

6. HANTAVIRUS PULMONARY SYNDROME SURVEILLANCE AND CASE DEFINITION

In order to permit immediate epidemic control or to prevent the transmission of hantavirus infection, a surveillance system must be simple in its structure and operation. In the case of hantavirus infection, the surveillance system must address the disease from an integrated clinical, laboratory, and environmental perspective. The case definition provided below (Figure 1), initially developed by CDC, is also used in Canada and several South American countries for HPS surveillance. Serological tests on acute sera are needed to provide precise diagnosis, and molecular biological techniques are useful in establishing the type(s) of circulating virus. All clinical samples must be accompanied by a form identifying the patient, the individual's age and sex, the date of symptom onset, the date of sample collection, a short list of important manifestations, clinical laboratory data, the place of hospitalization, and the final outcome (see Annex 2).

6.1 OUTBREAK INVESTIGATION

6.1.1 When to Investigate

The occurrence of an unusual number of cases in an area of known hantavirus transmission requires an explanation and may also provide an opportunity to expand our knowledge of hantaviruses. This is particularly relevant with case clusters, since they provide an opportunity to address the problem of interhuman transmission.

A single case in an area where hantavirus infection has not previously been reported requires a full medical and epidemiological assessment, individual risk factor/exposure analysis, and an ecological/environmental evaluation as outlined in Section 6.1.2. Determinations of the virus type in circulation as well as potential reservoirs in these new areas are essential in designing future control and prevention strategies.

If a single new case occurs in an area with previous infection, current knowledge about the mode of transmission, clinical manifestations of disease, individual risk factors, circulating virus type, and potential reservoirs in

the region should be taken into account and further investigations conducted if circumstances suggest.

In all cases, response procedures should include an evaluation of rodent infestation in domestic and peri-domestic settings in order to propose appropriate rodent control measures.

6.1.2 Conducting the Investigation

In conducting the investigation, it is essential to establish a multidisciplinary investigative team involving epidemiologists, laboratorians, and ecologists. Each outbreak investigation should begin with a medical and epidemiologic assessment that includes the following steps:

- define the magnitude of the outbreak:
 - conduct active case finding through interviews and medical chart reviews
 - determine the relative frequency of infection versus disease (via serological survey)
 - map case locations with attention to results of the serological survey
- determine mode(s) of transmission
- characterize the clinical manifestation of disease within the outbreak
- ensure that in each activity above, clinical specimens are collected in a systematic manner with attention to use of specimens for serological diagnosis, PCR analysis, and possibly virus isolation.

The second major activity of the investigation involves individual risk factor/exposure assessment. A culturally appropriate individual risk factor/exposure questionnaire should be developed for use with case-patients, surrogates of case-patients, household or other close contacts, and/or control-patients if used.

The best methodological approach for the situation should be determined, including whether or not to use a case-control design.

FIGURE 1. Hantavirus pulmonary syndrome case definition.

Hantavirus Pulmonary Syndrome (HPS)

Rationale for Surveillance

HPS in the Americas is a rare, but usually severe, disease transmitted through close contact with the urine, feces, or saliva of infected rodents. Although HPS cases have been reported only from Argentina, Brazil, Canada, Chile, Paraguay, the United States of America, and Uruguay, the potential for disease exists throughout the Americas due to the widespread distribution of existing rodent reservoirs. Surveillance is therefore essential for all countries.

Recommended HPS Case Definition

Clinical Case Definition:

- A febrile illness ($T > 38.3$ °C [101 °F] oral) requiring supplemental oxygen, *plus*
- Bilateral diffuse infiltrates (may resemble adult respiratory distress syndrome [ARDS]), *plus*
- Develops within 72 hours of hospitalization in a previously healthy person, **OR**
- Unexplained illness resulting in death *plus* an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death

Laboratory Criteria for Diagnosis:

- Presence of hantavirus-specific IgM antibodies or a 4-fold or greater increase in IgG antibody titers **OR**
- Positive reverse transcriptase-polymerase chain reaction (RT-PCR) results for hantavirus RNA **OR**
- Positive immunohistochemical results for hantavirus antigens.

Case Classification:

Suspected: Presentation compatible with the clinical case definition

Confirmed: A suspected case that is laboratory confirmed

Recommendations for Surveillance

- Establish HPS as a reportable (compulsory reporting) disease in all PAHO Member Countries.
- Develop a case report form that identifies standard minimum data to be collected by all countries of the Americas (see Annex 2).
- If HPS is suspected, a blood count, chest X-ray, oxygen saturation, and hantavirus serology should be performed. Rodent exposure should be evaluated (see Annex 2).
- Postmortem blood, fresh frozen tissue, and formal fixed tissue should be collected from deceased HPS patients and properly transported to the nearest laboratory capable of HPS confirmation (see Section 6.1.4 and Annex 3).
- If hantavirus infection not meeting the case definition of HPS is suspected, specimens may also be submitted for testing along with a description of clinical manifestations.

The third main component of the investigation is an ecological/environmental assessment. This includes using standardized data collection forms and conducting systematic environmental assessments to evaluate indices of rodent presence/infestation at suspected sites of rodent exposure. Following the guidelines outlined in Section 6.1.5, the investigation team should initiate systematic assessments of potential rodent reservoirs in the outbreak region, including proper taxonomic evaluations.

6.1.3 Local Response to a Hantavirus Pulmonary Syndrome Case

Local officials should take action when a possible HPS case is laboratory confirmed, even though many cases meeting the screening case definition will not be HPS. Some actions may be taken if clinical evolution makes a positive laboratory diagnosis highly unlikely.

An essential step is to consult local and state public health authorities immediately. The management of zoonoses is specialized, and advice, explanations, and policy guidelines may be needed. Also, special samples from both humans and rodents may be required for investigation and analysis.

It should be suggested to family members that they reside elsewhere until domestic and peridomestic structures have been evaluated and rodents removed. This should be strongly recommended in cases where heavy rodent infestation is evident, especially in the home. The risk of removing clothing and possessions needed immediately is negligible. It may be necessary to obtain rodents from the house for study, depending on the situation and national policy. If rodents are not needed for study, it is sufficient to kill all those in the house, building, or peridomestic structure and properly dispose of them.

Household contacts should be placed under surveillance and any fever reported immediately. About 10% of hantavirus cases occur in clusters, and rare instances of person-to-person transmission occur with Andes virus. Early recognition can improve case management. In addition, contacts must be reassured.

A media strategy should be prepared. Intense interest often follows the first cases, and the media can be helpful in allaying anxiety and spreading public health messages. An effective media strategy can also counteract stigmatization of infected individuals or the community.

Finally, an educational campaign appropriate to the community situation should be developed. Its characteristics will depend on whether there is a single case or multiple cases and whether this is the first recognized case in the area or there is an established endemic. The

campaign should target cases' family members as well as physicians.

6.1.4 Recommendations for Sample Storage and Preservation

Serum samples for serological tests can be stored at 4 °C for a few days but preferably should be frozen at -20 °C or at -60 °C. Acute serum for PCR tests should be kept frozen at -60 °C. Tissues from fatal cases should be frozen at -60 °C for PCR tests and fixed in 10% buffered formalin for histopathology and for immunohistochemical analysis. A formalin buffer (pH = 7.4) can be prepared as follows:

100 ml	pure formalin
900 ml	distilled water
4.0 g	monosodium phosphate
6.5 g	disodium phosphate

Lung is the most sensitive tissue for immunohistochemical diagnosis of HPS, but a complete autopsy should be performed and multiple tissues taken because of the limited information available on the pathology and pathogenesis of the different hantaviruses.

6.1.5 Reservoir Surveillance

The intensity and methodology of reservoir surveillance and case follow-up will depend on the resources available to public health authorities. As a minimum, the public health response to the first case(s) of HPS in a country or region where hantavirus infection was previously not identified should include small-mammal trapping in potential areas of human exposure. Trapping should be conducted in accordance with established safety and methodological guidelines (56). Primary objectives should include:

- identification of the principal reservoir species
- collection of samples to identify hantaviruses present and to provide a genetic link to human cases
- measurement of the relative density and prevalence of infection in potential reservoir populations
- determination of the most likely ecological zones, specific sites, and mechanisms of human infection

As resources permit, reservoir studies may be expanded to include specific trapping and sampling protocols designed to investigate:

- the potential (as indicated by reservoir presence and evidence of viral infection) for human cases of HPS in distinct geographic areas of the country
- the prevalence, incidence, and temporal patterns of infection in reservoir species
- the effect of climate, habitat quality, and host population dynamics on the viral transmission cycle
- potential mechanisms of transmission among reservoir populations, and from rodents to humans
- effects of infection on movement, longevity, and population dynamics of the host
- the identity of other hantaviruses that may cause human infection, including their hosts and geographic distribution
- potential methods for reservoir control and for de-

creasing the frequency of human contact with host species

- the relationship between reservoir population density, virus activity in reservoir populations, and the incidence of human disease

Discussions and examples of the application and utility of these kinds of studies are available (14, 52, 56–59). Investigators should be encouraged to establish a working relationship with museum taxonomists, universities, government agencies, and private consultants to ensure proper identification and permanent archiving of voucher specimens for all captured small mammals. Methodologies for voucher specimen preparation and preservation have been described (56, 60).