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# Epidemiological Alert

## Hemorrhagic fever due to Arenavirus in Bolivia

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In the Plurinational State of Bolivia, an investigation of an outbreak of hemorrhagic fever due to Arenavirus is ongoing, with reported cases among healthcare workers. Given this, the Pan American Health Organization / World Health Organization (PAHO/WHO) reminds Member States of the need to remain vigilant and to strengthen the implementation of infection prevention and control measures at all levels of healthcare services.

### Summary of the Situation

On 28 June 2019, the Ministry of Health of the Plurinational State of Bolivia received a report of 3 cases of hemorrhagic febrile syndrome of unknown etiology with suspected human-to-human transmission. As of 17 July 2019, there are a total of 5 cases, including 3 deaths. Of the total cases, 3 have been laboratory-confirmed (one fatal) and 2 have been classified as probable cases (both fatal).

The cases had symptom onset between 29 April and 29 May 2019.

Four of the 5 cases are male, with ages ranging between 21 to 65 years (median 42 years). Three of the cases are healthcare workers and the other 2 cases are agricultural workers.

The probable site of exposure for the healthcare workers was the hospital setting, where they had direct contact with blood, respiratory, and gastrointestinal secretions during invasive procedures (intubation and endoscopy) that were

### Hemorrhagic fevers due to Arenavirus

These are zoonoses produced by a virus belonging to the Arenavirus genus of the *Arenaviridae* family and are generally associated with human disease transmitted by rodents. Among the 21 known New World Arenaviruses, five have been linked to hemorrhagic fevers in humans, including two in Bolivia: Machupo and Chapare. Transmission in humans occurs mainly by inhalation of fine aerosol particles from droppings or saliva from rodents that contain the virus. Some Arenaviruses are associated with human-to-human transmission in community and/or healthcare settings. This occurs when there is direct or indirect contact with blood or other bodily fluids of infected persons (1, 2).

The clinical manifestations of hemorrhagic fevers due to Arenavirus in South America are acute viral febrile illnesses that last between 6 to 14 days. The illness starts gradually, with general malaise, headache, retro-orbital pain, conjunctival hyperemia, and moderate but sustained fever, followed by signs and symptoms related to the digestive system. There may be bruises and ecchymosis, accompanied with erythema on the face, neck, and upper chest. Progressive leukopenia and thrombocytopenia are characteristic of severe cases. Symptoms typically resolve 10 to 15 days after the onset of illness in patients who survive. In documented cases, the incubation period is generally 6 to 14 days, but can vary from 5 to 21 days (1, 2, 3).

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performed for one of the cases. For the agricultural workers, exposure likely occurred during the rice harvest in the Siliamo community, Guanay Municipality, La Paz Department.

Laboratory confirmation has been carried out by the Center for Tropical Diseases (CENETROP, per its acronym in Spanish), in close collaboration with the Viral Special Pathogens Branch (VSPB) of the United States Centers for Diseases Control and Prevention (US CDC) as a WHO Collaborating Center, which has reported the identification of an Arenavirus. The Arenavirus identified was partially sequenced and shows a high identity with Chapare virus.

### **Actions implemented by national authorities**

The Bolivia Ministry of Health, along with the La Paz Departmental Health Service and the hospitals involved, with the support from PAHO/WHO, are implementing the corresponding public health measures.

## **Guidance for national authorities**

PAHO/WHO recommends that Member States remain vigilant and ensure awareness among healthcare workers for detecting and managing cases of hemorrhagic fever as well as ensuring strict compliance with infection prevention and control measures.

### **Surveillance**

#### *Case detection*

Based on the epidemiological context of the country or territory, surveillance should be aimed at detecting suspected cases of hemorrhagic fever, considering the clinical manifestations, travel history, and exposure history.

#### *Contact identification and monitoring*

Any person who had contact with blood or bodily fluids of a suspected, probable, or confirmed case during his/her illness is considered a contact.

Contact monitoring should be performed for a maximum putative incubation period of 21 days (4) (following the last known exposure).

### **Laboratory diagnostics**

Laboratory confirmation of Arenavirus infection can be performed by various methods, including both virological (RT-PCR, viral isolation, ELISA, and immunohistochemistry), and serological (IgM/IgG ELISA and indirect immunofluorescence). However, the dynamics of infection (duration of viremia vs. appearance of antibodies) by Arenavirus have not been fully established (particularly for New World Arenaviruses and recently identified strains), which leads to limitations of the techniques as well as additional challenges for interpreting the results and discarding cases.

### *Virological diagnosis*

During the acute phase of the disease, the virus can be detected (in serum or whole blood) from the third day after the onset of febrile symptoms using molecular techniques (RT-PCR), viral isolation in cell culture (only under BSL-4 conditions), or antigen capture ELISA with monoclonal antibodies. Although the duration of viremia has not been fully established, detection of the virus has been documented for up to 10 days after the onset of symptoms, depending on the virus and patient conditions. Similarly, the virus can also be detected in other types of samples, such as nasopharyngeal swab, but the time duration for how long the virus can be detected has not yet been established. While molecular methods are relatively rapid and sensitive, the only diagnostic tests available so far are based on endpoint (conventional) RT-PCR with agarose gel results, which decreases the detection sensitivity.

### *Serological diagnosis*

Although serological diagnosis of Arenavirus infections (antibody detection) can be carried out using indirect immunofluorescence (indirect IF) or antigen capture ELISA (for IgM or IgG), no serological assay is currently validated for Chapare virus.

### *Biosafety considerations*

All biological samples (whole blood, serum, swab/respiratory aspirates, fresh tissue) should be considered as potentially infectious. Arenavirus infection can occur through exposure to aerosols from samples; therefore, additional measures should be taken to protect the respiratory tract (including the use of N95 masks) and minimizing the use of procedures that generate these aerosols. Additionally, it is recommended to perform any procedure inside a certified Class II biosafety cabinet, taking extreme measures to avoid accidents due to puncture or spillage. Furthermore, it is necessary to consider the inactivation of samples (as a step prior to nucleic acid extraction for molecular diagnosis or serological methods) under BSL-3 conditions. Attempts at Arenavirus viral isolation should only be carried out under BSL-4 conditions. For deceased patients, it is recommended to obtain blood by cardiac puncture. Likewise, samples of lung tissue or respiratory tract (fresh or preserved in formaldehyde) are useful for molecular detection and histopathological analysis, provided there are adequate conditions to perform the autopsy, particularly respiratory protection.

In the Americas Region, there are two WHO Collaborating Centers for hemorrhagic fevers due to Arenaviruses: the US CDC and the National Institute of Human Viral Diseases "Dr. Julio I. Maiztegui" (INEVH, per its acronym in Spanish) in Argentina, which can be contacted through PAHO/WHO.

### **Case management**

It is recommended to keep the patient in strict isolation during the acute febrile period, with healthcare workers attending to the patient using personal protective equipment for droplet and contact precautions: apron, N95 mask, face shield or glasses, and gloves.

Concurrently, disinfection of all secretions as well as material contaminated with blood should be performed.

The use of immune plasma is only standardized for the Junin virus in the treatment of Argentine hemorrhagic fever. For the management of hemorrhagic fevers caused by New World Arenaviruses, the use of ribavirin has been described; however, its efficacy and safety has not been proven in clinical trials. It is important to note that ribavirin has hematological side effects that can worsen the clinical condition of patients.

Hydration, rest, and supportive treatment of possible complications are recommended after excluding diseases such as malaria, dengue, or bacterial infections.

#### *Organization of healthcare services/provision of services*

For all patients presenting to healthcare services, standardized forms should be used to collect clinical information and to identify patients suspected with hemorrhagic fever due to Arenavirus. Once a patient is identified as a suspected case, he/she should be placed in an isolation area using standard droplet and contact precautions.

#### *Transfer of patients*

The transfer of a patient within the healthcare facility should be restricted as much as possible. For referral of patients to facilities with more complex services, healthcare workers should wear personal protective equipment for droplet and contact precautions: apron, N95 mask, face shield or glasses, and gloves. The patient must wear a surgical mask.

### **Infection prevention and control**

Human-to-human transmission of Arenavirus occurs mainly in the hospital setting, when biosafety measures are not followed and health professionals come into contact with contaminated bodily fluids, mainly blood. Aerosol-generating procedures such as orotracheal intubation, non-invasive mechanical ventilation, and upper airway aspirations, are also involved in human-to-human transmission.

Standard precautions, in addition to droplet and contact precautions, must be strictly complied with; specifically: (i) hand hygiene, (ii) the use of personal protective equipment according to the risk assessment, (iii) proper disposal of sharp materials, (iv) proper cough etiquette and respiratory hygiene, and (v) proper use of sterile equipment and handling of hospital waste.

Patients should be isolated in a single room, with a bathroom and separate sinks. The patient's movement in the hospital environment must be restricted.

In case of death of the patient, handling of the corpse must follow the respective protocols, including the following: comprehensive use of personal protective equipment, disinfection of the corpse with 0.5% sodium hypochlorite solution, and incineration of hospital waste, while respecting the grieving of the family.

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