
Situation summary in the Americas

Between January 2017 and November 2018, six countries and territories of the Region of the Americas reported confirmed cases of yellow fever: Bolivia, Brazil, Colombia, Ecuador, French Guiana, and Peru. The number of human cases and epizootics reported in the Region of the Americas during this period is the highest in decades.

Since the 20 March 2018 Epidemiological Update on Yellow Fever published by the Pan American Health Organization / World Health Organization (PAHO/WHO)¹, **Bolivia, Brazil, Colombia, French Guiana, and Peru** reported new yellow fever cases; the following is a summary of the epidemiological situation in these countries and territories.

In **Bolivia**, between epidemiological week (EW) 1 and EW 47 of 2018, 34 suspected yellow fever cases were reported in the departments of Beni, Cochabamba, La Paz, and Santa Cruz. Of these, one case was laboratory-confirmed in a 15-year-old male with no history of vaccination and who is a resident of San Ramón Municipality in Beni Department, which is an area considered to be at-risk for yellow fever. The case had traveled to the city of Costa Marques, Brazil, prior to onset of symptoms in EW 12 of 2018. The patient was discharged from the hospital and was laboratory-confirmed by ELISA IgM and reverse transcription polymerase chain reaction (RT-PCR). In 2017, 5 confirmed cases were reported.

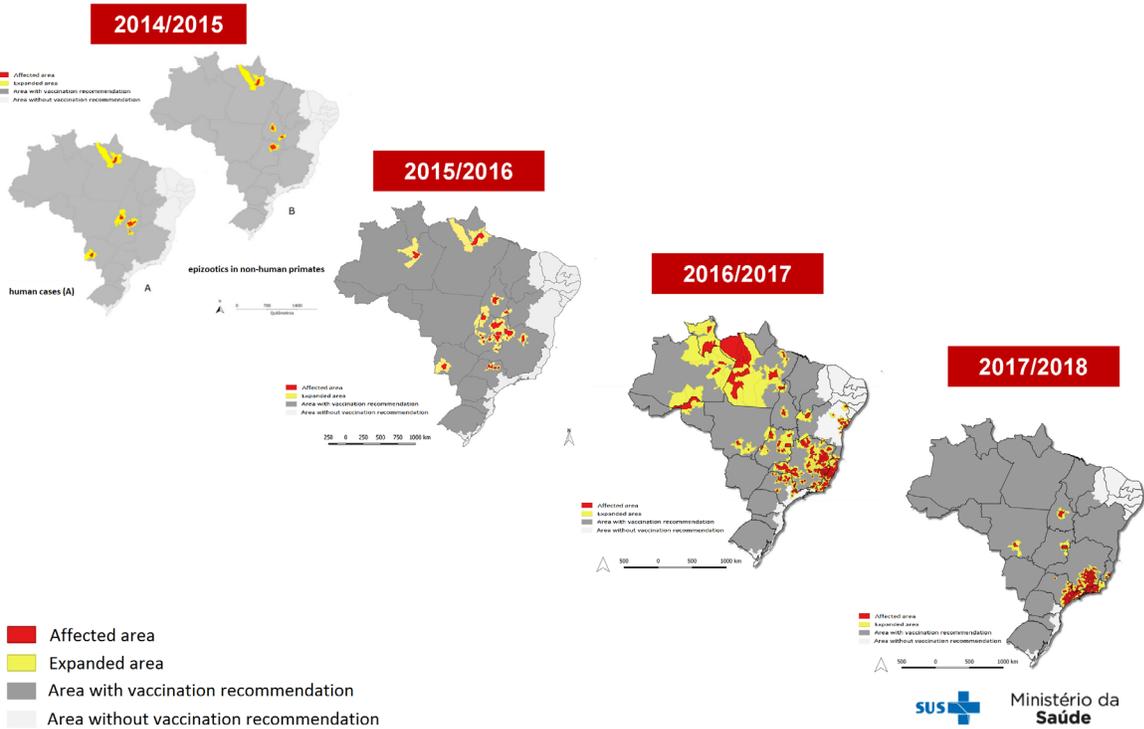
In **Brazil**, yellow fever has a seasonal pattern, based on historical analysis of human cases and epizootics due to yellow fever in the past 20 years, with two different periods: higher transmission occurring between December and May (seasonal period) and lower or interrupted transmission occurring between June and November.

In the last 3 years, there has been an expansion of the historical area of transmission of yellow fever in the country. In 2014-2015, transmission that initially occurred in the North Region spread from east to south, and in 2015-2016, it mainly affected states in the Central-Western Region. From the end of 2016 until June 2017, there was a large outbreak that mainly affected the states in the Southeast Region, with 778 human cases including 262 deaths and 1,655 epizootics due to yellow fever. A second wave of transmission was reported the following year during the same period (end of 2017 until June 2018) which also affected the Southeast Region though with higher transmission in the state of São Paulo; there were 1,376 human cases reported, including 483 deaths, and 864 epizootics. The

¹ PAHO/WHO. Epidemiological Update: Yellow Fever. 20 March 2018, Washington, D.C.: PAHO/WHO; 2018. Available at: <http://bit.ly/2prvpJ>

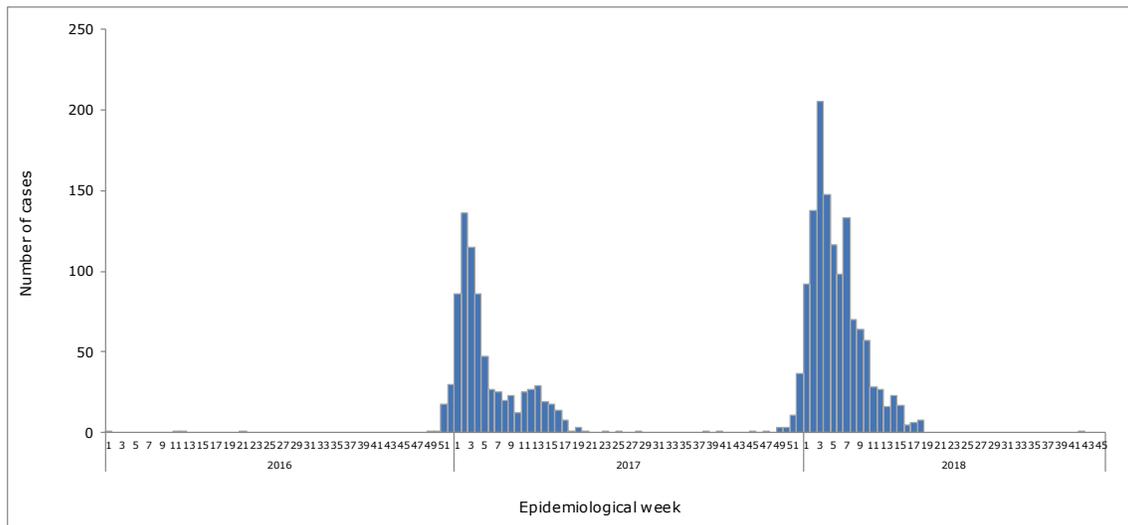
reported cases in both periods, 2016-2017 and 2017-2018, exceeded what was reported in the last 50 years. (Figure 1 and Figure 2).

Figure 1. Distribution of confirmed human yellow fever cases and epizootics by year. Brazil, 2014–2018



Source: Data published by the Brazil Ministry of Health and reproduced by PAHO/WHO

Figure 2. Distribution of confirmed human yellow fever cases by epidemiological week. Brazil, 2016–2018



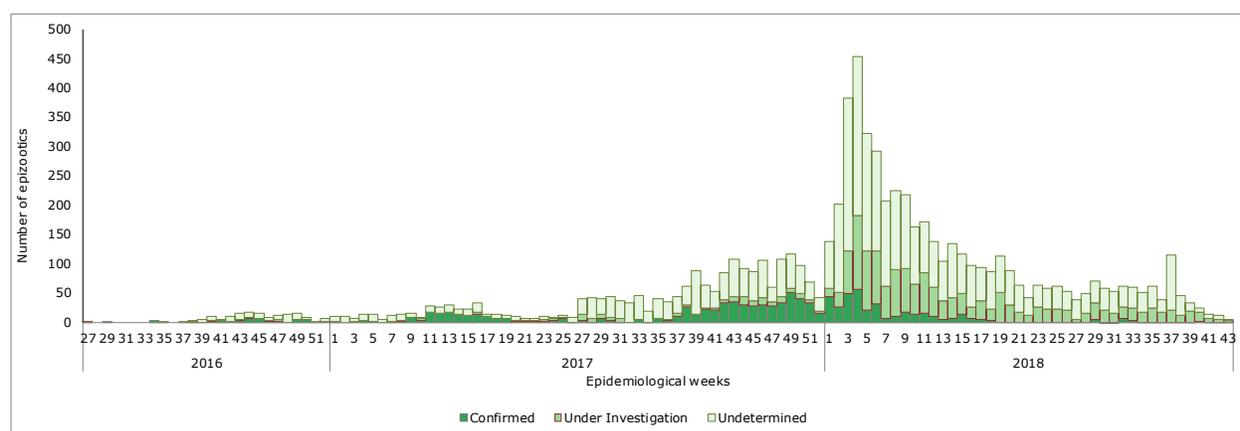
Source: Data published by the Brazil Ministry of Health and reproduced by PAHO/WHO

During 2018, the epidemic curve for epizootics (**Figure 3**) shows that viral circulation continued during the period of low transmission (June to November). Between 1 July and 8 November 2018, a total of 271 suspected yellow fever human cases were reported, of which one (fatal) case was confirmed, 120 remain under investigation, and 150 were discarded. There were 1,079 epizootics among non-human primates reported, of which 13 were confirmed for yellow fever in the states of São Paulo (8), Rio de Janeiro (3), Minas Gerais (1), and Mato Grosso (1), which are the same areas or surrounding areas as those affected during the 2016-2017 outbreak, indicating that the risk of transmission to unvaccinated populations persists.

The fatal confirmed case was reported in EW 42 of 2018 and had a probable site of infection in Caraguatatuba Municipality in São Paulo State; epizootics among non-human primates due to yellow fever were detected within this area in prior months.

Aedes albopictus naturally infected with yellow fever virus has been reported in Brazil, during the peak of the 2017-2018 outbreak, mainly as a result of overlap in the distribution of both primate and mosquito populations in areas with active transmission. However, its involvement in the transmission of the virus to humans has not been established.²

Figure 3. Distribution of epizootics by epidemiological week. Brazil, EW 26 of 2016 to EW 45 of 2018



Source: Data published by the Brazil Ministry of Health and reproduced by PAHO/WHO

Given the size of the outbreaks that Brazil has faced during the last two years, the country has had to modify its vaccination policies for yellow fever, increasing the number of areas with recommended vaccination from 3,526 municipalities in 2010 to 4,469 municipalities in 2018, and to the entire country starting in 2019. In addition, the vaccination scheme shifted from two doses in children under 5 years and a booster after 5 years of age, to a single dose scheme from 9 months of age. The use of fractional doses to respond to outbreaks, especially in large cities, was also adopted. This strategy was implemented in São Paulo, Rio de Janeiro, and Bahia.

² There is no information system at the national level with records of vectors collected, investigated, and detected with the yellow fever virus. However, based on reports presented at technical meetings and scientific events, viruses or fragments of virus have been detected in several vectors, with no evidence of their link with human cases.

As of EW 39 of 2018, preliminary results of the mass vaccination campaign against yellow fever indicate that 13.3 million people in São Paulo, 6.5 million in Rio de Janeiro, and 1.85 million in Bahia states were vaccinated, which represents vaccination coverage of 53.6%, 55.6% and 55.0%, respectively.³

In **Colombia**, between EW 1 and EW 36 of 2018, a laboratory-confirmed case of yellow fever was reported. The case is a 21-year-old male of the Desano indigenous community from Mitú Municipality, Vaupés Department. Symptom onset was in EW 35 of 2018 and the case died in EW 36. The case was confirmed for yellow fever by ELISA IgM and immunohistochemical testing of liver samples.

The last reported case of yellow fever in this department was in 2016 in Caruru Municipality. Yellow fever vaccination coverage for children under 18 months of age is 81.2% in Vaupés Department and 89.9% in Mitú Municipality.

In **French Guiana**, in EW 32 of 2018, a confirmed case of yellow fever was reported who had symptom onset in EW 31. The case is a 47-year-old male with a history of stay in the forest in Roura, French Guiana. The case was hospitalized in Cayenne, French Guiana, and in EW 32 presented with fulminant hepatitis and was transferred to Paris, France, for a liver transplant. The case was confirmed for yellow fever by PCR.

In **Peru**, between EW 1 and EW 45 of 2018, there were 15 cases of yellow fever reported, of which 9 were laboratory-confirmed and the remaining 6 are under investigation. This figure is higher than those reported during the same period of 2017, when 6 yellow fever cases were reported.

In 2018, the confirmed cases are from the departments with forests: Loreto, San Martín, Ucayali, and Madre de Dios.

Advice for national authorities

The continued occurrence of epizootics in Brazil in the months when climatic conditions are less favorable to the circulation of the virus (June to November) is cause for concern and indicates that the risk of transmission to unvaccinated humans persists; accordingly, PAHO/WHO encourages Member States with areas at-risk for yellow fever to continue efforts to immunize the at-risk populations and take the necessary actions to keep travelers informed and vaccinate prior to traveling to areas where yellow fever vaccination is recommended.

On 16 January 2018, new recommendations for yellow fever vaccination for international travelers were published, available at: <https://bit.ly/2B8LT1T>

Updated guidelines related to laboratory diagnosis and vaccinations are shared below.

³ It should be noted that these figures include 11.3 million people vaccinated in the three states prior to the start of the mass vaccination campaign, which began on 25 January 2018 in São Paulo and Rio de Janeiro and on 19 February 2018 in Bahia.

Laboratory diagnosis

The diagnosis of yellow fever is performed through virological and/or serological techniques. Serum is used for diagnosis and, for fatal cases, tissue samples can also be used. All laboratory personnel who come in contact with biological samples should be vaccinated against yellow fever and use appropriate personal protective equipment. As with other laboratory test, results should be considered in the epidemiological and clinical context.

Virological diagnosis

- *Molecular diagnostics:* It is possible to detect viral ribonucleic acid (RNA) in serum samples during the first 10 days following onset of symptoms (or even more than 10 days in severe cases) using the conventional RT-PCR test or in real time. A positive result by molecular testing (when using the appropriate controls and interpretation) confirms the diagnosis of yellow fever virus infection.
- *Post-mortem diagnosis:* In fatal cases, it is recommended to take tissue samples (preferably liver, kidney, spleen, brain, lung, heart, and lymph nodes) for histopathological and immunohistochemical analysis. Additionally, molecular diagnostic methods using fresh tissue (taken in dry tube and preserved by refrigeration) or fixed in formalin (embedded in paraffin) can be used for the confirmation of fatal cases or to perform differential diagnosis.
- *Viral isolation:* Viral isolation can be performed in cell culture (usually in Vero or C6/36 cells) or by intracerebral inoculation in suckling mice. Because of its complexity, this methodology is rarely used as a first-line diagnostic tool and is recommended only for research studies or as complementary characterization to public health surveillance.

Serological diagnosis

- *IgM detection:* Anti-yellow fever virus IgM antibodies can be detected by MAC-ELISA or another immunoassay from the sixth day after onset of symptoms. Currently, there are no commercial IgM ELISA kits validated for the detection of yellow fever. Therefore, in-house protocols using purified complete antigens are widely used. As with other IgM tests, a positive result in a single sample is presumptive of an acute infection. Laboratory confirmation requires seroconversion in paired samples (acute and convalescent specimens taken at least a week apart) in the absence of seroconversion for other relevant flaviviruses.
- *Cross-reactivity:* Serological cross-reactivity with other flaviviruses (such as dengue and Zika viruses) has been documented. Therefore, it is recommended to perform the detection of antibodies by ELISA for other flaviviruses in parallel. A positive result for yellow fever IgM in the absence of IgM for other relevant flaviviruses will be presumptive of yellow fever virus infection. However, a positive result for yellow fever combined with a positive result for another flavivirus can only be inferred as a recent infection by a flavivirus and does not confirm any etiologic agent. For this reason, the results should be analyzed taking into account the clinical characteristics and the epidemiological context of the case.

- *Post-vaccine immune response*: In areas where active vaccination campaigns are implemented, post-vaccine antibodies can be detected. Vaccination induces an immune response that cannot be differentiated from the response induced by a natural infection. Thus, an IgM vaccine response can be detected around day 5 and onwards, with a peak that generally occurs 2 weeks after vaccination. Subsequently, the levels of these antibodies tend to decrease. Therefore, the interpretation of serological results in vaccinated persons, particularly those that have been recently vaccinated, is complex and the results should be carefully assessed.
- *Adverse events following immunization (AEFI)*: In recently vaccinated persons who develop classic symptoms of yellow fever, surveillance should focus on differentiating between infections by wild virus and those due to the vaccine strain. Severe AEFI associated with the vaccine are rare (about 1.6 cases per 100,000 doses of vaccine applied). In areas where yellow fever virus circulates, the differentiation between infections due to wild virus and AEFI requires the implementation of sequencing techniques.
- *Other serological techniques*: For example, the detection of IgG antibodies by ELISA and neutralizing antibodies by plaque reduction neutralization technique (PRNT). In general, PRNT offers better specificity than the detection of total IgM and IgG antibodies. However, cross-reactivity between flaviviruses in neutralization assays has also been documented. Thus, it is recommended to perform this technique with a flavivirus panel.

The algorithms for laboratory confirmation, as well as additional information on diagnostic techniques and their interpretation, are available in the document, *Laboratory Diagnosis of Yellow Fever Virus infection* (PAHO/WHO, September 2018), at: <https://bit.ly/2zuEwE0>

Vaccination

The yellow fever vaccine is safe and affordable and provides effective immunity against the disease in the range of 80-100% of those vaccinated after 10 days and 99% immunity after 30 days. A single dose is enough to confer immunity and provide life-long protection against yellow fever disease, without the need for a booster dose.

PAHO/WHO reiterates its recommendations to national authorities:

1. Implement **universal vaccination** in children in endemic countries at 12 months of age, administered simultaneously with the measles, mumps, and rubella (MMR) vaccine.
2. Endemic countries that have planned follow-up campaigns for Measles/Rubella among children under 5 years of age should take the opportunity to **integrate** vaccination for yellow fever and administer these two vaccines simultaneously.
3. Update a **risk assessment** to guide vaccination and control measures. The updated risk assessment should take into account changes in ecological factors, migration patterns, vaccination, socio-economic activities, as well as the risk of re-urbanization.

4. Vaccination of the population living in at-risk areas, reaching **at least 95%** coverage among residents in these areas (urban, rural, and jungle), through different strategies:
 - a. At the intramural level, make rational use of the vaccine and avoid missed opportunities for vaccination.
 - b. At the extramural level, when there is greater availability of the yellow fever vaccine, countries should conduct catch-up campaigns, identifying sub-vaccinated populations and sub-optimal age groups; for example, young men who do not readily accept vaccination.
5. Ensure vaccination of **all travelers to at-risk areas** at least 10 days before traveling.
6. Member States should have a **vaccine reserve stock** to respond to outbreaks.

Precautions

It is recommended to individually assess the epidemiological risk of contracting disease when faced with the risk of an adverse event occurring in persons over 60 years who have not been previously vaccinated.

- The vaccine can be offered to individuals with asymptomatic HIV infection with CD4+ counts ≥ 200 cells / mm³ requiring vaccination.
- Pregnant women should be vaccinated in emergency epidemiological situations and following the explicit recommendations of health authorities.
- Vaccination is recommended in nursing women who live in endemic areas, since the potential risk of transmitting the vaccine virus to the child is far lower than the benefits of breastfeeding.
- For pregnant or lactating women traveling to areas with yellow fever transmission, vaccination is recommended when travel cannot be postponed or avoided. They should receive advice on the potential benefits and risks of vaccination to make an informed decision. The benefits of breastfeeding are superior to those of other nutritional alternatives.

The following are usually excluded from yellow fever vaccination:

- Immunocompromised individuals (including those with thymus disorders, symptomatic HIV, malignant neoplasms under treatment, and those that are receiving or have received immunosuppressive or immunomodulatory treatments, recent transplants, and current or recent radiation therapy).
- People with severe allergies to eggs and their derivatives.

Sources of information

- Bolivia Ministry of Health, Epidemiological Reports. Available at: <https://bit.ly/2SdXZQd>
- Brazil Ministry of Health. Yellow Fever Reports. Available at: <http://bit.ly/2sq3aV6>
- Colombia International Health Regulations (IHR) IHR National Focal Point (NFP)
- France International Health Regulations (IHR) IHR National Focal Point (NFP)
- Peru Ministry of Health. Situation room for the Health Situation Analysis: Yellow fever. Available at: <https://bit.ly/2LbENZV>

Related Links

- PAHO/WHO Yellow Fever. Available at: <https://bit.ly/2P66Ph9>
- PAHO/WHO. Guidance on Laboratory Diagnosis of Yellow Fever Virus Infection. Available at: <https://bit.ly/2zMYTfZ>
- PAHO/WHO. Requirements for the International Certificate of Vaccination or Prophylaxis (ICVP) with proof of vaccination against yellow fever. Available at: <https://bit.ly/2BbNaoV>