

In light of the circulation of yellow fever in several areas of the Region, and considering current outbreaks in countries outside of this Region, the Pan American Health Organization / World Health Organization (PAHO/WHO) advises Member States to maintain the capacity to detect and confirm cases of yellow fever, provide updated information for health professionals and train them to enable them to properly detect and manage cases, especially in areas at risk for yellow fever circulation. In addition, Member States are encouraged to maintain high vaccination coverage in at risk populations.

Situation summary

In the Region of the Americas, over the past decade, cases of yellow fever were reported in Argentina, Bolivia, Brazil, Colombia, Ecuador, Paraguay, Peru, and Venezuela. In 2015, three countries in the Americas confirmed yellow fever virus circulation (Bolivia, Brazil, and Peru) and in 2016 only one country, Peru, confirmed cases of yellow fever. Brazil is currently investigating the occurrence of epizootics in areas where the virus had circulated.

In December 2015, **Bolivia**¹ reported the detection of epizootics (deaths of non-human primates) due to yellow fever in the municipality of Monteagudo, Chuquisaca Department. No human cases were detected.

In July 2014, **Brazil** declared the reemergence of yellow fever virus in the country due to epizootics in non-human primates in which the presence of the virus was confirmed. Between July 2014 and June 2015 seven cases of yellow fever including four deaths were confirmed. The distribution of cases by location of exposure is: Goiás (5 cases), Mato Grosso do Sul (1 case), and Pará (1 case). All cases were non-vaccinated males with their ages ranging between 7 and 59 years. Four had been exposed to the virus during tourism, two through rural activities and one from residing in a rural area.

In addition, the Secretary of Health of Rio Grande do Norte reported a fatal case under investigation. The case is a patient who died in Natal in July 2015, whose initial tests resulted positive for yellow fever. The patient had no history of travel to endemic areas. No other cases

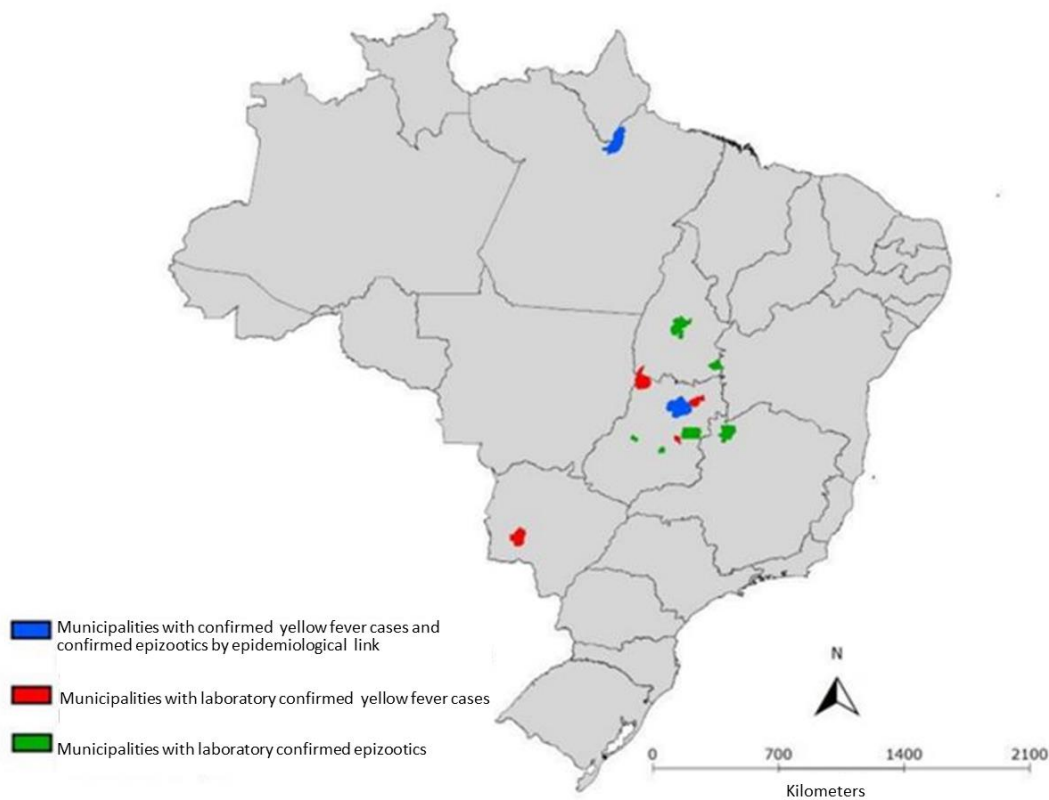
¹ Notification provided by the Bolivia International Health Regulations National Focal Point.

were registered in the municipality.² The last case of yellow fever registered in that municipality was in 1930.³

Epizootics due to yellow fever have been confirmed in Brazil in the municipalities of the states of: Tocantins (1 municipality in 2014 and 4 in 2015), Goiás (3 municipalities in 2015), Minas Gerais (1 municipality in 2015), Para (1 municipality in 2015), and in the Federal District (1 municipality in 2015). In 2016, epizootics were under investigation in the state of Minas Gerais and the results are expected soon.

The occurrence of human cases and epizootics caused by yellow fever demonstrates the circulation of the virus which is confined to the center-east region of the country. **Figure 1.**

Figure 1: Geographical distribution of confirmed yellow fever cases and epizootics. Brazil, July 2014 - December 2015.



Source: Brazil Ministry of Health. Publication: "Situação Epidemiológica / Dados" accessed 22 April 2016 at: <http://portalsaude.saude.gov.br/index.php/situacao-epidemiologica-dados-febreamarela>

In **Peru**, up to epidemiological week (EW) 14 of 2016, there were 25 suspected cases of yellow fever reported, including two deaths. Of the reported cases, nine were confirmed, 11 were classified as probable, and five were discarded. The departments reporting the highest

² The State Secretary of Health Rio Grande do Norte: <http://www.saude.rn.gov.br/Conteudo.asp?TRAN=ITEM&TARG=101194&ACT=&PAGE=&PARM=&LBL=NOT%CD CIA>

³ Brazil Ministry of Health Portal: <http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/21464-esclarecimento-sobre-caso-suspeito-no-rn>

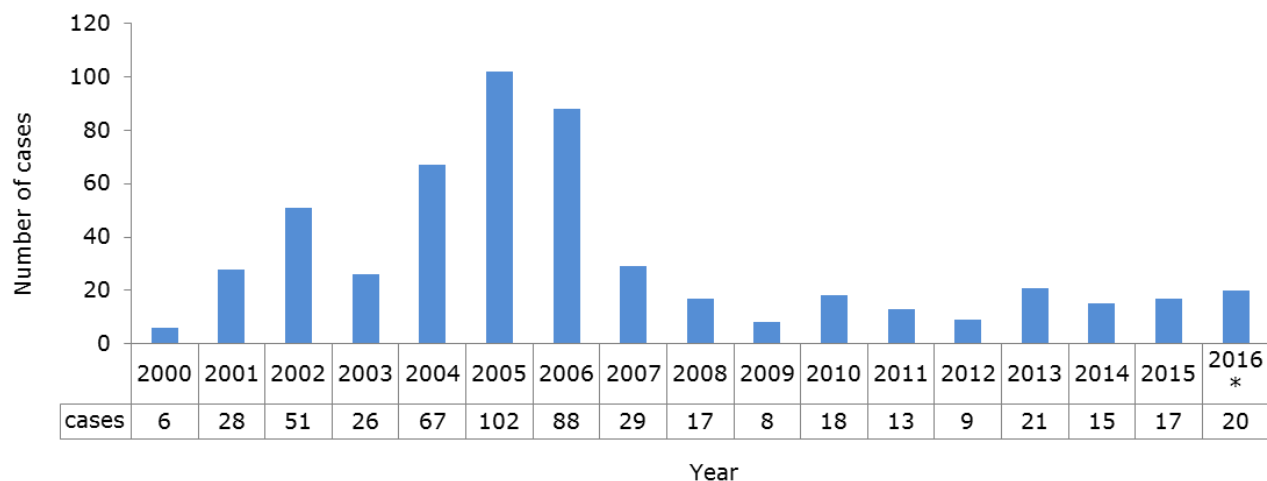
number of cases – confirmed and probable – were Junin (8 cases) and San Martin (6 cases). **Figure 2.**

Figure 2. Departments with probable and confirmed cases of yellow fever, Peru, 2015-2016.



The number of cases reported up to EW 14 of 2016 exceeds the total of cases reported in the preceding two years; with 15 cases reported in 2014 and 17 cases reported in 2015 (**Figure 3**). In 2005 and 2006 a total of 102 and 88 confirmed and suspected cases were reported respectively; this coincided with the occurrence of El Niño in the central Pacific during 2004-2005 and 2006-2007.

Figure 3. Number of confirmed and probable yellow fever cases by years. Peru 200-2016*



*Up to EW 14 of 2016

Source: Published by the National Center for Epidemiology, Disease Control and Prevention in Peru and reproduced by PAHO/WHO.

Situation in other Regions

Outside of the Region of the Americas, Angola, the Democratic Republic of Congo, and Uganda have reported yellow fever outbreaks occurring in 2016. In addition, cases of yellow fever were exported to China (9 cases) and Kenya (2 cases) due to the exposure of unvaccinated persons to the yellow fever virus in Angola.

The largest outbreak is occurring in Angola where from December 2015 through 19 April 2016, there have been 1,908 suspected cases reported, including 250 deaths (case fatality rate of 13%).⁴ The majority of the cases are concentrated in Luanda and in two other provinces, Huambo and Huila. In order to contain the outbreak outside of the capital, nearly 2.15 million people will be vaccinated in the densely populated urban districts of Huambo and Benguela.

In the Democratic Republic of Congo, from January 2016 to 22 March 2016, a total of 151 suspected cases (9 confirmed), including 21 deaths (case fatality rate of 14%) have been registered.

Unvaccinated travelers heading to areas with active yellow fever outbreaks pose a risk of introducing the virus in to areas where yellow fever risk factors (human susceptibility, prevalence of competent vector, and animal reservoirs) are present.

Vaccine Supply

The global supply of yellow fever vaccines has been insufficient for years. The PAHO/WHO Revolving Fund provides about 50% of the demand in the Region of the Americas. The Revolving Fund allocates vaccines based on country epidemiological risk. The Revolving Fund together with the WHO and UNICEF jointly undertake the actions needed to meet the challenge of vaccine supply.

The current outbreak in Angola has stretched existing yellow fever vaccine supplies. During outbreaks, available vaccines are prioritized for the emergency response. The yellow fever emergency vaccine stockpile was replenished in late March 2016 through the collaboration of partners such as the International Coordination Group (ICG) and UNICEF.

Recommendations

The occurrence of yellow fever cases in unvaccinated persons entering in areas where the virus is circulating or an outbreak is occurring reinforces the importance of Member States to implement necessary actions to properly inform and ensure vaccination of travelers heading to areas where certification of yellow fever vaccine is mandatory.

PAHO / WHO does not recommend any restrictions on travel or trade to countries with ongoing outbreaks of yellow fever.

The recommendations issued in the [Yellow Fever Epidemiological Alert of 31 December 2015](#) remain in effect and are highlighted below.

⁴ Information available at: <http://www.afro.who.int/en/media-centre/pressreleases/item/8528-angola-extends-yellow-fever-vaccination-campaign-to-huambo-and-benguela-provinces.html>

Surveillance

Yellow fever epidemiological surveillance must be aimed at (i) achieving early detection of virus circulation to enable timely adoption of appropriate control measures to keep new cases from appearing, (ii) interrupting outbreaks, and (iii) preventing the reurbanization of the disease.

The method of surveillance should be a combination of:

- Surveillance of clinical compatibility with the classic form of the disease, based on WHO case definitions
- Surveillance of febrile jaundice syndrome
- Surveillance of epizootics
- Monitoring post-vaccination events allegedly attributable to yellow fever vaccination

The surveillance of febrile jaundice syndrome usually conducted through sentinel sites, uses a more sensitive case definition and rules out cases through laboratory testing.

Laboratory Diagnostics

Laboratory diagnosis of yellow fever is conducted by detecting the genetic material of the virus in blood or tissue using the polymerase chain reaction (PCR), and through serological tests for IgM antibodies detection.

Virologic test

In the acute phase (viremia period) viral RNA can be detected in serum by using molecular techniques, such as conventional or real time RT-PCR. A positive result obtained with appropriate controls, confirms the diagnosis.

Viral isolation can be performed by intracerebral inoculation in mice or in cell culture, but due to its complexity it is rarely used as a diagnostic method and is recommended for research studies only as a complement to public health surveillance.

Serologic test

Serology (detection of specific antibodies) is useful for diagnosis of yellow fever during the acute and convalescent phase of the disease (i.e., after day 6 after the onset of symptoms).

A positive IgM reaction by ELISA (MAC-ELISA or other immunoassay) in a sample taken after the 6th day of onset, is presumptive of recent yellow fever infection. Moreover the diagnostic confirmation can only be made by demonstrating an increase in antibody titer (four times or more) in two serum samples (one from the acute phase and one from the convalescent phase) by using quantitative techniques.

Serological tests could have cross-reactions, especially in areas where different flavivirus are circulating. Therefore, in those places serological confirmation should be made with other more specific serologic techniques such as plaque neutralization test (PRNT) and once infections by other causal agents have been ruled out as part of the differential diagnosis. In

any case, the results of serological tests should be interpreted carefully, and taking into account the patient's vaccination history.

Post-mortem test

Histopathology in liver tissue is the "gold standard" for the diagnosis of suspected yellow fever fatal cases. The analysis includes the typical microscopic description of yellow fever lesions (midzonal necrosis, fatty change, among others), detection of Councilman bodies (pathognomonic), and immunohistochemistry which reveal viral proteins inside the hepatocytes. While immunohistochemistry for yellow fever is specific, given the possibility of cross reaction with other antigenically related flaviviruses, it is nonetheless recommended to confirm cases by using the polymerase chain reaction (PCR) technique on fresh tissue samples or those preserved in paraffin.

Biosafety

Serum samples from acute phase are considered infectious. All laboratory personnel who manage yellow fever samples in a laboratory setting must be vaccinated against yellow fever. The use of Class II certified biosafety cabinets, for the handling of samples, is also recommended to exercise caution and avoid puncture accidents.

Given the differential diagnosis of yellow fever that includes hemorrhagic fevers caused by arenaviruses, samples should be handled under BSL3 containment conditions, and a risk assessment and analysis of the medical history should be conducted before handling of samples in the laboratory setting.

Clinical Management

There is no specific antiviral treatment for yellow fever; therefore, supportive therapy is critical. Severe cases should be treated in intensive care units. General supportive therapy with administration of oxygen, intravenous fluids, and vasopressors is indicated to treat hypotension and metabolic acidosis. Gastric protectors should be included to reduce the risk of gastrointestinal bleeding.

Treatment in severe cases includes mechanical ventilation, treatment of disseminated intravascular coagulation, use of frozen fresh plasma to treat hemorrhage, treatment of secondary infections with antibiotics, and management of liver and kidney failure. Other supportive measures include the use of nasogastric tube for nutritional support or prevention of gastric distention, and dialysis for renal failure or patient with refractory acidosis.

In mild cases the symptoms are treated. Salicylates should not be used as they can produce hemorrhage.

Differential diagnosis

The different clinical forms of yellow fever must be differentiated from other febrile diseases that progress with jaundice, hemorrhagic manifestations, or both. In the Americas, the following diseases should be considered in the differential diagnosis of yellow fever:

- Leptospirosis

- Severe malaria
- Viral hepatitis, especially the fulminating form of hepatitis B and D
- Viral hemorrhagic fevers⁵
- Dengue
- Typhoid and typhus fever
- Hepatotoxicity or fulminating secondary hepatitis due to drugs or toxics.

Patient Isolation

To prevent infection of other persons, a patient infected with yellow fever virus should avoid being bitten by *Aedes* mosquito for at least for the first 5 days of illness (viremic phase). The patient is recommended to stay under a bed net (treated or without insecticide), or stay in a place with intact window/door screen. In addition, health care personnel attending patients with yellow fever should be protected from mosquito bites by using repellents and wearing long sleeves and pants.

Prevention and control measures

Vaccination

Vaccination is the single and key measure for preventing yellow fever. Preventive vaccination can be performed by routine vaccination schedule for children and one-time mass campaigns to increase the vaccination coverage in at risk areas, as well as for travelers to yellow fever risk areas.

The yellow fever vaccine is safe and affordable, providing effective immunity against yellow fever within 10 days for 80-100% of people and 99% immunity within 30 days. **A single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease and a booster dose of yellow fever vaccine is not needed.** Serious adverse events have been reported rarely following immunization.

Given the limited availability of the vaccines it is recommended that national authorities carry out an assessment of vaccination coverage against yellow fever in at risk areas in order to target the distribution of vaccines. Additionally, a national reserve of the vaccines should be maintained to respond to potential outbreaks.

The yellow fever vaccine should not be administered to:

- People with acute febrile disease, whose general health status is compromised
- People with a history of hypersensitivity to chicken eggs and/or their derivatives
- Pregnant women, except in an epidemiological emergency and at the express recommendations from health authorities

⁵ Infection Prevention Control (IPC) measures corresponding to the suspected hemorrhagic fever should be implemented.

- People with severe drug related or disease related (e.g., cancer, leukemia, AIDS, etc.) immunosuppression
- Children under 6 months old (consult the vaccine's laboratory insert)
- People of any age with a disease involving the thymus

Note: It is recommended to individually assess the epidemiological risk of contracting the disease against the risk of an adverse reaction in persons over 60 years that have not previously been vaccinated.

Vector Control

The risk of transmission of yellow fever in urban areas can be reduced through effective vector control strategy. Combined with emergency vaccination campaigns, the application of insecticide spray to kill adult mosquitoes during urban epidemics can reduce or halt yellow fever transmission, while populations are vaccinated to acquire immunity.

Mosquito control programs targeting wild mosquitos in forested areas are not practical for preventing jungle yellow fever transmission.

References

1. Yellow fever epidemiological situation and recommendations to enhance surveillance in Brazil. Brazil Ministry of Health site. Available at: <http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/426-secretaria-svs/vigilancia-de-a-a-z/febre-amarela/20139-situacao-epidemiologica-da-febre-amarela-e-as-recomendacoes-para-intensificar-a-vigilancia-no-brasil>
2. Peru Ministry of Health, Department of Epidemiology; Situation Update, Epidemiological Week 46 of 2015. Available at: http://www.dge.gob.pe/portal/index.php?option=com_content&view=article&id=14&Itemid=154
3. Yellow fever control. Practical Guide. 2005. Pan American Health Organization. Scientific and Technical Publication No. 603.
4. McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. *Lancet*. 2006;367(9513):859–69.
5. WHO. Disease Outbreak News (DON). Yellow Fever in Angola, 13 April 2016. Available at: <http://www.who.int/csr/don/13-april-2016-yellow-fever-angola/en/>
6. WHO. Disease Outbreak News (DON). Yellow Fever in the Democratic Republic of Congo, 11 April 2016. Available at: <http://www.who.int/csr/don/11-april-2016-yellow-fever-drc/en/>
7. WHO. Disease Outbreak News (DON). Yellow Fever in China, 6 April 2016. Available at: <http://www.who.int/csr/don/6-april-2016-yellow-fever-china/en/>
8. WHO. Disease Outbreak News (DON). Yellow Fever in Kenya, 6 April 2016. Available at: <http://www.who.int/csr/don/6-april-2016-yellow-fever-kenya/en/>
9. Peru. Registro histórico del Niño. Ministerio del Medio Ambiente de Perú. <http://www.minam.gob.pe/fenomenodelnino/el-nino-en-el-peru-y-sus-caracteristicas/registro-historico-de-el-nino/>
10. WHO. Vaccines and vaccination against yellow fever WHO Position Paper – June 2013. <http://www.who.int/wer/2013/wer8827.pdf?ua=1>