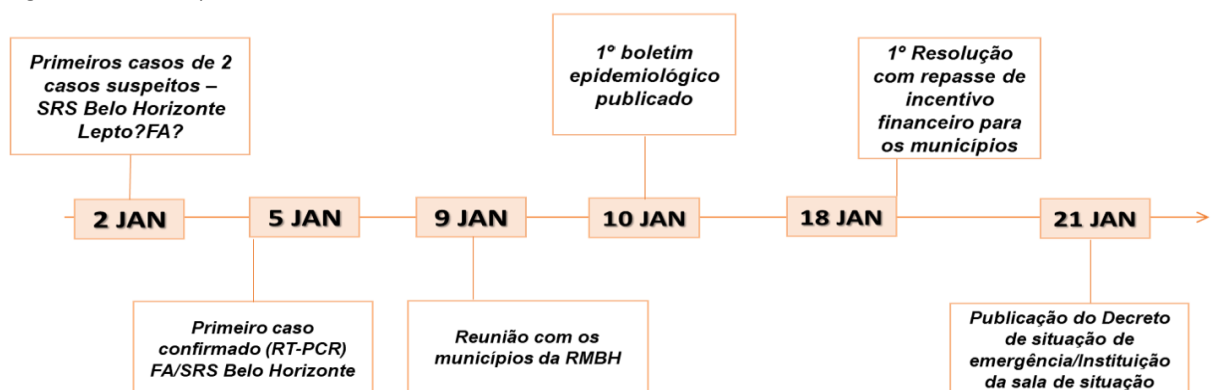
Fig. 8. NHP outbreak response timeline 2017, Minas Gerais



Source: Avaliação de Meio Período da Estratégia de Eliminação de Epidemias de Febre Amarela (EYE) 2017–2026 [Mid-term evaluation of the yellow fever epidemic elimination strategy (EYE) 2017–2026], PowerPoint® presentation, Directorate for Surveillance of Communicable Diseases, 2022 (in Portuguese).

The speed of the response of the subsequent yellow fever outbreak in 2018 was maintained with the publication of the first yellow fever bulletin taking place 8 days after the first two cases were confirmed. Eleven days later, a public health emergency was declared (see timeline below). This was announced in a State Decree on January 19, 2018, and covered 94 municipalities.<sup>12</sup> In addition, with training supported by PAHO, the Centers for Disease Control and Prevention (CDC) and others, the NHP surveillance, including laboratory capacity, improved substantially and, as of 2021, genome sequencing can confirm yellow fever in 10 days (11). Overall sustained actions to contain the yellow fever spread in the period from 2016 to 2019 lasted 5 months in 2017 and 4 months in 2018.

Fig. 9. Outbreak response timeline 2018, Minas Gerais



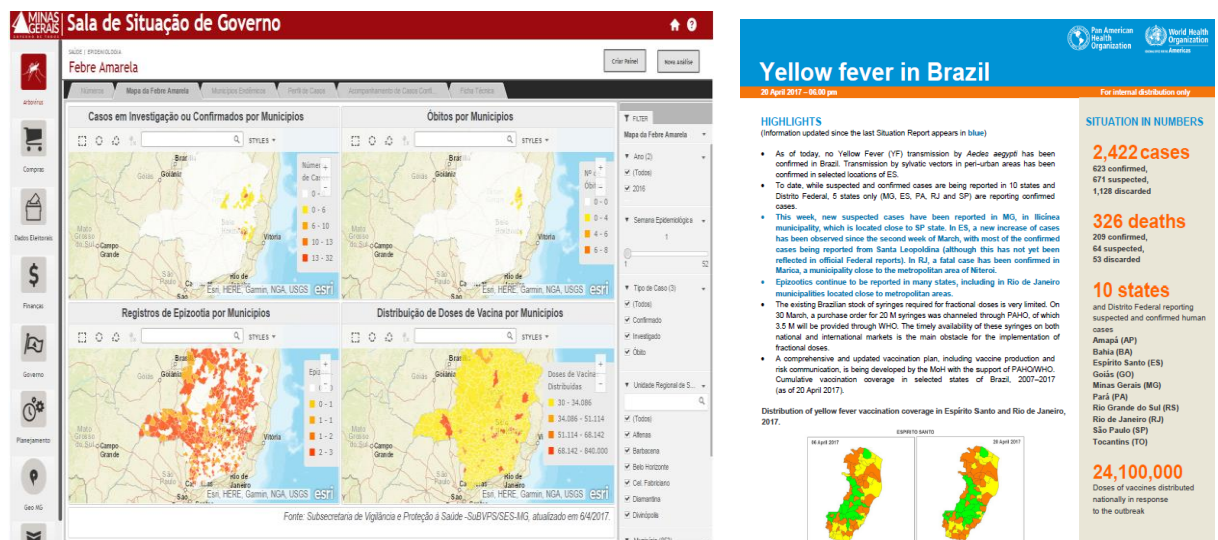
Source: Avaliação de Meio Período da Estratégia de Eliminação de Epidemias de Febre Amarela (EYE) 2017–2026 [Mid-term evaluation of the yellow fever epidemic elimination strategy (EYE) 2017–2026]. PowerPoint® presentation, Directorate for the Surveillance of Communicable Diseases, 2022 (in Portuguese).

<sup>12</sup> State decree NE No. 31, of 19 January 2018 updated in State Decree NE No.45, of 24 January 2018 to include an additional 68 municipalities <https://g1.globo.com/mg/minas-gerais/noticia/minas-gerais-decreta-situacao-de-emergencia-por-cao-do-surto-de-febre-amarela.ghml>

In addition to the demonstrated political will of the Government of Minas Gerais, a further BRL 11 million were made available by the state government in 2017 and over BRL 15 million in 2018 to manage the yellow fever epidemic<sup>14</sup> apart from funding from normal channels. As one professional put it, it was an “operação de guerra” with respect to the precision, quickness, coordination and human resources required to respond to a “threat”.

**Situation room:**<sup>15</sup> With significant guidance and support from PAHO, a situation room was established in Belo Horizonte (see under **Clinical response and management**). A coordinated effort of public health professionals from the State Health Secretariat, regional health superintendents, HemoMinas (blood service provision in Minas Gerais), Ezequiel Dias Foundation (Funed), Hospital Foundation of the State of Minas Gerais, Eduardo de Menezes Hospital and Belo Horizonte Municipal Health Secretariat ensured that the situation room was functional during both outbreaks. This platform guided the management of the yellow fever outbreak and garnered the leadership and decision-making capacity to coordinate information and resources throughout the state including in the regions and municipalities. See Fig. 10 for an example of a daily bulletin.

**Fig. 10. Mapping human and epizootic cases (situation room), SitRep bulletin**



Source: Avaliação de Meio Período da Estratégia de Eliminação de Epidemias de Febre Amarela Amarela (EYE) 2017–2026 [Mid-term evaluation of the yellow fever epidemic elimination strategy (EYE) 2017–2026]. PowerPoint® presentation. Directorate for Surveillance of Communicable Diseases, 2022 (in Portuguese).

Bulletins were produced initially on a daily basis and eventually once a week during the outbreak and later once a month up to the present time. These bulletins, developed with support from PAHO and the MoH, publish information on the yellow fever situation in numbers (for example, cases and their location, human and epizootic deaths, vector characteristics, vaccinations, public health responses). These publications informed decision-making, both programmatically and financially and served as effective

<sup>14</sup> Avaliação de Meio Período da Estratégia de Eliminação de Epidemias de Febre Amarela Amarela (EYE) 2017–2026 [Mid-term evaluation of the yellow fever epidemic elimination strategy (EYE) 2017–2026]. PowerPoint® presentation. Directorate for Surveillance of Communicable Diseases, 2022 (in Portuguese).

<sup>15</sup> A space where experts systematically analyse information to characterize and engage in decision-making processes in responding to and solving a health situation, especially during emergencies in collaboration with various institutions and social sectors.

communication tools at various levels. They were used by all levels of public health responders, by municipalities to ramp up vaccination efforts and by state health officials to advocate to the MoH for additional support in the form of manpower, vaccines, training, etc.

Following the outbreak, the Yellow Fever Surveillance and Control Programme was restructured and it is now located in the State Arbovirus Surveillance Coordination. This move was thought to further enhance the establishment and functioning of comprehensive surveillance systems for human cases, epizootics, and entomology in relation to Dengue, Zika, chikungunya and yellow fever.

Based on the tremendous efforts outlined above, “not a single municipality that had cases in the first wave had cases in the second wave”; and transmission was considered to have been controlled. The current state of affairs with yellow fever in Minas Gerais is that there were no confirmed epizootics from October 2018 to August 2021 and no confirmed human cases from 2019 to 2022. However, a new epizootic wave was detected in Minas Gerais in August 2021. It was considered “new” as the virus strain was not related to the virus circulating up to that time in 2021 (11).

See Box 1. on how one nurse’s efforts saved the residents of Franciscópolis, a small municipality surrounded by seven municipalities in Minas Gerais.

Situation rooms were also established, based on the Minas Gerais example, in São Paulo and Rio de Janeiro. In the latter city, Biomanguinhos/Fiocruz engaged extensively in coordination efforts with the MoH and SES (particularly in Rio de Janeiro where the institute is located) including in the municipalities of Rio de Janeiro. During 2016–2019, they established a situation room to help coordinate the response in Rio de Janeiro. In addition, they have engaged in and published numerous research projects including closely scrutinizing yellow fever virus dose response. This research has influenced policy-setting

**Box 1. “Ilha no meio do surto” – an island in the middle of an outbreak – how access to information and the commitment of one nurse saved the residents of Franciscópolis**



In Franciscópolis (a small municipality surrounded by seven municipalities in Minas Gerais— see map above) the community was largely unvaccinated and were not actively seeking the vaccine. One nurse who was informed about the epidemic through reading the bulletins where NHP cases were being discussed (as reported by presenters) took matters into her own hands. She travelled door-to-door offering vaccinations to all community members within the municipality and the result was astonishing. The vaccination rate was high particularly in comparison to the municipality which surround Franciscópolis, and very low cases were recorded. The dedication of the nurse, her access to knowledge (thanks to surveillance systems and communication of the looming pandemic), and putting that knowledge to use, saved the community of Franciscópolis from potentially much worse fate seen in neighbouring municipalities.

*Source:* Experiência CIEVS Minas no enfrentamento da epidemia de Febre Amarela 2016–2018 [Experience of CIEVS Minas in facing the epidemic of yellow fever 2016–2018], PowerPoint® presentation, Information Center Health Surveillance Strategies; n.d. (in Portuguese).

throughout the country with regard to vaccination schemes.

**Clinical response and management:** The spectrum of yellow fever ranges from asymptomatic infections to non-specific symptomatic illness to severe and fatal cases (haemorrhagic). The virus is, however, often associated with rapid clinical decline and requires quick decision-making by health-care professionals, access to adequate care and constant evaluation during the critical phase. When the yellow fever virus broke out in 2016, experience of managing clinical care particularly in intensive care units (ICUs), was scarcely documented or not available through the historical knowledge of health-care providers in Minas Gerais (and beyond). This lack of standard protocols challenged the response to patient’s needs.<sup>17</sup> It was up to the frontline workers to learn-from-doing to reduce the high mortality rates seen in the yellow fever circulating initially in Minas Gerais (2016–2017), and to share lessons learned that subsequently informed the production of clinical-care management guidelines.

A critical step in ensuring proper clinical management was the updating of the clinical management of the yellow fever manual and guide for health professionals (12,13) developed by the State Secretariat for Health in Minas Gerais in 2017, along with the MoH, PAHO and other key players. This initial guideline was continuously updated, based on lessons learned during the first and second outbreaks of yellow fever including more efficacious treatment regimens and led to the development of a federal clinical management manual. A key feature of the manual was the definition of three classification groups of cases, from mild to moderate and finally serious with the accompanying laboratory examinations and treatment regimens necessary per group.

A call-in centre was established to respond 24 hours a day, 7 days a week, to inquiries from the health centres across the state, assist in identifying the status of patients, and help with decisions on testing, treatments, etc. This call-in function was part of the overall “situation room” established at the hospital where staff discussed patient treatment courses, reasons for deaths or resolution of cases, required changes to protocols, etc. As delays in transporting both laboratory specimens and the results had been identified as a major stumbling block in the initial days and weeks of the response, a dedicated vehicle was assigned to the hospital to improve transportation schedules so that treatment regimens could be administered promptly to critically ill patients and to improve surveillance statistics.

Another major step in the establishment and improvement of clinical management was to concentrate all referral cases in one public sector hospital. Additional health-care workers were recruited (financed largely by PAHO) for the hospital and for outreach purposes (surveillance and vaccination campaigns). The gathering of all severe cases in one referral hospital resulted in an invaluable learning experience that helped shape clinical care of yellow fever during the second period with a reduction in deaths in the ICUs from around 70% in 2017 to under 40% in 2018 (and in neighbouring states where the same model was applied – see percentage changes in São Paulo in Table 1 below). The referral hospital served as a focal point for gathering critical data which have been the subject of various analyses and studies resulting in publications and the development of understanding of the

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<sup>17</sup> The most recent clinical management guideline was from the early 1950’s and was, therefore, very outdated.

disease and treatment courses, for example, the persistence of hepatitis after yellow fever (14), and severe metabolic acidosis in severe cases of yellow fever (15).

Table 1. Improvement in yellow fever case outcomes from 2016–2019, hospitalized patients, São Paulo

Year	No. of cases	No. of deaths	Mortality rate %
2016	3	3	100.00
2017	75	38	50.70
2018	503	175	34.80
2019	67	13	19.40

Source: Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization]. PowerPoint® presentation, n.d. (in Portuguese).

It should be noted that the advances in clinical management were probably only possible as a result of the large number of cases. Outbreaks with a small number of cases would not have enabled the generation, application and incorporation of extensive new knowledge as it did in 2016 and beyond. The availability of hospitals with new equipment, new testing capabilities and well prepared staff was a contributory factor to clinical care advances when compared to previous yellow fever outbreaks.

#### **3.2.4 Research informing practice**

Brazil is renowned for its public health and yellow fever research emerging from world class research institutions, universities and extensive publications authored by MoH and State Secretariats of Health employees based upon their hands-on experience. This research culture and drive for evidence-based programming ensures that yellow fever remains relevant. There is the most up-to-date information on epidemiological (for example, genomic sequencing), entomological and zoological surveillance and trends in the disease, effective clinical responses (for example, treatment of severe cases, plasma transfusion, transplants), and vaccine efficacy (for example, fractional dosing, protective duration of vaccinations).

As outlined by the MoH and the Undersecretariat for Health (Minas Gerais), “Our nation is peculiar in this respect; we are poor enough to have our shortcomings result in epidemics like the one we are experiencing, but also rich enough to respond, react and learn from them” (12). This learning emerged equally from hands-on experience but also from publications and research related to yellow fever prevention and response efforts.

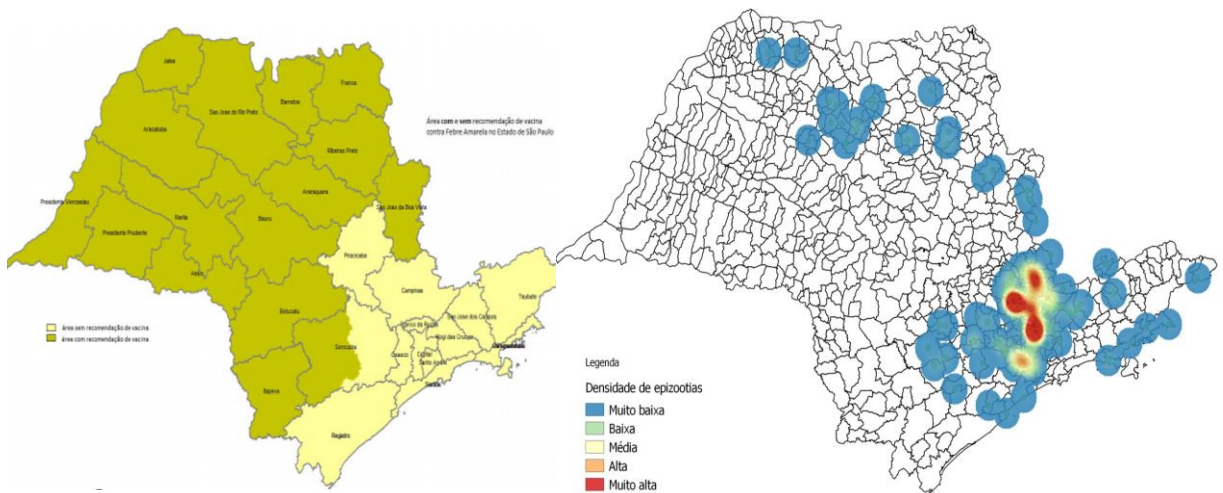
The country has taken the results of its tireless research efforts into consideration when designing yellow fever responses. This includes mapping the corridors of transmission to better inform vaccination response times (for example, resulting in a low case rate and zero case fatality rate in 2018–2019 in Minas Gerais). This is associated with the vaccination campaigns being carried out prior to the first human cases and improved clinical management based on the 2017 clinical management manual (Minas Gerais) which led to the development of a federal clinical management manual. Other examples of putting research into practice is the portrayal of the interwoven patterns of NHP and mosquito characteristics to help predict the spread of the disease in humans to establish a de facto early warning system. This type of research also helped inform country-wide vaccination protocols which transformed targeted vaccinations that depend on the perceived geographical risk of the obligatory vaccination for children nationwide.

Examples of research and publications are woven through these sub-sections as well as in the bibliography and the further reading list.

### 3.2.5 Adapting vaccination strategies and monitoring adverse effects

Vaccination remains the single most efficient tool for preventing and controlling yellow fever. The debate is ongoing regarding ideal coverage, but some schools of thought adhere to 80% coverage to prevent and control outbreaks while others favour tailored approaches based on risk profiles (16). Through SUS, Brazil offers vaccination for free. At the onset of the 2016 outbreak, vaccination for yellow fever was recommended in large part based on previous epizootics and/or human cases and geographical risk factors (including environmental factors) and was *not* recommended for the entire country (see Fig. 11 below for the example of São Paulo in the map on the left). The figure shows a notable disconnect between areas not recommended for vaccination in 2016 (map on the left, light yellow) and where confirmed cases of NHP infection occurred during 2016–2018 (map on the right, red having the highest concentration). Due to the scale and severity of the 2016–2019 yellow fever virus spread, coupled with evidence generated through surveillance efforts (as per the map on the right in Fig. 11), the government adjusted its protocol to include routine vaccination for yellow fever across the entire country to halt the spread. The maps should be interpreted with caution as bias may exist (for example, potentially better surveillance systems in municipalities with "red" areas and a more real-time surveillance system could result in greater number of cases; areas of high vaccination coverage may have weaker NHP surveillance as the risk of death among humans is less).

**Fig. 11. Recommended vaccination areas (left) and confirmed NHP cases in 2016–2018 (right)**



Note: map on left – recommended areas for yellow fever vaccination (both routine immunization and general population) in 2016 – São Paulo State (vaccination coverage of 25.7%), light yellow shows non-recommended vaccination areas.

Map on right – confirmed NHP cases in São Paulo State, 2016–2018.

Source: Lang D’Agostini T. Presentation. Board of Directors of the Center for Epidemiological Surveillance “Prof. Alexandre Vranjac”, São Paulo, Sep. 2022.

## São Paulo

Vaccination efforts during the outbreaks began in the peri-urban settings bordering forested and rural areas where previously reported cases were identified. Campaigns were then ramped up to include urban populations eventually followed by the entire state based

on surveillance data. The challenge was daunting given that 70% of residents in areas recommended for vaccination (n=10.7 million) were vaccinated while in areas not recommended for vaccination, residents numbered 35 million and had a coverage rate of only 10%<sup>24</sup> (Fig. 11).

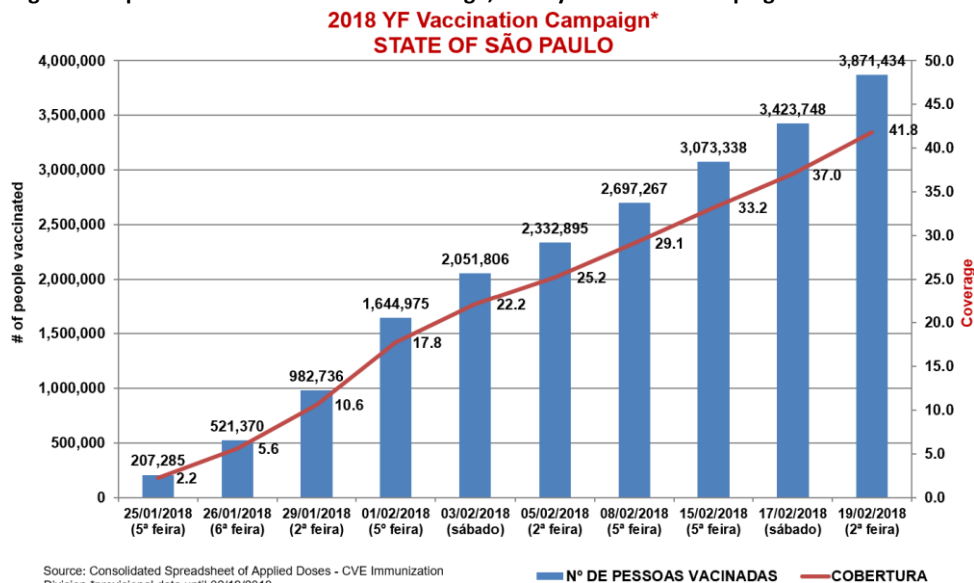
Speed was critical to the response, however, given the high-density population of the state and the lack of immediate supply of vaccines, fractional dosing of the vaccine was the only way to ensure adequate coverage rapidly. Building upon experiences and research in Angola and the Democratic Republic of the Congo where fractional dosing was used to combat the 2016 outbreaks, fractional dosing was initiated on 9 January 2018. It was administered in 54 municipalities with an estimated 6.3 million vaccinated. This effort was supported by 29 technical specialists from WHO recruited to assist with the campaigns (17). Studies undertaken during the outbreaks demonstrated that administering a fractional dose of the yellow fever vaccine was effective at inducing seroconversion which confirmed the use of fractional-dose vaccinations for outbreak control (18).

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<sup>24</sup> Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization], PowerPoint® presentation, n.d. (in Portuguese).

Fig. 12 provides an overview of the speed at which more than 2.6 million people were vaccinated in 10 days of campaign implementation.

Fig. 12. People vaccinated and vaccine coverage, 10-day vaccination campaign



Source: Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization], PowerPoint® presentation, n.d. (in Portuguese).

Despite massive efforts and a significant increase in coverage (9 million in 2017 and 12 million in 2018 6.2 regular doses, 5.8 fractional doses) struggles still existed. A substantial hurdle was communicating the shifting vaccination protocols during the outbreaks which left populations frustrated, confused and, in some cases, hostile. This was attributed to: (1) initial communication of vaccination campaigns only in targeted areas of high risk (not necessarily covering an entire municipality); (2) reducing the vaccination to one dose, whereas the government had previously recommended two doses of the vaccine; (3) the announcement that everyone should be vaccinated; and (4) announcing the use of fractional dosing. There was mistrust in the efficacy of fractional dosing, “the fractional dose is weak”, confusion as to why “interior” municipalities were receiving the full dose while the capital was receiving the fractional dose, why international travellers received the full dose, coupled with fears of adverse events. These misbeliefs and fears led to people relocating to other municipalities, travelling to Minas Gerais (where fractional dosing was not used) to obtain the vaccine or refusing vaccination. Social media exacerbated the situation portraying the response as slightly chaotic and reporting deaths due to vaccines, including in a three-year-old child.

São Paulo has a strong surveillance system designed to measure adverse events post-vaccination, as mentioned above in the small child who was suspected to have died from adverse events. Health officials reviewed over 4600 cases of adverse events during 2017 and 2018 associated with the vaccination of more than 21 million people (15.2 million with full doses and 5.8 million with fractional doses). They found that, of the 3169 events from 2017–2018 (that were not associated with errors in vaccination) 852 were considered serious (of those 264 were associated with fractional dosing). Overall, there were 15



confirmed deaths (14 viscerotropic and 1 neurotropic) due to adverse effects from the vaccine (4 associated with fractional dosing)<sup>27</sup> (see Table 2 below).

**Table 2. Viscerotropic adverse events surveillance data 2017 and 2018, São Paulo**

Year/type of dose	Likely and confirmed		
	Cases	Deaths	%
2017 – Full dose	4	4	100.0
2018 – Full dose	8	6	75.0
2018 – Fractional dose	6	4	66.7
<b>Total</b>	<b>18</b>	<b>14</b>	<b>77.8</b>

Note: overall case notification rate for viscerotropic disease associated with yellow fever vaccination is .06/100 000 doses administered.

Source: Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization], PowerPoint® presentation, n.d. (in Portuguese).

Identification of these adverse events is attributed to increased surveillance sensitivity and increased capability of health professionals to identify and refer patients rather than increase the threat of adverse events due to vaccination.

### Minas Gerais

Vaccination efforts in Minas Gerais saw continual improvements including many changes in the recommendations during 2017 from vaccination only in regions at risk<sup>28</sup> to categorization of municipalities for immunization based on epizootics.<sup>29</sup> The classification of municipalities included: **routine** (no human cases and no epizootics confirmed, under investigation or rumoured – normal vaccination scheme was recommended); **intensification of routine** (if there was a rumour of epizootics or a epizootic under investigation – normal vaccination scheme recommended but carried out door-to-door); and **intensification of outbreak** (if a confirmed human case or epizootic – intensified and accelerated door-to-door vaccination in the municipality with extended hours of operation at health facilities). With the onset of the second period of yellow fever virus spread in 2018 all three categories followed the same protocols: intensification in rural and urban zones with door-to-door vaccination and increased opening hours for vaccination rooms in health centres.

To implement the massive ramping up of vaccinations, over 70 vaccinators and drivers were contracted to support the regional health secretariats. This included targeting work to cover special groups including communities in rural and indigenous regions as well as camps and settlements of landless rural workers (mainly men working in forest regions). This was achieved by working with the district indigenous health services, state

<sup>27</sup> Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization], PowerPoint® presentation, n.d. (in Portuguese).

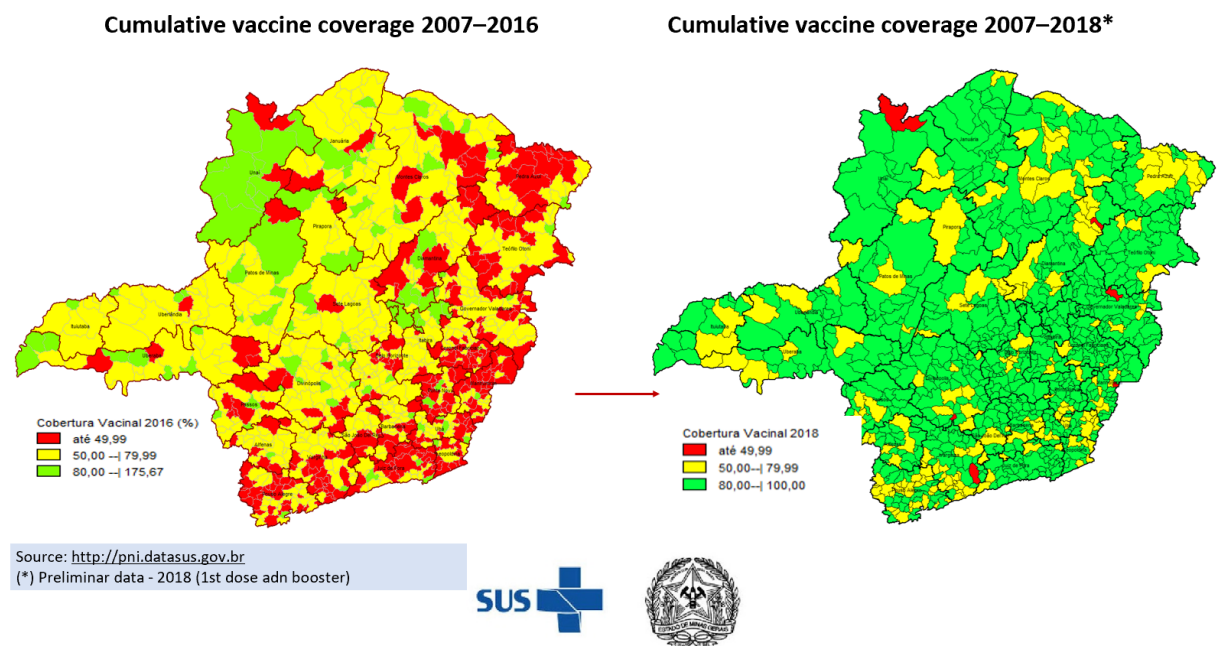
<sup>28</sup> Technical note issued in 03/2017

<sup>29</sup> Technical note issued in 05/2017

administration departments<sup>30</sup> (fisheries, agriculture, social assistance), cooperatives and big companies, to name a few. The overall efforts saw the distribution of 5.4 million doses in 2017 and 1.76 million in 2018. Fig. 13 below shows the evolution of vaccination coverage in Minas Gerais.

Following the door-to-door vaccination campaigns a rapid monitoring of vaccination coverage was carried out (recommended by PAHO) which aimed to find individuals who had not been reached. In each house, vaccination cards were checked and those not vaccinated were offered the vaccine. The team conducting the work also gathered data on why people were not vaccinated in the household, akin to a vaccination scanning and census exercise, to better inform communication efforts about vaccination. A team travelled to 27 regional health units covering 504 municipalities. They found that 18 regions had less than 10% unvaccinated population, inferring that the door-to-door campaign had been effective in those regions. The staggering difference in vaccination from 2017 to 2018 is clearly evident in Fig. 13. It was attributed to increased efforts, particularly, through the door-to-door campaigns.

**Fig. 13. Vaccination coverage Minas Gerais cumulative, 2007–2018**



Coverage at the culmination of 2016 was estimated at 57.4% and by the end of 2018 this had increased to over 93% coverage.<sup>31</sup>

Adverse events were monitored in Minas Gerais from 2016 to 2018 with 1252 notified cases reviewed. Of 909 events not associated with errors in vaccination, 264 were

<sup>30</sup> Reunião para discussão de estratégias para vigilância e controle da Febre Amarela em Minas Gerais [Meeting to discuss strategies for surveillance and control of yellow fever in Minas Gerais]. PowerPoint® presentation. State Department of Health of Minas Gerais, Undersecretary of Health Surveillance, Superintendence of Epidemiological Surveillance and Board of Surveillance and Communicable Diseases; 2022 (in Portuguese).

<sup>31</sup>With 698 municipalities recording 80% coverage or above (including 392 with more than 95% coverage) and only 155 of the total 853 municipalities with under 80% coverage (according to Immunization Coordination. Data extracted from August 2019: <http://pni.datasus.gov.br>).

considered serious.<sup>32</sup> No deaths were attributed to adverse post-vaccination in Minas Gerais. As in São Paulo, the identification of these adverse events is attributed to increased surveillance sensitivity and health professionals' increased knowledge of how to identify and refer patients rather than an increased threat of adverse events due to vaccination.

### **3.2.6 Vaccine supply ensured by local production**

Management of routine yellow fever in addition to outbreak response predicates a supply of vaccines which often presents a challenge during outbreak periods. The role played by Bio-Manguinhos/Fiocruz (of the Oswaldo Cruz Foundation), a Latin America excellence institute in immunobiologicals production based in Rio de Janeiro, has been invaluable for Brazil's yellow fever response as well as for the Americas as a whole. They have provided a sense of national security ensuring a continual stock of the vaccine for decades including during critical outbreak periods. Bio-Manguinhos has the ability, based in part on its infrastructure expansion, to increase production.

Bio-Manguinhos began production of yellow fever vaccine in 1937 (then called Oswaldo Cruz Institute) and delivered the first yellow fever vaccine in response to outbreaks in 1998–1999. They have provided a continuous supply of the vaccine to the Government of Brazil, and other countries through agreements with PAHO and UNICEF, for routine immunization and outbreak response. The current capacity for yellow fever vaccine is 60 million doses per year including a 10-dose format for the Brazilian market submitted to WHO for pre-qualification. This supply covers Brazil as well as many neighbouring countries and beyond and includes exports to 75 countries to date. This is possible through continuous improvement of the attenuated yellow fever vaccine, increased production capacity, product availability and product quality, and the optimization of resource and infrastructure usage.<sup>33</sup>

SUS distributed 45.1 million doses of the vaccine in 2017 and 23.8 million in 2018 (19) produced by Bio-Manguinhos. During the outbreaks in 2016–2019 fractional dosing was recommended (see sub-section on vaccination adaptations) corresponding to 1/5 of a standard dose for which PAHO procured syringes to supplement those available through the government. Bio-Manguinhos continued to provide the vaccines needed to stay ahead of the outbreak. It should be noted that following fractional dosing, the government has encouraged those receiving the 1/5 dose to return for a subsequent full dose.

### **3.2.7 Risk analysis and data modelling**

An understanding and mapping of the factors that favour the circulation of the virus is critical to predict at-risk areas. Brazil has advanced initiatives on risk analyses and data modelling for yellow fever surveillance based on epizootic surveillance, registration of NHP deaths, overall investigation, sample collection and laboratory support to detect potential outbreaks. This work is led by a collaborative yellow fever modelling study group (GRUMFA) whose members include MoH, Imperial College London, University of Minnesota, UNICEF, Fiocruz, PAHO, WHO, state health secretariats, etc. They meet biannually in line with the yellow fever contingency plan of the MoH and the seasonal periods of yellow fever. The

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<sup>32</sup> Fernandes EG. Vacinação de febre amarela e eventos adversos supostamente atribuíveis a vacinação ou imunização [Yellow fever vaccination and adverse events presumably attributable to vaccination or immunization]. PowerPoint® presentation, n.d. (in Portuguese).

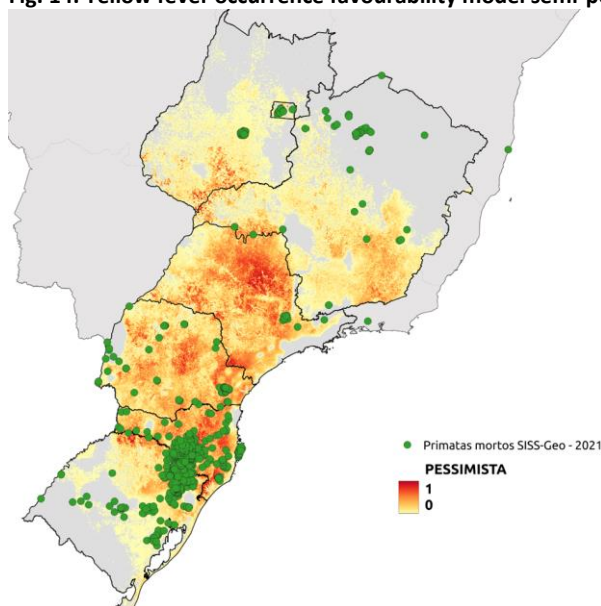
<sup>33</sup> Bio-M manufacturing updates, PowerPoint® presentation. Ministry of Health and Institute of Technology in Immunobiologicals, 2022.

group engages in planning and research targeting endemic-epidemic processes, undertaking risk and vulnerability analyses, developing virus spread corridor maps and dispersion paths, prioritizing areas and populations at risk, determining potential distribution models (viruses, hosts and vectors), and defining ecological and environmental factors associated with yellow fever and emergency prediction capability.

GRUMFA is responsible for continuously evaluating the different methodologies for data modelling and the risk and vulnerability analyses in use and development processes in Brazil (1). The MoH is currently using the model of affected and expanded areas (assumes dispersion of yellow fever can occur in any direction based on a single case) and the model of virus spread in corridors (estimating risk in a vectoral way, showing routes of favourable dispersion). Although these models show corridors where expansion is favourable, the uniqueness of the corridor also needs to be assessed to answer the “\$1000 question is when in some moments does the virus move to another area”, an area outside of that predicted. The work can also help answer the question of “why sometimes the virus spreads from endemic area being able to reach the south-eastern and even south regions in Brazil and what is the trigger to that event”. This points to the continual need to monitor NHPs and look at macro factors (temporal analysis). These models are further described in the Contingency plan for emergency response in public health yellow fever, 2nd Edition, 2021 (1).

Most recently, GRUMFA elaborated a concept note in preparation for the 2021–2022 seasonal period which included data modelling and the elaboration of a surveillance action plan for yellow fever. The group used data from previous transmissions to predict the timing of the next outbreak. The mapping, based in part on notification of deceased NHP, helps determine where the virus is heading (corridors of transmission). These mappings are used to help the municipalities plan their yellow fever preparedness and response activities. An example of a data map for use in decision-making is presented in Fig. 14. Additional examples of risk assessment models based on affected and expanded areas, ecological corridors and favourability are presented in Annex 2.

**Fig. 14. Yellow fever occurrence favourability model semi-pessimistic scenario, Brazil**



Source: Ramos DG. Initiatives on risk analyses and data modelling for yellow fever surveillance and decision-making in Brazil, PowerPoint® presentation, 2022.

The work of GRUMFA, and the use of the results from modelling exercises (by state and municipal health secretariats and a variety of other institutions) has both fostered improved surveillance and helped shape the response to yellow fever as seen with the second period 2018–2019 and the planning of vaccination campaigns. See Fig. 6 where São Paulo was able to plan vaccination campaigns based on modelling exercises that predicted the time of arrival of yellow fever in different geographical locations.

The next steps for GRUMFA and the country include the following.<sup>37</sup>

- Exploring further how to combine different models – spatial/statistical models (favourability, vulnerability, risk assessment and stratification) and mathematical models (compartmental, transmission dynamics).
- Incorporating new data (immunization, vectors, genomic studies).
- Establishing distinct approaches for different contexts and purposes:
  - routine verses emergencies
  - vaccine coverage verses risk to human populations (vaccine coverage milestones)
  - outbreak/risk prediction (from NHP data)
  - vaccine production and distribution (based on historical data analyses)
  - laboratory supplies and network
  - health-care network.

### **3.3 Key enablers and critical factors**

Many of the critical and enabling factors are described above and include the following.

- The political will of government at all levels including both technical and financial support.
- Production and use of evidence-based research for decision-making – including surveillance data used for mapping corridors and transmission patterns of yellow fever.
- Coordination across various health departments with the federal, state, regional and municipalities to ensure an integrated response build on what the data were revealing about human cases and vaccination patterns, epizootics, and entomological information.
- Management – ensuring that the most up-to-date information was being used for decision-making and that there was sufficient human resources and infrastructure to carry out surveillance including laboratory resources, immunization response and clinical-care activities.
- Communication – real time through various platforms (WhatsApp, SISS-GEO) and tools (bulletins, websites, media) in addition to campaigns.
- Door-to-door vaccination strategies and their extensive reach and subsequent monitoring following implementation.
- Continual intensification of surveillance of NHP (outside of outbreak periods) and continuously engaging in NHP including during non-epidemics periods, is the best way to guarantee early detection of yellow fever virus circulation. For example, São Paulo is also increasing the resilience of yellow fever laboratory surveillance for NHP by focusing on improving governance structures (communication and learning, information and system flow), ensuring sufficient resources, an adequate and motivated workforce in addition to guaranteeing a variety of flexible systems to deliver results.

In addition to the above factors, the support and dedication demonstrated by PAHO in the continuous fight against yellow fever cannot be underestimated. Both the financial and

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<sup>37</sup> Ramos DG. Initiatives on risk analyses and data modelling for yellow fever surveillance and decision-making in Brazil, PowerPoint® presentation, 2022.

technical contributions were lauded by those who participated in the week-long data collection exercise. Their continual presence in the affected states during the 2016–2019 period was a game changer. PAHO staff established a rotating schedule where one member of the Emergency Team was constantly present in Minas Gerais as well as other states during the yellow fever virus circulating periods. These individuals were pivotal in helping to establish the situation rooms which were critical in ensuring that the states were responding rapidly with the most up-to-date information and in the most efficient and effective way possible. PAHO also financed reinforcements and provided commodities when and where needed to the health workforce to ensure both an efficient clinical response and a successful vaccination campaign response.

A quote from the clinical-care management manual produced by the MoH sums up what may be the biggest critical enabling factors in responding to the outbreaks:

It was up to those teams involved in this unprecedented contact between modern medicine and yellow fever, to learn from the disease and look for ways to reduce the staggering lethality. The result of this work, essentially empirical, was a huge reduction in this lethality, although still very high. Much of this response is due to cooperation between reference centers, knowledge was not stagnant in a hospital, laboratory or federated entity, the network created to allow support expedited diagnosis, allowed new interventions and fostered research. Solidarity and cooperation were genuinely the keynote. (Translated from Portuguese.) (12)

The evaluation did not find substantial evidence of the actual linkage or contribution of the EYE strategy to the results in Brazil. It is likely that Brazil, even without the global EYE strategy, would have initiated a successful response to the outbreaks. However, there was evidence that the annual EYE partners' meeting in 2017 held in Brazil contributed to increased awareness of yellow fever in Brazil as well as the surrounding countries and presented opportunities for Brazil to share best practices through the EYE communication channels and partnership in future.

### **3.4 Potential for replication, scale-up and sustainability**

The potential for replication, scale-up and sustainability have been tested and have shown positive results in Brazil. As detailed above, the outbreak response mechanisms from human resources, to infrastructure, to financial inputs were mobilized at a faster and more efficient pace during the second period of yellow fever virus spread (particularly in Minas Gerais) with demonstrated ability for putting learning into practice and scaling up in real time. Sao Paulo has published a book about their yellow fever response during the outbreaks as a learning tool for other states (20).

The range of partners involved in yellow fever surveillance and response continues to grow to include zoonoses laboratories and state forests to ensure closure of parks or restricted areas as an example. The teams from Minas Gerais and Sao Paulo took their expertise in emergency outbreak response to other states in the country to help them improve their surveillance systems, learn from the operation of a management structure for outbreak response and to share and adapt clinical management systems. This work has also been carried out in Brazil's neighbouring countries.

It is anticipated that the SISS-GEO app, which has been shown to neighbouring countries, will be put in place as a surveillance tool in those countries. Fiocruz has the hardware and

expertise to bring other countries online. The system is less applicable in Africa where, although the primary hosts of yellow fever are NHP, African monkeys appear to be more resistant to the virus and therefore have low death rates. Given this, the NHP in Africa do not act as an early warning mechanism (21).

The surveillance system in place and the capacity of laboratories that have been built to respond to yellow fever continue to grow stronger with the support of the federal ministry, PAHO, WHO, CDC and other key stakeholders. The associated dissemination of epizootic surveillance information as a strategic tool for surveillance is critical and the strategy developed in Brazil can be replicated in the Americas. Historically in Brazil, states with well-structured surveillance of epizootics identify the arrival of the virus in their territories by detecting the death of primates, while states with more fragile surveillance of primates are surprised by the occurrence of human cases. Strengthening the use of surveillance tools at the regional level is a surveillance strategy that can make a decisive contribution to preventing human cases and deaths.

Research continues to evolve on vaccines and vaccination strategies, the patterns of mosquito migration, and the evolution of the virus and of primate and humans exposed to the virus, all of which enables the country to engage in appropriate programming for yellow fever.

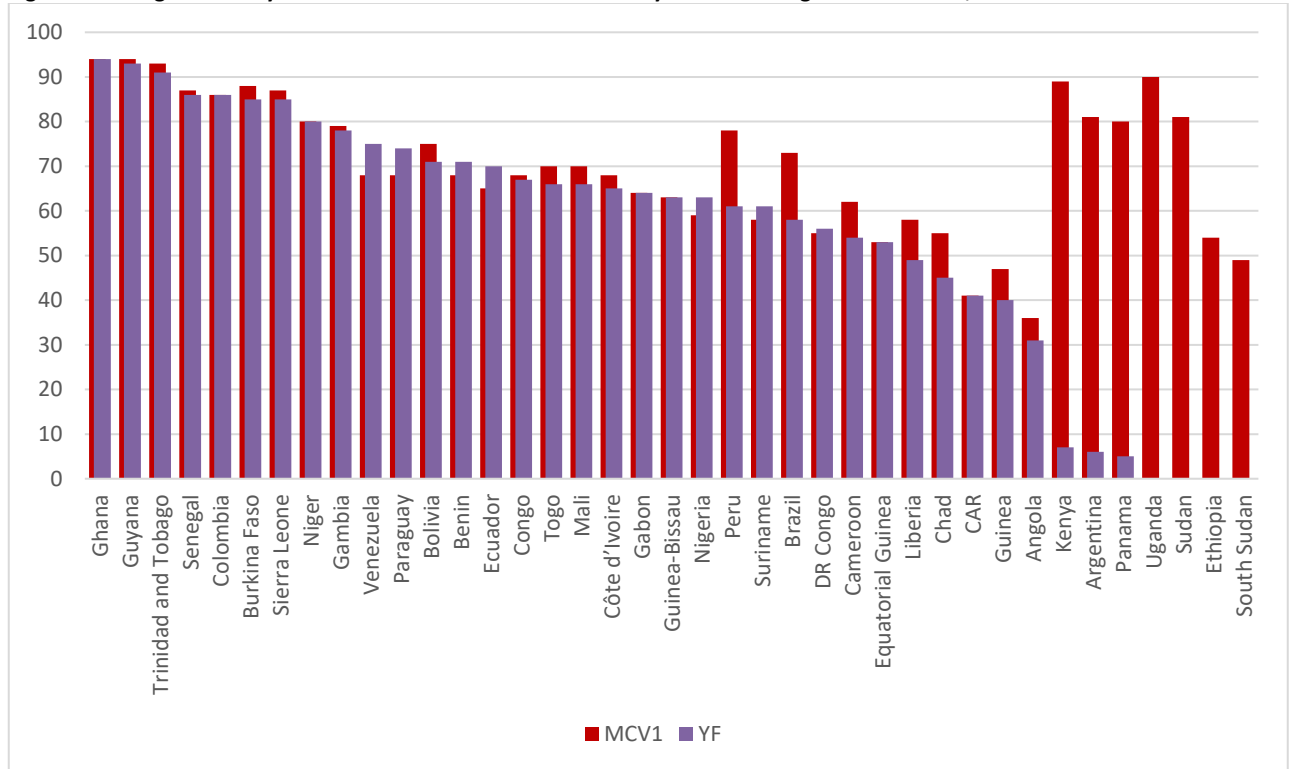
A major risk to sustainable results in Brazil is the low coverage of yellow fever vaccination in routine immunization programmes (58% in 2021) also relative to other countries and relative to measles containing vaccine first dose (MCV1) in Brazil (73% in 2021, with a distinct decreasing trend since 2020). Of note is the almost 15 percentage points difference between yellow fever vaccine coverage and that of MCV1 (Fig. 15); Brazil is one of the few high-risk countries that have such a large difference globally (Fig. 16). This calls for an urgent need to invest more on achieving higher coverage rates of yellow fever virus in routine immunization schemes to increase resilience and sustainability.

**Fig. 15. Comparison of yellow fever vaccine and MCV1 coverage rates, Brazil, 2017–2021**

Country / Region	Antigen	Category	2021	2020	2019	2018	2017
Brazil	Measles-containing vaccine, 1st dose	ADMIN	73.46%	79.46%	91%	92%	97.12%
		OFFICIAL	73.46%	79.45%	91%	92%	90.85%
		WUENIC	73%	79%	91%	92%	91%
	Yellow fever vaccine	ADMIN	57.73%	57.14%	60%	58%	55%
		OFFICIAL	57.73%	57.14%	60%	58%	55%
		WUENIC	58%	57%	60%	58%	55%

Source: WUENIC dataset 2017–2021 (<https://immunizationdata.who.int/>, accessed 4 May 2023).

Fig. 16. Coverage rates of yellow fever virus and MCV1 across all yellow fever high-risk countries, 2021



Source: WUENIC dataset 2021 (<https://immunizationdata.who.int/>, accessed 4 May 2023).



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# ANNEXES

## ANNEX 1. RISK ASSESSMENT MODEL EXAMPLES

### LEVEL 1 – FOCUS DETECTION AND CONTROL

**MINISTÉRIO DA SAÚDE**

**CENÁRIO 1 – Foco primário de transmissão do vírus da FA**

REGISTRO DE CASO HUMANO OU DE EPIZOOTIA EM PRIMATA NÃO HUMANO OU DETECÇÃO DO VÍRUS EM MOSQUITOS, EM QUALQUER LOCAL DO TERRITÓRIO NACIONAL.

Fonte: Cgarb/Deidt/SVS/MS.

**Description:** considering the severity, high lethality and epidemic potential of YF, the **detection of the virus anywhere in the national territory** poses a risk of local transmission and of dispersion to new areas, in addition to require the adoption of timely prevention and control measures , in order to prevent outbreaks and deaths. As the virus is endemic in the Amazon region and re-emerges unpredictably in the extra-Amazonian region, this level of activation is intended **to favor the early detection of YF to increase the opportunity for decision-making and the adoption of preventive and control** in order to reduce the effects of transmission on human populations.

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### LEVEL 2 - REGIONAL OUTBREAK AND/OR FOCUS WITH RISK OF NATIONAL/INTERNATIONAL DISPERSION

**MINISTÉRIO DA SAÚDE**

**CENÁRIO 2 – Surto regional ou focos múltiplos com risco de dispersão nacional ou internacional OU detecção em município na região de divisa com outros estados ou em área de fronteira**

Fonte: Grumfa; Cgarb/Deidt/SVS/MS.

**Description:** the detection of the virus in a cluster of municipalities regardless of the area and the epidemiological status, characterizes the occurrence of a **regionalized outbreak of YF, whose response action must be integrated and coordinated at the regional level**. Despite the recommendation for vaccination throughout the country, evidence of A associated spatially and temporally may reveal pockets of susceptible and/or risk situations for viral spread. Likewise, the detection of the virus in border regions between states or frontiers with other countries increases the complexity of the response, insofar as **different levels of management must act in an integrated and coordinated way** demanding timely communication between different entities of the Federation and /or with neighboring countries and international health representations, such as WHO and PAHO. Thus, this level of activation is intended to delimit the affected area and the population at risk, to alert managers of states and countries close to transmission areas and minimize the potential impact of the event.

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### LEVEL 3 - OUTBREAK IN HIGH VULNERABILITY AREA AND/OR WITH GREAT PUBLIC HEALTH IMPACT

**MINISTÉRIO DA SAÚDE**

**CENÁRIO 3 – Surto em área de elevada vulnerabilidade, com risco de maior impacto à saúde pública ou de dispersão nacional**

DETECÇÃO DA FA EM MUNICÍPIO RECÉM-INCLuíDO NA ACRV (A PARTIR DE 2016) E/OU COM BAIXA COBERTURA VACINAL E/OU EM REGIÃO METROPOLITANA (COM RISCO DE REURBANIZAÇÃO DA TRANSMISSÃO).

Fonte: CGPNI/Deidt/SVS/MS; Cgarb/Deidt/SVS/MS.

**Description:** the **detection of the virus in areas with low vaccination coverages or with recent recommendation of vaccination**, and which, therefore, may present vaccination coverages lower than those recommended, characterizes the greater vulnerability of resident populations, insofar as the risk of occurrence of outbreaks increases considerably. In the same sense, **municipalities located in metropolitan regions, infested by Aedes aegypti and with frequent outbreaks of dengue, chikungunya and/or zika**, can favor a process of reurbanization of transmission, from the adaptation of the virus to an urban cycle in which man act as the primary host. Both scenarios require the maximum effort from the health system to mitigate damage to human populations and prevent the urban cycle from being reestablished.

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Sources: Ramos DG. Initiatives on risk analyses and data modelling for yellow fever surveillance and decision-making in Brazil, PowerPoint® presentation, 2022. (1)

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