

In light of the circulation of yellow fever in several areas of the Region, and in the context of the ongoing El Niño Southern Oscillation (ENSO) the Pan American Health Organization / World Health Organization (PAHO/WHO) advises Member States to establish and maintain the capacity to detect and confirm cases of yellow fever and keep health professionals up to date to enable them to identify suspected cases and manage cases properly, especially in areas at risk for yellow fever. In addition, Member States are advised 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, only three countries in the Americas reported yellow fever virus circulation: Bolivia, Brazil, and Peru.

In December 2015, **Bolivia**¹ reported the detection of epizootics (deaths of non-human primates) in the municipality of Monteagudo, Chuquisaca Department. The National Center for Tropical Diseases (CENETROP) analysis indicated positive result for yellow fever. 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 male with ages ranging between 7 and 59 years old. None of them were vaccinated and 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 they are investigating the death of a patient in Natal in July 2015, for which initial tests resulted positive for yellow fever. The patient had no history of travel to endemic areas and no other cases have been registered in the municipality;² the last evidence of yellow fever transmission in that municipality was in 1930.³

In Brazil, epizootics due to yellow fever have also been confirmed 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).

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

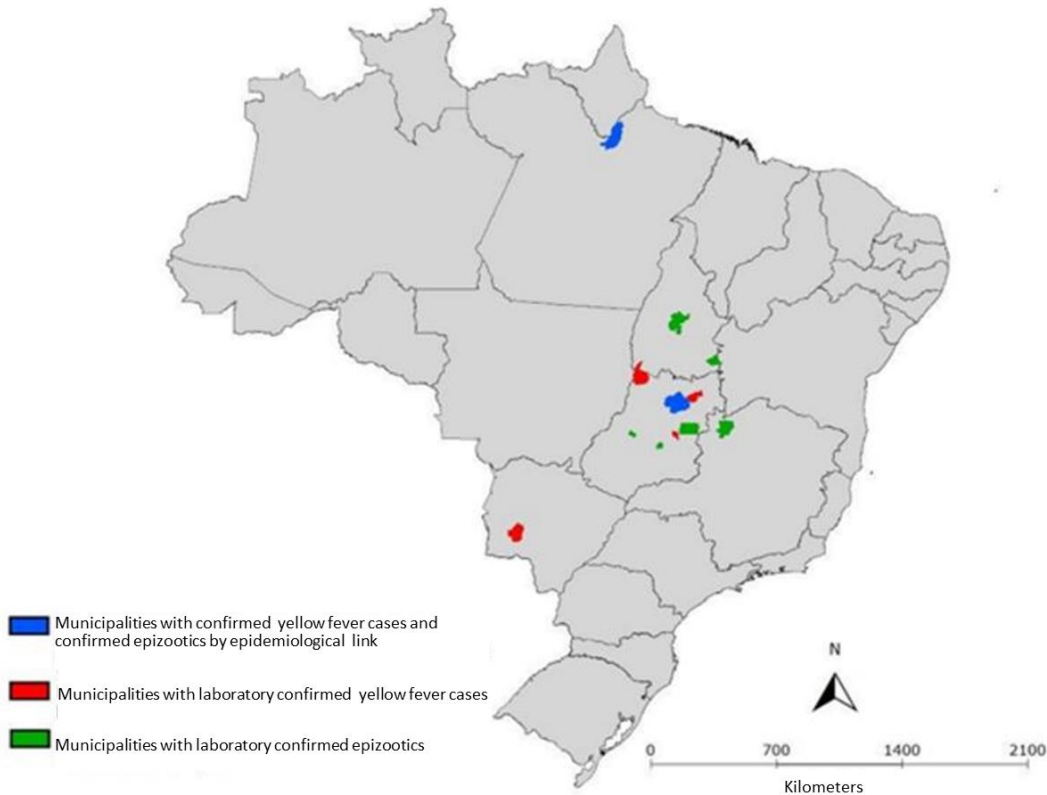
² The State Secretary of Health Rio Grande do Norte:

<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>

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 28 December 2015 at: <http://portalsaude.saude.gov.br/index.php/situacao-epidemiologica-dados-febreamarela>

In **Peru**, up to epidemiological week (EW) 49 of 2015, there were 56 suspected cases of yellow fever reported, including three deaths. Of the reported cases, 11 were confirmed, 12 were classified as probable, and the rest were discarded. The number of combined probable and confirmed cases in 2015 (23), is higher than observed in 2014 (15).

In descending order, the confirmed and probable cases were geographically distributed in the following departments: Loreto (8 cases), Junin (5 cases), San Martín (5 cases), Pasco (2 cases), Cusco (1 case), Huanuco (1 case), and Madre de Dios (1 case).

Recommendations

The occurrence of epizootic and human cases in certain areas of the Americas is indicative that the risk for urban yellow fever remains, primarily due to the high density and broad presence of *Aedes aegypti*, combined with the movement of persons to and from areas of sylvatic circulation of the virus.

Additionally it should be noted that climate changes caused by ENSO are expected to continue during 2016. These changes could impact the incidence, geographical distribution and seasonal transmission of various vector-borne diseases including yellow fever.

In this regard and in the context of the ENSO phenomenon, PAHO/WHO encourages Member States to establish and maintain the capacity to detect and confirm cases, keep health care professionals up to date so they can suspect cases and treat them appropriately, and also maintain adequate vaccination coverage in at risk populations.

Below are key recommendations related to yellow fever surveillance, clinical management, and prevention and control measures.

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. In addition, molecular methods from samples preserved in paraffin or fresh tissue may also be used for confirmation of suspected cases.

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 fevers⁴
- 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.

⁴ Infection Prevention Control (IPC) measures corresponding to the suspected hemorrhagic fever should be implemented.

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

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.

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