Epidemiological Alert Yellow fever in the Americas Region

13 March 2026

Since September 2024, cases of yellow fever have been reported in areas with no history of transmission, including cases identified outside the Amazon region. In response to this situation, the Pan American Health Organization / World Health Organization (PAHO / WHO) is reinforcing its call to Member States to strengthen surveillance, intensify vaccination of at-risk populations, and take the necessary measures to ensure that people traveling to areas with reported cases are properly informed and protected against yellow fever. In addition, it highlights the need to strengthen clinical management, with an emphasis on the detection and timely treatment of severe cases. PAHO/WHO also recommends having reserve doses available, according to the availability of vaccines in each country, to ensure a rapid response to possible outbreaks.

Summary of the situation

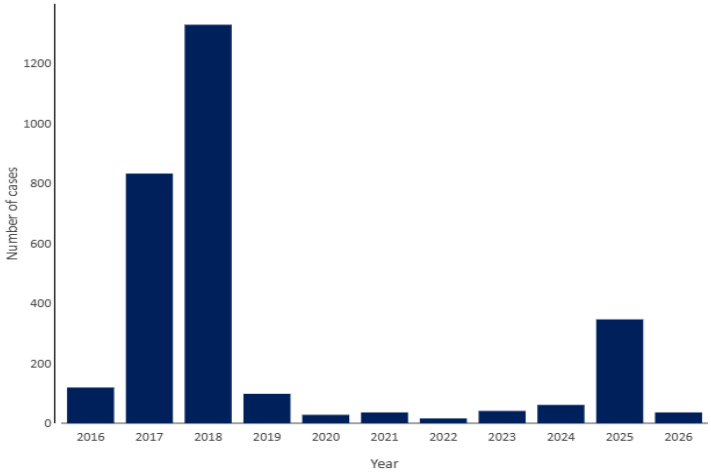
Between epidemiological week (EW) 1 and EW 53 of 2025, 346 confirmed human cases of yellow fever were reported in seven countries in the Americas Region, including 143 deaths (case fatality rate [CFR] 41%) *(1-10)*. This represents a 5.6-fold increase compared with 2024, when 61 confirmed cases of yellow fever were reported (**Figure 1**). In 2025, cases were reported in: the Plurinational State of Bolivia (n= 8 cases, including two deaths), Brazil (n= 120 cases, including 48 deaths), Colombia (n= 125 cases, including 46 deaths), Ecuador (n= 11 cases, including eight deaths), Guyana (one death), Peru (n= 49 cases, including 19 deaths), and the Bolivarian Republic of Venezuela (n= 32 cases, including 19 deaths) (**Figure 2**) *(1-10)*.

In 2026, between EW 1 and EW 7, 34 confirmed human cases of yellow fever were reported in four countries in the Americas Region, including 15 deaths (CFR: 44%) *(1-10)*. Cases were reported in: the Plurinational State of Bolivia (one death), Colombia (n= 25 cases, including 13 deaths), Peru (n= 2 cases), and Venezuela (n= 6 cases, including one death) (**Figure 2**) *(1-10)*.

Compared to the annual number of cases reported in the Americas between 1960 and 2024, the number of cases reported in 2025 is high, but similar to that observed in other years with high incidence, such as 1966 (n= 304 cases), 1998 (n= 280 cases), and 2003 (n= 243 cases) *(11)*.

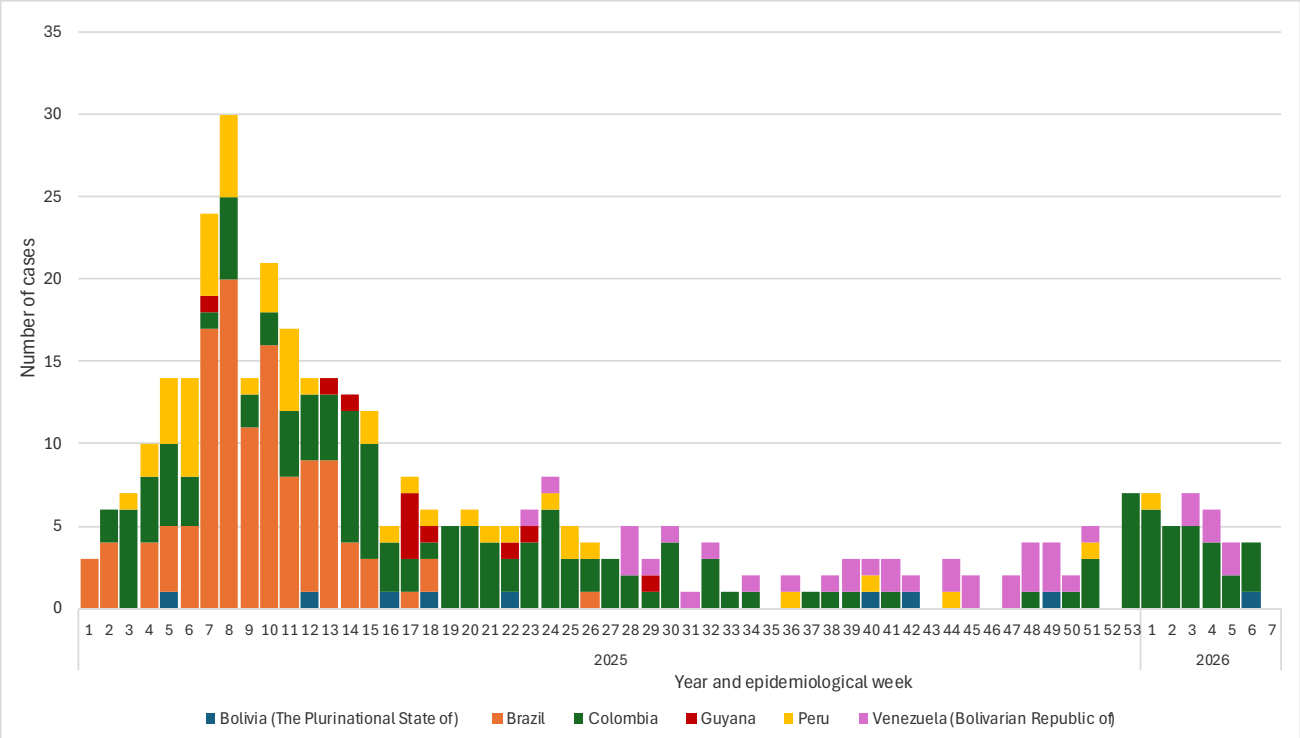
Suggested citation: Pan American Health Organization/World Health Organization. Epidemiological Alert: Yellow fever in the Americas Region, 13 March 2026. Washington, D.C.: PAHO/WHO; 2026.

Figure 1. Confirmed cases of yellow fever in humans by year in the Americas Region, between 2016 and 2026.



Source: Pan American Health Organization. Yellow Fever Dashboard in the Americas Region. Washington, D.C.: PAHO; 2025 [cited 5 March 2026]. Available from: https://shiny.paho-phe.org/yellowfever/. *(11)*.

Figure 2. Confirmed cases of yellow fever in humans by country and epidemiological week (EW) of symptom onset in the Americas Region*, EW 1 of 2025 to EW 7 of 2026.



***Note**: Includes only cases for which information on symptom onset by epidemiological week is available.

Source: Adapted from data provided by countries or published by ministries of health *(1-10)*.

Occurrence of cases outside the Amazon region

Since mid-2024, human cases of yellow fever have been observed in a wider geographical area than in previous years, including mountain forest areas in Colombia (Bosque de Galilea Regional Natural Park, on the western slope of the Eastern Cordillera connecting with the Sumapaz páramo) (**Figure 3 and Figure 4**) *(4, 12)*.

In Brazil, most human cases, during 2025, were reported in 29 municipalities in six regions of the state of São Paulo: Araracuara (two municipalities), Campinas (eight municipalities), Macro Metropolitana Paulista (eight municipalities), Piracicaba (two municipalities), São José do Rio Preto (one municipality), and Vale do Paraíba Paulista (eight municipalities) (**Figure 3**) *(2)*.

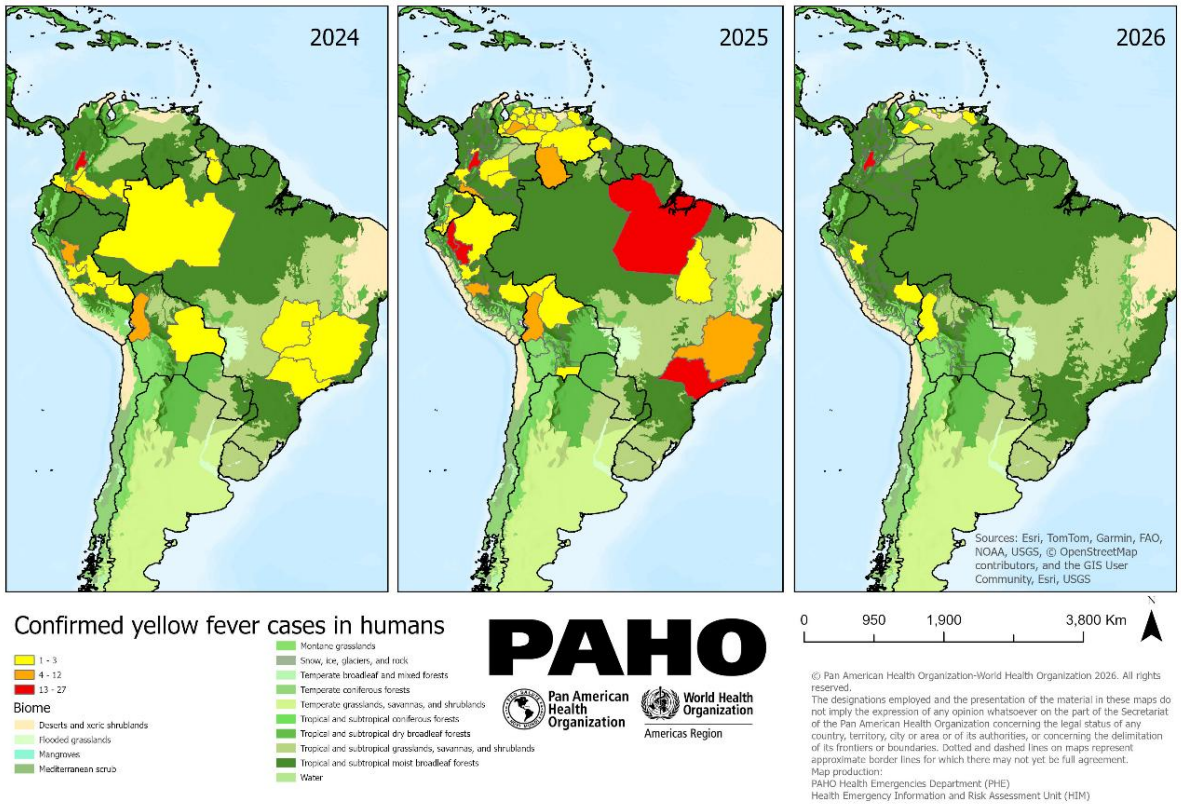
In 2025, a similar situation was reported in Venezuela with cases of yellow fever in humans occurring in an expanded geographical area that included 22 parishes that had not previously been classified as risk areas in four states of the country (Aragua, Barinas, Lara, and Portuguesa). The states close to the expansive enzootic wave of San Camilo (Apure, Táchira, Lara, Mérida, Barinas, Portuguesa, Cojedes, and Guárico) accounted for 61% of the cases reported in 2025 (**Figure 3 y Figure 4**) *(13)*.

In 2026, cases were mainly reported in Colombia in the department of Tolima and in Venezuela in the states of Aragua, Barinas, Lara, and Monagas (**Figure 3 y Figure 4**) *(1-13)*.

Overall, the report of yellow fever cases in an extended area of the continent highlights the ongoing spread of the sylvatic cycle in forest edges, where human activities intersect with highly biodiverse ecosystems. These areas provide ideal conditions for canopy-dwelling mosquitoes to transmit the virus to human populations from nonhuman reservoirs *(14, 15)*.

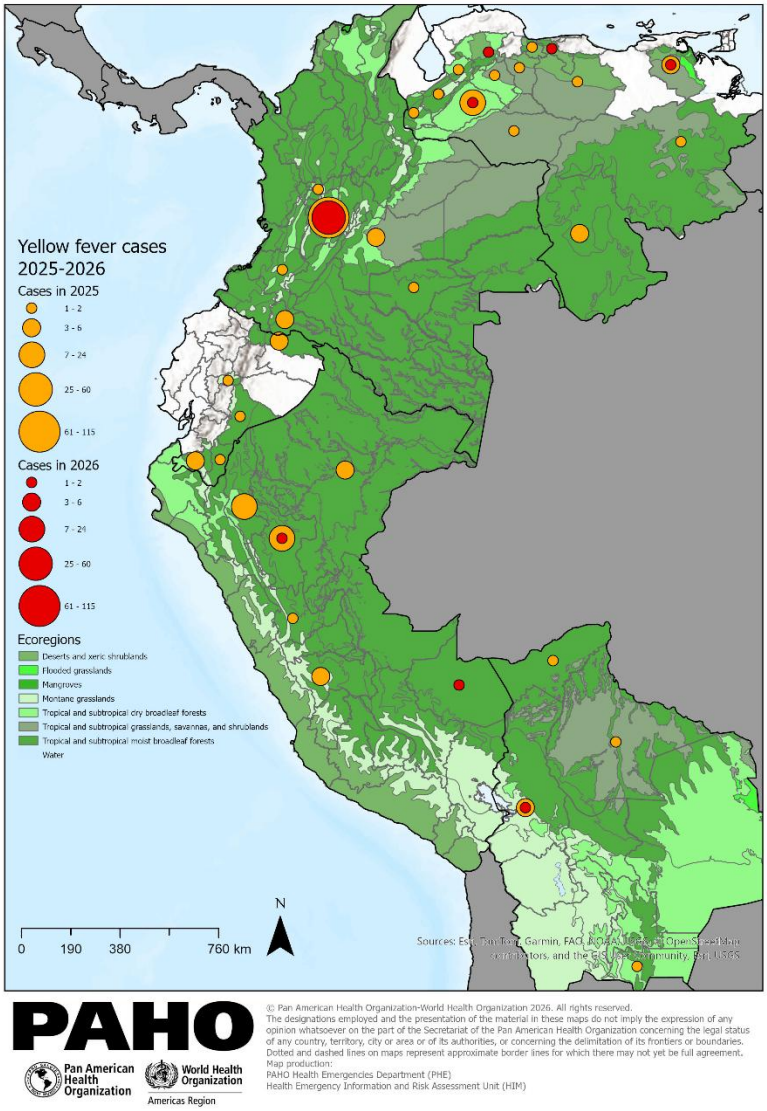
The detection of cases associated with sylvatic transmission in areas close to urban centers increases the risk of establishing urban transmission cycles *(14, 15)*.

Figure 3. Confirmed cases of yellow fever in humans by year in the Americas Region, between 2023 and 2026 (as of EW 7 of 2026).



Source: Adapted from data provided by countries or published by ministries of health *(1-10)*.

Figure 4. Confirmed cases of yellow fever in humans in Bolivia, Colombia, Ecuador, Peru, and Venezuela, 2025-2026 (as of EW 7 of 2026).



Source: Adapted from data provided by countries or published by Ministries of Health *(1-10)*.

The public health risk assessment related to the yellow fever situation in the Americas Region conducted by PAHO in February 2025 and updated in May of that same year, classified the **overall risk in the Americas as "High"**. Factors contributing to this assessment include the increase in the number of cases, high case fatality rates, and the spread to areas that had not previously reported circulation of the virus *(16)*.

The epidemiological situation of yellow fever in the countries that have reported confirmed cases between 2025 and 2026 is presented below, in alphabetical order.

In **Bolivia**, between EW 1 and EW 53 of 2025, eight confirmed cases of yellow fever in humans were reported, including two deaths (CFR: 25%). The cases were reported in the departments of Beni (n= 2 cases), La Paz (n= 4 cases, including two deaths), Pando (n= 1 case), and Tarija (n= 1 case) *(1)*.

The probable places of exposure were the municipalities of Rurrenabaque (n= 2 cases), department of Beni; the municipalities of Palos Blancos (n= 2 cases) and Guanay (n= 2 cases) in the department of La Paz; in the municipality of Tarija (n= 1 case), in the department of Tarija; and in the municipality of Santa Rosa (n= 1 case), in the department of Pando *(1)*.

Sixty-two percent of the cases reported in 2025 were in males (n= 5 cases). The ages of the cases ranged between 7 months and 46 years. Six of the cases reported a history of yellow fever vaccination, and the two deaths occurred in unvaccinated cases *(1)*.

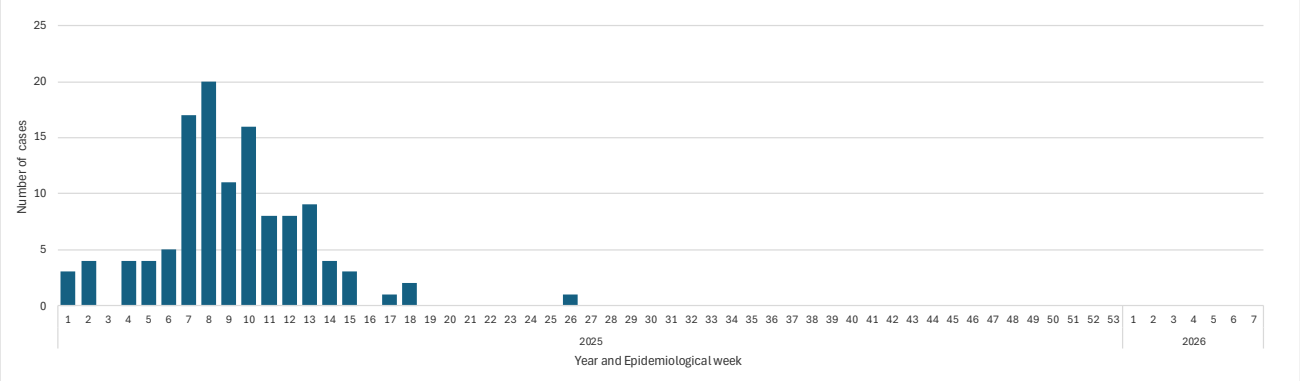
In addition, three epizootics were confirmed during 2025: two in the department of La Paz, specifically in the municipalities of San Buenaventura and Coroico, and one in the department of Beni, in the municipality of Rurrenabaque *(1)*.

Between EW 1 and EW 7 of 2026, one death due to yellow fever was reported. The case occurred in Apolo municipality, La Paz department. The patient was a 20-year-old male with a history of travel to endemic forested areas, consistent with exposure to the sylvatic cycle of the disease. The case had no history of yellow fever vaccination. During the same period, no epizootics in non-human primates were reported *(1)*.

In **Brazil**, in 2025, 120 confirmed cases of yellow fever in humans were reported, including 48 deaths (CFR: 40%) (**Figure 5**). Cases were reported in the states of Minas Gerais (n= 12 cases, including five deaths), Pará (n= 46 cases, including seven deaths), São Paulo (n= 61 cases, including 35 deaths), and Tocantins (one death) (**Figure 6**) *(2, 3)*.

Eighty-nine percent of the cases reported in 2025 were in males (n= 107 cases). The cases ranged between 10 to 85 years of age, and symptoms began between 2 January and 22 June 2025. Only one of the cases had a history of yellow fever vaccination *(2, 3)*.

Figure 5. Human yellow fever cases by epidemiological week of symptom onset in Brazil, 2025 - 2026 (as of EW 7 of 2026).



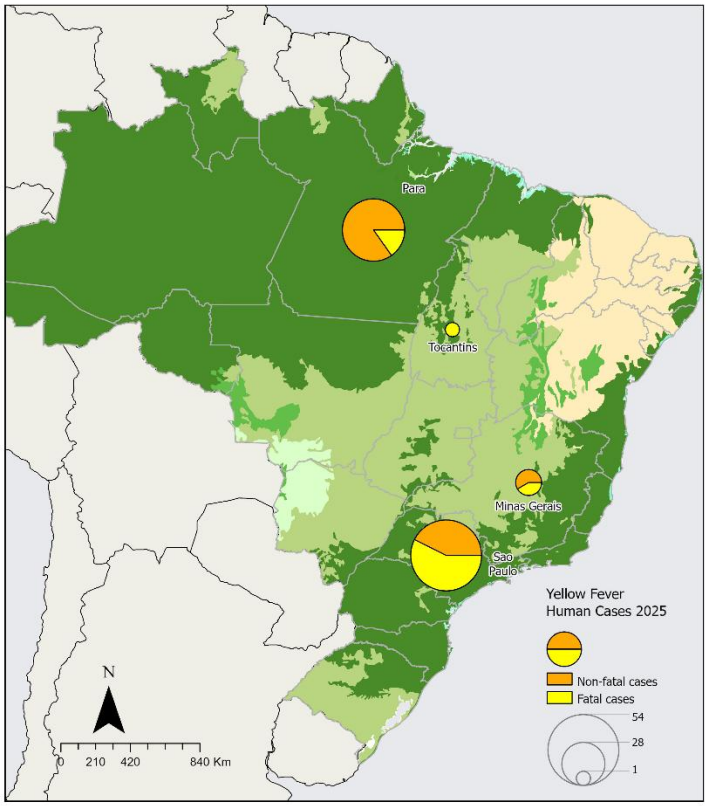
Source: Adapted from data provided by the International Health Regulations (IHR) National Focal Point (NFP) in Brazil *(2)*.

The probable places of exposure of the cases reported in 2025 were reported in the state of Minas Gerais, in the municipalities of Cambuí (n= 1 case), Carmo de Minas (n= 2 cases), Extrema (n= 1 case), Gonçalves (n= 1 case), Maria da Fé (n= 1 case), Monte Sião (n= 1 case), Poços de Caldas (n= 1 case), Pouso Alegre (n= 1 case), Sapucaí-Mirim (n= 1 case), Silvianópolis (n= 1 case), and Soledade de Minas (n= 1 case); in the state of Pará, to the municipalities of Afuá (n= 1 case), Breves (n= 44 cases) and Cametá (n= 1 case); in the state of São Paulo, in the

municipalities of Águas de Lindóia (n= 1 case), Amparo (n= 2 cases), Bragança Paulista (n= 3 cases), Brotas (n= 3 cases), Caçapava (n= 6 cases), Campinas (n= 3 cases), Itatiba (n= 1 case), Itirapina (n= 1 case), Jambeiro (n= 3 cases), Joanópolis (n= 9 cases), Jundiaí (n= 2 cases), Monteiro Lobato (n= 1 case), Nazaré Paulista (n= 4 cases), Paraibuna (n= 1 case), Pedra Bela (n= 2 cases), Pedreira (n= 2 cases), Pindamonhangaba (n= 1 case), Piracaia (n= 3 cases), Redenção da Serra (n= 1 case), Santa Rita do Passa Quatro (n= 1 case), São Carlos (n= 1 case), São José dos Campos (n= 1 case), São Pedro (n= 1 case), Socorro (n= 3 cases), Taubaté (n= 1 case), Tuiuti (n= 1 case), Valinhos (n= 1 case), Vargem (n= 1 case), and Vinhedo (n= 1 case); and in the state of Tocantins, in the municipality of Monte do Carmo (n= 1 case) (**Figure 6**)*(2)*.

All cases had a history of exposure in jungle and/or forested areas associated with occupational or recreational activities and were laboratory confirmed. The date of symptom onset of the last confirmed case in Brazil was 22 June 2025. Since then, and up to EW 7 of 2026, no additional yellow fever cases have been confirmed in Brazil *(2, 3)*.

Figure 6. Human yellow fever cases by state in Brazil, 2025 (as of EW 53).



Source: Adapted from data provided by the Brazil International Health Regulations (IHR) National Focal Point (NFP) *(2)*.

During 2025, 124 epizootics of yellow fever in non-human primates were confirmed in Brazil. Of these, 70 were reported in the state of São Paulo, 38 in the state of Goiás, and 16 in the state of Minas Gerais. Between EW 1 and EW 7 of 2026, there were no confirmed epizootics *(2, 3)*.

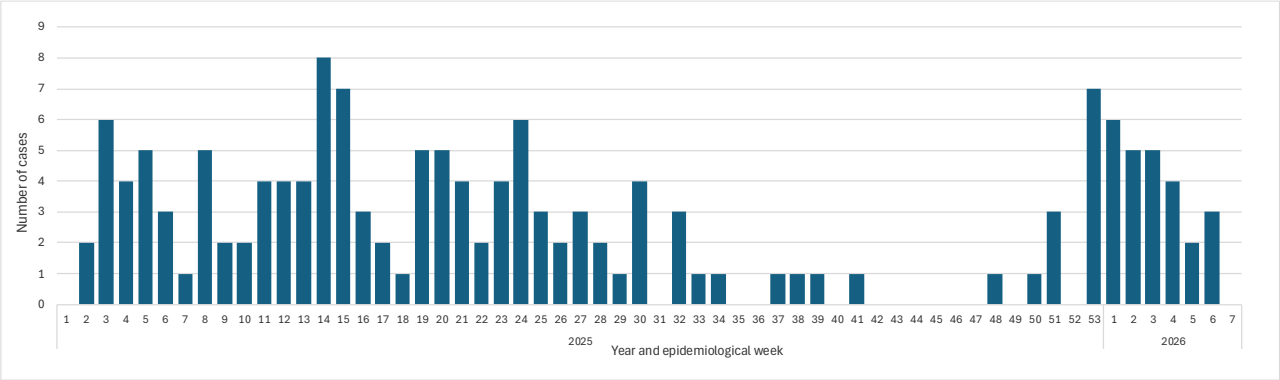
In **Colombia**, between EW 1 and EW 53 of 2025, 125 confirmed cases of yellow fever in humans were reported, and three cases originating abroad; including 46 deaths[1] confirmed for yellow fever (CFR: 37%) (**Figure 7**). The cases were reported in the departments of Caldas (one death), Cauca (one death), Guaviare (one death), Meta (three deaths), Putumayo (n= 4 cases, including two deaths), and Tolima (n= 115 cases, including 43 deaths) *(4, 5)*.

The probable places of exposure were the municipality of Neira (n= 1 case) in the department of Caldas; the municipality of Piamonte (n= 1 case) in the department of Cauca; the municipalities of Granada (n= 1 case), La Macarena (n= 1 case), and San Martin (n= 1 case) in the department of Meta; the municipalities of Orito (n= 3 cases) and Villagarzón (n= 1 case) in the department of Putumayo; the municipalities of Ataco (n= 27 cases), Chaparral (n= 11 cases), Cunday (n= 20 cases), Dolores (n= 4 cases), Espinal (n= 1 case), Ibagué (n= 1 case), Palocabildo (n= 1 case), Prado (n= 18 cases), Purificación (n= 6 cases), Rioblanco (n= 8 cases), Valle de San Juan (n= 1 case), and Villarica (n= 17 cases) in the department of Tolima (**Figure 8**) *(4, 5)*.

Eighty percent of the cases were male (n= 100 cases). The ages of the cases ranged from under one year to over 80 years. All cases had a history of exposure to areas at risk for yellow fever *(4)*.

Between EW 1 and EW 7 of 2026, 25 confirmed cases were reported, including 13 deaths (CFR: 52%); all cases were reported in the department of Tolima *(4, 5)*.

Figure 7. Human yellow fever cases by year and epidemiological week of symptom onset in Colombia, 2025-2026 (as of EW 7 of 2026).



Source: Adapted from data provided by the Colombia International Health Regulations (IHR) National Focal Point (NFP) *(4)*.

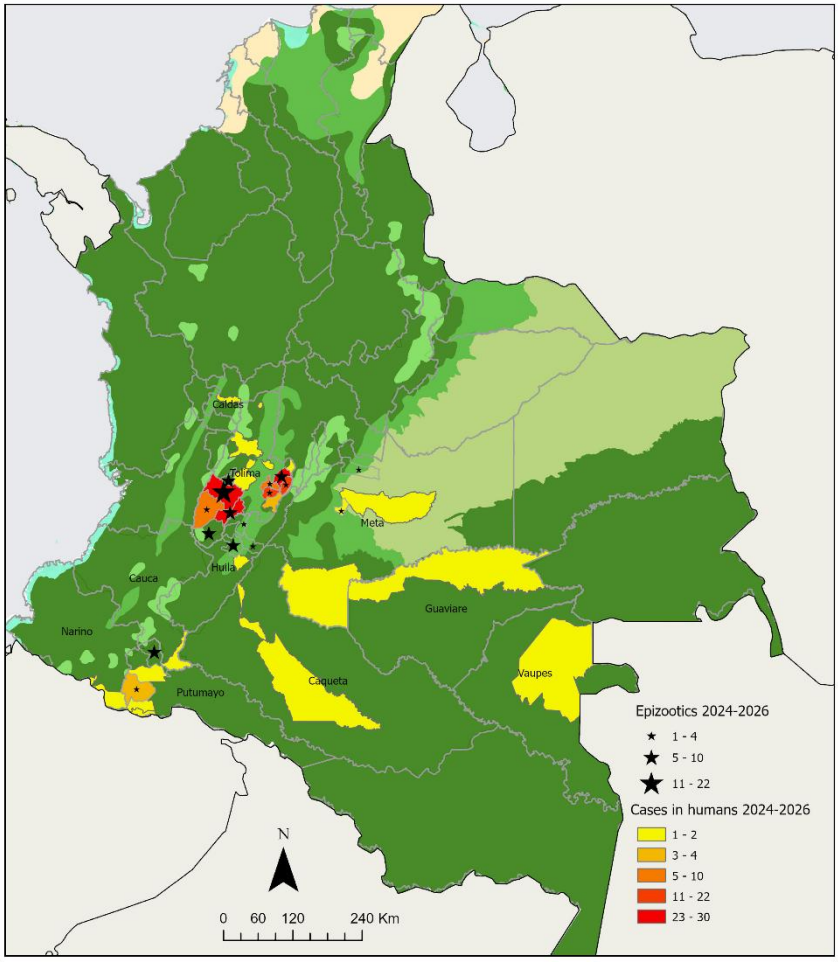
In the current outbreak in the department of Tolima, between 2024 and 2026, 153 confirmed human cases of yellow fever were reported, including 62 deaths (CFR: 41%). This outbreak, which began in EW 37 of 2024 and continues throughout 2025 and 2026, started in the rural area adjacent to the southwestern part of the Bosque de Galilea Regional Natural Park, continuing into the Magdalena Valley, and has affected thirteen municipalities identified as high risk: Ataco (n= 27 cases, including ten deaths), Chaparral (n= 27 cases, including nine deaths), Cunday (n= 30 cases, including 16 deaths), Dolores (n= 4 cases, including one death), Espinal (one death), Ibagué (n= 1 case), Ortega (n= 1 case), Palocabildo (n= 1 case), Prado (n= 20 cases, including seven deaths), Purificación (n= 8 cases, including five deaths), Rioblanco (n= 10 cases, including four deaths), Valle de San Juan (one death), and Villarica (n= 22 cases, including eight deaths). Seventy-eight percent of the cases were males (n= 120 cases), the ages of the cases ranged

[1] Of the total reported cases, 51 deaths were recorded; 46 were attributed to yellow fever, while five were related to other causes.

from 10 to 80 years and older, and the date of symptom onset was between 8 September 2024, and 13 February 2026 *(4, 5)*.

During 2025 and as of EW 7 of 2026, 82 epizootics of yellow fever were confirmed by laboratory criteria, 65 in the department of Tolima in the municipalities of Chaparral (n= 22), Ataco (n= 10), Cunday (n= 9), Planadas (n= 6), San Antonio (n= 5), Rioblanco (n= 4), Villarica (n= 3), Prado (n= 3), and Purificación (n= 3); eight in the department of Huila in the municipalities of Neiva (n= 3), Palermo (n= 3), and Aipe (n= 2); eight in the department of Putumayo in the municipalities of Mocoa (n= 6) and Orito (n= 2); and one in the department of Meta in the municipality of Villavicencio (n= 1) (**Figure 8**) *(4, 5)*.

Figure 8. Human yellow fever cases and confirmed yellow fever epizootics by department. Colombia, 2024-2026 (as of EW 7 of 2026).



Map production:
PAHO Health Emergencies Department (PHE)
Health Emergency Information and Risk Assessment Unit (HIM)

PAHO
Pan American Health Organization
World Health Organization
Americas Region

Source: Adapted from data provided by the International Health Regulations (IHR) National Focal Point (NFP) of Colombia *(4)*.

In **Ecuador**, between EW 1 and EW 31 of 2025, 11 confirmed cases of yellow fever in humans were reported, including eight deaths (CFR: 73%). The cases were reported in the provinces of

Morona Santiago (n= 2 cases, including one death), Sucumbios (n= 3 cases, including one death), and Zamora'Chinchipe (six deaths) *(6)*.

The probable places of exposure were the cantons of Sucúa (n= 1 case) and Taisha (n= 1 case) in the province of Morona Santiago; the cantons of Lago Agrio (n= 1 case), Gonzalo Pizarro (n= 1 case), and Putumayo (n= 1 case) in the province of Sucumbíos; and the cantons of Zamora (n= 2 cases), Nangaritza (n= 1 case), Yantzaza (n= 1 case), Centinela del Cóndor (n= 1 case), and Zuma (n= 1 case) in the province of Zamora-Chinchipe *(6)*.

Eighty-two percent of cases were male (n= 9 cases). The ages of the cases ranged from 13 to 71 years. Three of the cases reported a history of yellow fever vaccination. From EW 31 of 2025 to EW 7 of 2026, no confirmed cases or deaths were reported in Ecuador *(6)*.

In **Guyana**, one human death from yellow fever was reported in EW 39 of 2025. The likely place of exposure was the village of Sukapai, in the Cuyuni-Mazaruni region. The case had a history of yellow fever vaccination and was reported to have been exposed in areas at risk for yellow fever in the context of agricultural logging and mining activities. Since EW 39 of 2025, no suspected or confirmed cases have been reported *(7)*.

In **Peru**, between EW 1 and EW 53 of 2025, 49 confirmed cases of yellow fever were reported, including 19 deaths (CFR: 39%). The likely places of exposure were the departments of Amazonas (n= 24 cases, including nine deaths), Huánuco (one death), Junín (n= 6 cases), Loreto (n= 3 cases, including one death), Madre de Dios (one death), and San Martin (n= 14 cases, including seven deaths). Eighty percent of the cases were males (n= 39 cases). The ages of the cases ranged from 2 to 78 years *(8, 9)*.

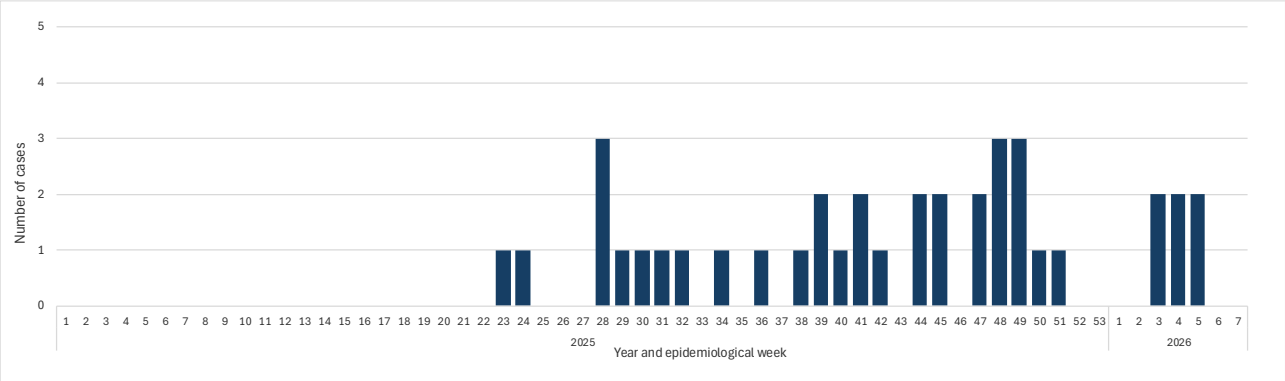
Between EW 1 and EW 7 of 2026, two cases were confirmed in the department of Madre de Dios; additionally, seven cases are under investigation in the departments of Cusco (n= 3 cases), Junín (n= 2 cases), Madre de Dios (n= 1 case), and San Martin (n= 1 case). No deaths were reported *(8, 9)*.

In **Venezuela**, between EW 1 and EW 53 of 2025, 32 confirmed cases of yellow fever in humans were reported, including 19 deaths (CFR: 59%). The probable places of exposure were the states of Amazonas (n= 4 cases, including one death), Apure (n= 2 cases, including one death), Barinas (n= 11 cases, including seven deaths), Bolívar (n= 2 cases, including one death), Carabobo (one death), Cojedes (one death), Guárico (one death), Lara (one death), Mérida (two deaths), Monagas (n= 3 cases), Portuguesa (n= 2 cases, including one death), Táchira (one death), and Trujillo (one death) (**Figure 9 y Figure 10**)*(10)*.

Sixty-three percent of the reported cases were males (n= 20 cases), and ages ranged between two and 70 years, with an average age of 36 years *(10)*.

Human cases spread to areas not considered risk zones within the states of Aragua, Barinas, Lara, and Portuguesa. Between EW 1 and EW 7 of 2026, six confirmed cases of yellow fever were reported, including one death (CFR: 17%). The probable place of exposure for the cases was the states of Aragua (n= 2 cases), Barinas (n= 1 case), Lara (one death), and Monagas (n= 2 cases) (**Figure 10**) *(10)*.

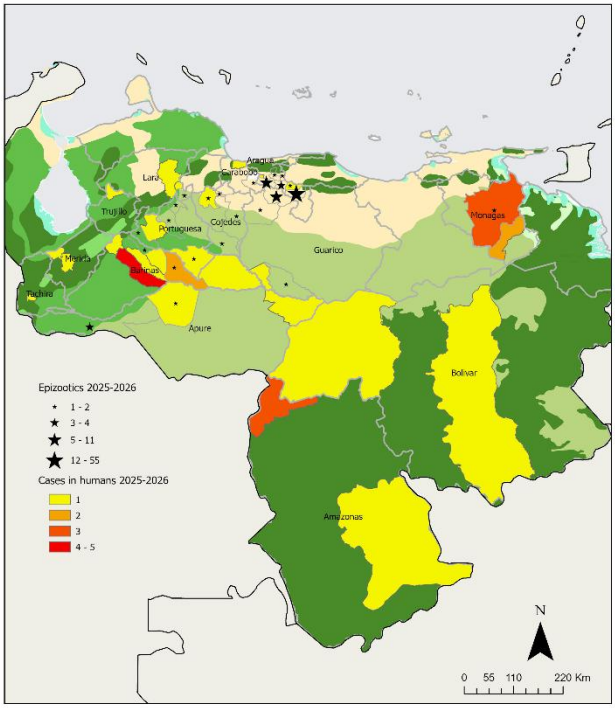
Figure 9. Human yellow fever cases by year and epidemiological week of symptom onset in Venezuela, 2025-2026 (as of EW 7 of 2026).



Source: Adapted from data provided by Venezuela International Health Regulations (IHR) National Focal Point (NFP) *(10)*.

During 2025, as of EW 53, 90 epizootics of yellow fever in non-human primates were reported in the states of: Apure (n= 3), Aragua (n= 66), Barinas (n= 2), Carabobo (n= 2), Cojedes (n= 2), Guárico (n= 7), Lara (n= 1), Portuguesa (n= 6), and Monagas (n= 1), of which eight epizootics were confirmed by laboratory testing. In 2026, as of EW 9, 19 epizootics in non-human primates were reported but not confirmed by laboratory testing in the states of Aragua (n= 8), Cojedes (n= 5), Apure (n= 2), and Guárico (n= 4) (**Figure 10**) *(10)*.

Figure 10. Cases of yellow fever in humans and confirmed epizootics of yellow fever by state. Venezuela, 2025-2026 (as of EW 7 of 2026).



Map production:
PAHO Health Emergencies Department (PHE)
Health Emergency Information and Risk Assessment Unit (HIM)

Source: Adapted from data provided by the Venezuela International Health Regulations (IHR) National Focal Point (NFP) *(10)*.

Recommendations for health authorities

In the Americas Region, the risk of yellow fever outbreaks is high. Although immunization remains one of the most effective public health interventions for preventing this disease, most cases of yellow fever in humans reported during 2024, 2025, and 2026 had no history of yellow fever vaccination. Adequate preparedness and response to yellow fever outbreaks requires the integration of several components in addition to vaccination; epizootic surveillance and entomological surveillance, vector control, and risk communication should be considered.

PAHO/WHO encourages Member States with risk areas to continue their surveillance and vaccination efforts in endemic areas. It is essential that countries achieve vaccination coverage of at least 95% in populations in risk areas, in a homogeneous manner, and that health authorities ensure that they have a strategic reserve inventory that allows them to maintain routine vaccination and, at the same time, respond effectively to possible outbreaks *(17)*.

The recommendations on epidemiological surveillance, laboratory diagnosis, clinical management, and vaccination are reminded below. Concerning vaccination, **new orientations are provided for preventive or update campaigns, as well as vaccination during outbreak response**.

Epidemiological surveillance

Member States with areas at risk for yellow fever are recommended to implement the following strategies to strengthen surveillance *(15)*:

- Issue epidemiological alerts to municipalities and health services, with an emphasis on case definitions. Case notification should be immediate, even if the case is suspected and regardless of yellow fever vaccination status.
- Conduct an active search for cases with symptoms compatible with the definition of a suspected case and/or with acute febrile icteric syndrome in the areas where cases have occurred, as well as in the surrounding municipalities and places visited by the cases during the 3 to 6 days prior to the onset of the disease.
- Conduct retrospective investigations of death certificates to identify possible cases compatible with the case definition.
- Intensify epizootic surveillance activities, given that the death of non-human primates can serve as an early warning to identify the circulation of yellow fever, which would indicate the need to reinforce vaccination activities, especially in areas where human cases have not yet been detected. In areas with confirmed transmission, efforts to identify locally involved vectors and primates can provide valuable information to support risk communication, health education, and targeted vaccination activities.
- If possible, geo-reference the points of occurrence of death of non-human primates and the probable place of exposure of human cases to establish the "ecological corridors" of yellow fever in order to identify the areas of greatest risk to anticipate preventive measures and optimize vaccination actions Collaborate with the agricultural sector and involve companies that employ workers in activities involving exposure to forest areas to implement health communication measures. It is recommended to act based on the support of community surveillance in areas considered to be at higher risk.

Epizootic surveillance

Epizootic surveillance in non-human primates is a key component in strengthening yellow fever surveillance, as they act as natural sentinels for viral activity in their sylvatic cycle. Early detection and confirmation of mortality or disease in primates allows for the identification of viral circulation before cases occur in humans, facilitating the timely activation of response measures, such as intensified epidemiological surveillance in humans, field investigation, vector control, and, especially, preventive vaccination in at-risk populations. In this regard, systematic surveillance of epizootics, integrated under a One Health approach, strengthens the capacity of health systems to anticipate and prevent outbreaks, reducing the risk of transmission and the occurrence of human cases of yellow fever *(14, 15)*.

Laboratory diagnosis

The diagnosis of yellow fever is mainly carried out using virological methods (detection of the virus or genetic material in serum or tissue) or, in some cases, serological tests to detect antibodies *(18)*.

Virological diagnosis

- ***Molecular detection:*** During the first 5 days after the onset of symptoms (viremic phase), it is possible to detect viral RNA from serum using molecular techniques such as conventional or real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR). Sometimes, viral RNA can be detected for up to 10 days (or more) from the onset of symptoms. For this reason, it is recommended that PCR be performed on samples taken up to 10 days after the onset of symptoms. A positive PCR result (in the presence of adequate controls) confirms the diagnosis regardless of the day on which the sample was taken *(18)*. It is important to note that in patients who have recently been vaccinated against yellow fever (within the last 10 days prior to sample collection), a positive result may indicate detection of the vaccine virus. In this scenario, a positive sample should be further processed using a differential PCR protocol to exclude or confirm the presence of the vaccine virus.
- ***Post-mortem* diagnosis*:*** Histopathological study with immunohistochemistry on liver sections is the "gold standard" for the diagnosis of yellow fever in fatal cases. Additionally, molecular methods using fresh or paraffin-preserved tissue samples can also be used to confirm cases. Detection can be performed under BSL2 (biosafety level 2) containment conditions *(18)*.

Serological diagnosis

Serology (detection of specific antibodies) is useful for diagnosing yellow fever during the post-viremic phase of the disease (i.e., from day 5 after the onset of symptoms); however, serology should only be considered if PCR results (in samples up to 10 days old) are negative *(18)*.

A positive IgM result using the ELISA technique (mainly IgM capture, MAC-ELISA) or any other immunoassay (indirect immunofluorescence) in a sample taken from the fifth day after the onset of symptoms is prescriptive of recent infection with the yellow fever virus. Currently, there are no validated commercial kits for IgM detection by ELISA. Therefore, *in-house* procedures using purified whole antigen can be standardized *(18)*.

Confirmation of a case of yellow fever by ELISA IgM will depend on the epidemiological situation and the results of the differential laboratory diagnosis. Thus, in areas with circulation of other flaviviruses (mainly dengue and Zika), the probability of cross-reactivity is higher.

Other serological techniques include IgG detection by ELISA and neutralizing antibody detection by plaque reduction neutralization test (PRNT). The IgG ELISA is useful with paired samples (taken at least one week apart), while the PRNT (90%) can be useful with paired samples or with a single post-viremic sample as long as the assay includes multiple flaviviruses *(18)*.

A seroconversion (negative result in the first sample and positive in the second), a more than 4-fold increase in antibody titers in paired samples, or detectable titers of antibodies against yellow fever in a post-viremic sample (PRNT 90%) is presumptive of yellow fever infection. Confirmation of a case of yellow fever using these techniques will depend on the epidemiological situation and the differential laboratory result, since in areas of co-circulation with other flaviviruses, the possibility of cross-reactivity is greater *(18)*.

Also, in areas where active vaccination campaigns are carried out, the detection of postvaccination antibodies may occur, so the diagnosis must be carefully interpreted *(18)*.

Interpretation of serology results and differential diagnosis

The cross-reactivity of serological techniques observed mainly in secondary flavivirus infections should be considered in areas where co-circulation of yellow fever virus with other flaviviruses (dengue, St. Louis encephalitis, Zika, and others of the Japanese encephalitis complex) is documented and there is a likelihood that the population has been previously infected. It should also be noted that in individuals previously vaccinated against yellow fever, vaccine-induced IgM can be detected for several months or even years *(18)*.

Therefore, it is recommended to perform antibody detection for other flaviviruses in parallel and to interpret the results carefully, taking into account the vaccination history and available epidemiological information *(18)*.

In general, the plaque reduction neutralization test (PRNT) offers greater specificity than IgM and IgG detection. However, cross-reactivity has also been documented for neutralization assays, so it is also recommended that this technique be performed using antigens for several flaviviruses *(18)*.

On the other hand, the differential diagnosis of yellow fever should include other febrile and febrile-icteric syndromes such as dengue, leptospirosis, malaria, viral hepatitis, among others, depending on the epidemiological profile of the affected country or area.

A case of yellow fever will be confirmed by serological techniques only if the laboratory differential diagnosis, taking into account the epidemiological profile of the country, is negative for other flaviviruses.

Post-vaccination immune response

Vaccination induces a relatively low viremia that decreases after 4 to 7 days. Simultaneously, an IgM-type response develops that cannot be differentiated from the IgM response induced by natural infection. Approximately 10 days after vaccination, the person is considered protected against natural infection. Thus, the vaccine IgM response can be detected around

day 5 onwards, with a peak generally occurring two weeks after vaccination. Subsequently, the levels of these antibodies tend to decrease. In a significant proportion of vaccinated individuals, the IgM response can be detected for up to one month after vaccination, and in some cases (mainly travelers), even for up to 3-4 years. On the other hand, neutralizing antibodies induced by vaccination can be detected for several decades. All of this makes the interpretation of serological results in vaccinated individuals complex, particularly those who have been vaccinated recently, and therefore the results must be evaluated carefully *(18)*.

Guidelines for laboratory diagnosis in the Americas Region, including confirmation algorithms, are published in the PAHO document **Laboratory Diagnosis of Yellow Fever Virus Infection** dated 9 September 2018 *(18)*.

Clinical management

Yellow fever is a severe viral hemorrhagic disease with an abrupt onset and a fatality rate of between 30% and 60% in its severe forms *(19)*. It is a dynamic, systemic disease that occurs in three clinical phases: a) infection phase characterized by elevated body temperature, b) remission phase, with the presence of albuminuria, and c) toxemic phase, in which hemorrhagic manifestations and signs of acute liver failure appear, such as jaundice and hepatic encephalopathy *(20)*.

There is currently no specific treatment for yellow fever. Therefore, early detection of suspected or confirmed cases, monitoring of vital signs, life support measures, and management of acute liver failure remain the recommended strategies for its management *(20, 21)*.

Updated recommendations for the clinical management of critically ill patients include:

Table 1. Evidence-based questions and recommendations, according to strength of recommendation and certainty of evidence

No.	Question	Recommendation	Strength	Certainty	Observations
1	Should anticonvulsant prophylaxis be administered in critically ill patients with YF who have hepatic encephalopathy and elevated ammonia levels?	In critically ill patients with YF who show signs of hepatic encephalopathy and/or ammonium > 70 µmol/L, anticonvulsant prophylaxis is recommended.	Conditional	Low	Due to the risk of liver damage, it is preferable to use anticonvulsants that do not have a potentially hepatotoxic effect. Due to elevated ammonia levels, this is used as an important parameter for monitoring neurological damage, so it is preferable not to use valproic acid.
2	Should intensive plasmapheresis be administered in critically ill patients with suspected or confirmed YF?	In critically ill patients with suspected or confirmed YF, it is recommended to initiate intensive plasmapheresis.	Strong	Moderate	Patients who are candidates for this therapy are those who have two consecutive tests with: • factor V < 30% of the lower limit of normal; • serum ammonium concentration > 70 µmol/L; • INR > 1.8, and • fibrinogen < 100 mg/dL
3	Should liver transplantation be performed in critically ill patients with YF?	In critically ill patients with YF, liver transplantation is not recommended.	Strong	Very low	n/a
4	Should antivirals be administered in critically ill patients with YF?	In critically ill patients with YF, it is suggested that antivirals should not be administered.	Conditional	Very low	n/a

YF: yellow fever; INR: international normalized ratio.

Source: Adapted from Pan American Health Organization. Guía de manejo clínico del paciente grave con fiebre amarilla *(21)*.

Table 2. Good practice statements

No.	Good practice
1	In patients with suspected YF, in addition to the diagnostic tests that are routinely performed (complete blood count and transaminases) in the primary health care unit, the LDH test should be performed.
2	All patients with suspected YF should be hospitalized
3	All patients with suspected YF should be kept hospitalized, regardless of the severity of the disease.
4	In patients with suspected YF, clinical management of signs and symptoms should be performed in the most appropriate manner, even if the disease has not been confirmed
5	In patients with suspected YF, aggressive fluid therapy used in the treatment of patients with dengue should not be administered.
6	In patients with suspected YF who have hyporexia, feeding should not be induced.
7	In critically ill patients with YF, warning signs, and two consecutive serum bicarbonate tests < 19 mEq/L, renal replacement therapy should be initiated.
8	In critically ill patients with YF, pH should not be used as the primary criterion for initiating renal replacement therapy.
9	In critically ill patients with YF, without active bleeding and with platelets < 20,000 cells/µL, or with active bleeding and platelets < 50,000 cells/µL, a platelet transfusion should be performed.
10	In patients with massive bleeding and platelets < 75,000 cells/µL, platelet transfusion should also be considered.
11	In critically ill patients with YF and Hb < 7.0 g/dL, red blood cell concentrate transfusion should be performed.
12	In critically ill patients with YF, without active bleeding and fibrinogen < 100 mg/dL, or with active bleeding and fibrinogen < 150 mg/dL, a fibrinogen cryoprecipitate transfusion should be performed.
13	In critically ill patients with YF, without active bleeding and/or INR > 2.0, a fresh frozen plasma transfusion should be performed.
14	In critically ill patients with YF, with active bleeding and fibrinogen < 150 mg/dL, tranexamic acid should be administered.
15	In critically ill patients with YF who present hemodynamic abnormalities and an unsatisfactory response to volume replacement or the use of vasoactive drugs, the presence of viral myocarditis should be ruled out.
16	In critically ill patients with YF, intracranial or esophageal pressure monitoring catheters should not be used.
17	In critically ill patients with YF, nonessential invasive procedures should be avoided.
18	In critically ill patients with YF, the following should be done: • strengthen measures to prevent healthcare-associated infections • closely monitor for bacterial infections • avoid antibiotic prophylaxis
19	In critically ill patients with YF who are convalescing, any invasive procedures should be avoided for three months

No.	Good practice
20	In critically ill patients with convalescent YF, outpatient follow-up should be performed after hospital discharge for up to three months from the onset of the disease

YF: yellow fever; Hb: hemoglobin; INR: international normalized ratio; LDH: lactate dehydrogenase; n/a: not applicable; pH: hydrogen potential.
Source: Adapted from Pan American Health Organization. Guía de manejo clínico del paciente grave con fiebre amarilla *(21)*.

Complete recommendations for management are available in: a) Clinical management guidelines for critically ill patients with yellow fever, available from: https://iris.paho.org/items/1428363c-3af1-4f07-ad70-c11f8e97f680 *(21)* and b) Clinical Management of Yellow Fever in the Americas Region - Experiences and Recommendations for Health Services, available from: https://iris.paho.org/items/a32ea49e-3877-4854-9ffa-69d0dcab0696 *(20)*.

Vaccination

The yellow fever vaccine is safe, affordable, and a single dose is sufficient to confer lifelong immunity and protection, without the need for booster doses *(14)*.

PAHO/WHO reiterates the following recommendations to national authorities *(22)*:

Routine vaccination:

- **Universally vaccinate children** in endemic countries at 12 months of age or according to each country's national vaccination schedule. Considering the evidence supporting simultaneous administration with the measles, mumps, and rubella (MMR) vaccine, it is recommended that both vaccines be administered at the same visit at 12 months of age *(23)*.
- **Ensure vaccination of all travelers to endemic areas** at least **10 days before travel**. Recommendations for international travelers regarding yellow fever vaccination are available in the document International Travel and Health, which is available from: https://www.who.int/publications/i/item/9789241580472 *(24)*.
- **Maintain a reserve inventory in the country** to ensure routine vaccination and respond promptly in the event of outbreaks.

Preventive or update campaigns:

- **Update the risk assessment**, taking into account changes in ecological factors, migration, vaccination coverage, socioeconomic activities, and the risk of urbanization, to guide vaccination and control measures in areas at risk.
- **Estimate susceptibility by cohorts** in expanded age groups (2 to 59 years) to define the target population, determine the campaign goal and necessary supplies, and identify the population at highest risk, such as workers engaged in activities involving exposure in jungle or forest areas.
- **Conduct microplanning** to define vaccination strategies and tactics that ensure coverage of 95% or more in unvaccinated populations, age groups with suboptimal coverage, and occupational risk groups.

- **Plan the campaign in advance** to ensure timely and sufficient vaccine availability, considering that the global supply of yellow fever vaccines has been limited in recent years. Establish the vaccination schedule, preferably during inter-epidemic periods.

Vaccination during outbreak response:

- **Define the target population** based on exposure risk and vaccination history.
- **Design the campaign** based on the definition of prioritized vaccination scenarios through risk assessment. Depending on the level of risk and the temporal context, the vaccination areas and activities would correspond to:
    a. Areas with confirmed active transmission (confirmed human cases or epizootics): these should be the highest priority for immediate reactive vaccination activities (blocking), with the aim of interrupting the chain of transmission.
    b. High-risk areas with no evidence of current viral circulation: carry out early vaccination to reduce the risk of spread, especially in regions with high population density and movement, low immunization coverage, significant presence of the vector, enzootic corridors, among others.
    c. Low-risk areas: in these areas, preventive activities are reserved for inter-epidemic periods, including preventive campaigns and the recovery of schedules to close gaps in susceptibility. These measures help to keep the population protected and strengthen preparedness for future outbreaks.

- **Conduct ongoing verification of vaccine stocks** to reduce the possibility of stockouts in the event of outbreaks.
- **Train health personnel** in the use, registration, and subsequent follow-up of users who receive the fractional dose if it is used in the context of the outbreak response.
- **Communicate risk appropriately** to health workers and the general population regarding the term "split dose" in order to avoid resistance to vaccination and misinformation.

In the event of limited availability of doses, the use of **"split doses"** of the yellow fever vaccine (0.1 ml) administered subcutaneously is recommended, in accordance with the recommendations of the WHO Strategic Advisory Group of Experts (SAGE) and the PAHO Technical Advisory Group (TAG) *(25, 26)*. Children under two years of age, pregnant women, and people living with HIV who are eligible for vaccination should receive a standard dose of 0.5 ml. A "split" dose does not meet the requirements of the International Health Regulations as proof of vaccination for international travel.

Precautions and contraindications:

- Ages 6 to 8 months, ≥60 years, pregnancy, and breastfeeding are precautions for vaccination. A risk-benefit analysis is recommended for individuals with precautions for vaccination.
- The vaccine is contraindicated in:
    a. Children under 6 months of age and is not recommended in children aged 6 to 8 months, except in outbreak situations.

b. People with a history of severe hypersensitivity reactions to eggs.

c. People with immunodeficiency, such as patients with symptomatic HIV infection or with a CD4+ lymphocyte count <200/mm3 (or <15% of total lymphocytes in children under 6 years of age), people undergoing treatment with immunosuppressants, thymus diseases associated with abnormal immune function, primary immunodeficiencies, active malignant tumors, ongoing chemotherapy or radiotherapy treatments, and people who have received a transplant.

Surveillance of events supposedly attributable to vaccination or immunization (ESAVI):

- Surveillance of *events supposedly attributable to vaccination or immunization* (ESAVI) should be strengthened during the implementation of yellow fever vaccination campaigns, including all stakeholders: national regulatory authorities, national pharmacovigilance centers, and those responsible for epidemiological surveillance.
- It is essential to train vaccination teams in the precautions and contraindications of yellow fever vaccines and to define a standardized flow for selecting people to be vaccinated, in order to minimize immunization errors and the risk of ESAVI, for example: the vaccination of immunocompromised individuals.
- It is necessary to ensure the conditions for sample collection and processing and interpretation in the investigation of severe cases that may correspond to cases of neurotropic or viscerotropic disease. Case investigation should help meet the Brighton Collaboration certainty criteria and should be conducted according to the PAHO ESAVI surveillance manual *(27)*.

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Useful links

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