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Some considerations on hantavirus infections and Andes virus epidemic on the cruise ship Hondius

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The outbreak aboard the cruise ship Hondius in these days (May 2026), whose passengers are still under observation as these notes are being written, merits some reflections.

In less than fifty years, hantaviruses have become an emerging global threat [1].

Orthohantavirus is a genus of single-stranded negative-sense RNA viruses, belonging to the family *Hantaviridae* (subfamily *Mammantavirinae*) of the order *Bunyavirales* [2, 3]. The first isolated virus was named Hantaan virus by Lee et al., who found it in the lungs of its natural host, *Apodemus agrarius*, and identified it as the causative agent of Korean hemorrhagic fever, a disease that affected more than 3,000 United Nations soldiers during the Korean War (1950–53) [4, 5]. Interestingly, a similar disease was described in China long before, as early as the Warring States period (475–221 BCE) [6]. In 1980, a second hantavirus, named Puumala, was isolated in Finland from red voles (*Myodes glareolus*) and was found to be responsible for epidemic nephropathy, a disease reported in Fennoscandia since the early 1930s [7]. In 1993, an outbreak in the Four Corners region of the United States marked the first recognition in the Americas of a hantavirus, named Sin Nombre (SNV), capable of infecting humans [8, 9]. To date, at least 40 *Orthohantavirus* species have been isolated, and at least 25 of them have been shown to cause disease in humans [10]. In particular, 11 European and Asian virus species can cause hemorrhagic fever with renal syndrome (HFRS), while 14 American viruses can cause cardiopulmonary syndrome (HCPS).

It is estimated that 10,000 to over 100,000 hantavirus infections occur annually, with the vast majority caused by Eurasian species, while American viruses are responsible for about three hundred cases per year [11-14]. The fatality rate of HFRS ranges from more than 1% to 15%, while that of HCPS can reach up to 50% [1]. In 2025, the Region of the Americas reported 229 cases and 59 deaths, resulting in a case fatality ratio of 25.7%, as reported by eight nations [15].

Orthohantavirus infections are transmitted to humans by several species of wild rodents. Transmission is influenced by climatic and environmental variations, the ecology of rodent reservoirs, and human behavior [1]. Generally, such infections are the result of a "spillover" due to exposure to virus-contaminated and aerosolized rodent excreta (urine, feces, saliva). For all these viruses, except one, humans are "dead-end" hosts, unable to transmit the infection [16]. The only species of this genus that can be transmitted from human to human is Andes virus (ANDV, *Orthohantavirus andesense*), isolated in 1995 in the Andean region of Patagonia, of which five distinct lineages are known, named based on their geographic origin in Argentina and Chile [17, 18]. As of 2019, more than 1,200 confirmed cases of ANDV infection had been registered in Argentina [19]. The largest documented outbreak, which occurred from November 2018 to February 2019 in Epuyén, Chubut province (Argentina), resulted in 34 confirmed infections and 11 deaths, with a case fatality rate of 32.3%. There were up to four generations of hu-

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man infection, and the route of infection in secondary cases was possibly through inhalation of droplets or aerosolized virions. Transmission was driven by three symptomatic individuals attending crowded social events. The median reproductive number (the number of secondary cases caused by one infected person) was 2.12 and decreased to 0.96 after the implementation of containment measures. Patients with a high viral load were more likely than other patients to act as super-spreaders of the infection [20].

Although sampled 22 years apart, the ANDV strain involved (Epuyén/18–19) showed few genomic differences when compared to the strain implicated in the 1996 ANDV outbreak in El Bolsón, Río Negro Province, Argentina (Epilink/96) [20, 21]. Moreover, ANDV demonstrated high genomic stability following subsequent passage in vivo in Syrian hamsters, and a low number of mutations (two single nucleotide variants and one deletion) was found in the sequence isolated from semen 71 months after recovery from a HCPS survivor, suggesting limited replication activity in the infected host [22, 23].

The natural reservoir of ANDV is *Oligoryzomys longicaudatus* (*Rodentia, Sigmodontinae*), a small wild rodent that lives in Chile and Argentina, between 27° and 54° south latitudes, from sea level to approximately 1,000-1,500 meters above sea level. In Patagonia, it prefers clearings, roadsides, and bushy areas. It has been sighted in coastal and port areas, especially in central and southern Chile [24, 25]. Localized increases in populations of *O. longicaudatus*, named *ratadas* in Chile, occur variably from year to year, mainly in spring and summer, and are correlated with an increase in ANDV infections in rodents and humans [26, 27]. One Argentine study reported 9.2% antibody positivity in captured rodents [28].

In the Epuyén epidemic, the mean time from symptom onset in a primary case to the onset in a secondary case was 23 days, with a standard deviation of 7 days. The incubation periods ranged from 9 to 40 days [19]. The role of asymptomatic or pre-symptomatic individuals in transmitting the disease is not yet well defined, nor has it been established how frequent asymptomatic ANDV infections are. However, in Chile, follow-up of 476 household contacts of 76 confirmed ANDV infections identified 16 additional patients, resulting in a secondary attack rate of 3.4%. Sexual partners of a case had a risk of infection of 17.6%, compared with 1.2% for other household contacts [29]. Nosocomial transmission is rare [30, 31]. The risk of infection is higher in exposed individuals with the $_{\alpha V}\beta 3$ integrin TT genotype [32]. Based on these reports, the main risk factors for person-to-person transmission may include being a sexual partner, tongue kissing, and sleeping in the same room just before or during the symptomatic phase of the disease [1]. The persistence of the virus in semen for many months in a patient who recovered from ANDV-induced HPS supports the hypothesis that the virus could be sexually transmitted [23].

The entry receptor of ANDV is Protocadherin-1 (PCDH-1), expressed on the basolateral membrane of bronchial epithelial cells [33]. In human infections, the main pathogenic phenomenon is increased vascular permeability and acute thrombocytopenia, with marked enhancement of microvascular permeability [34, 35]. Thrombocytopenia can be observed early, even before the onset of cardiopulmonary symptoms, and is associated with progression to severe HCPS [36]. ANDV-infected patients may present hemorrhagic phenomena such as petechiae on the axilla and extremities [1]. ANDV-related HCPS is characterized by respiratory failure, pulmonary edema, and cardiogenic shock, with a case fatality rate of 21.4 – 35.9% [1]. In SNV infections, the cardiopulmonary phase lasts 2 – 4 days, and most deaths occur within the first 24 hours after hospital admission [35]. However, some patients do not progress to the cardiopulmonary phase after developing prodromal symptoms [37]. The risk of developing severe disease is 5.1-fold higher in individuals of European ethnicity compared to Amerindians [38]. IL-6 [39] and intestinal fatty acid-binding protein (I-FABP) [40] serum levels have been indicated as possible prognostic biomarkers for ANDV-associated HCPS severity and fatal outcomes. The replication cycle of SNV in infected patients is rather slow, resulting in late viremia on days 5 to 10 after infection [41]. An IgM humoral response against ANDV nucleocapsid protein was observed in almost all ANDV-related HCPS cases early after the onset of symptoms, while the IgG response becomes detectable after the first week. A weak IgG response is associated with higher mortality rates [1, 42]. Laboratory diagnosis is based on the detection of specific IgM antibodies and the viral genome in the blood using RT-PCR (Reverse Transcription Polymerase

Chain Reaction). Andes virus RNA is detectable in the blood two weeks before the onset of symptoms and antibody detection and remains detectable for weeks after the resolution of symptoms [43, 44]. White blood cells are the compartment with the highest viral load when compared to respiratory secretions, saliva, and urine, and are probably the best sample for diagnosis [45].

Currently, no drugs have been confirmed to be active against ANDV. Although ribavirin showed efficacy in animal models [46], no clinical benefit could be demonstrated in patients with HCPS caused by SNV [47], and management of HCPS remains primarily supportive. In SNV infections, higher neutralizing antibody titers at the onset of HCPS are associated with a greater likelihood of survival or experiencing a milder form of the disease [48]. Furthermore, neutralizing antibodies persist for prolonged periods after recovery, underscoring their importance in providing long-term immunity [48]. Studies are currently in progress on therapeutic monoclonal antibodies [49]. A vaccine candidate against ANDV has passed phase one trials [50].

What has emerged so far about the epidemic on the ship Hondius – as of 26 May, a total of 13 cases, including three death, with a case fatality ratio of 23% [51] – seems to be compatible both with the incubation times found in previous epidemics and with the available data on the basal reproductive number and the attack rate of this infection, both of which are quite low and containable by the precautions adopted during the epidemic. The high level of genetic similarity found in the preliminary analysis of the sequences obtained from patients' samples – with a maximum of one detected Single Nucleotide Polymorphism per individual – suggests that the outbreak originated from a single zoonotic spillover event, and seems to confirm the relative genetic stability of ANDV [52].

Although the presence of a virus causing a highly lethal disease on a cruise ship represents a sort of nightmare due to both the increased opportunities for infection to spread in a closed setting and the difficulty of monitoring people from many different countries for a long period after repatriation, this outbreak can be contained, and the characteristics of ANDV do not seem at present to make it a pandemic virus. However, particular attention should be paid to the spread of reservoir animals, partly due to climate change, and to the necessary precautions regarding potential contact with these animals, including during tourism activities. It should also be remembered that potentially dangerous viruses are also present in contexts close to large urban areas. For example, *Oligoryzomys flavescens* – a rodent belonging to the same genus as *O. longicaudatus* – that carries one ANDV lineages, the Lechiguanas virus, is abundant in Costanera Sur Ecological Reserve, a protected area in the city of Buenos Aires [53].

In conclusion, this incident deserves the full attention of international health authorities and its containment requires a strong, cohesive international collaboration. WHO has already published interim guidance for the management of contacts ANDV cases [54]. At a time when the WHO is weakened by the irresponsible exit of the US, this virus represents a further alarm bell about the possible cost of open loopholes in surveillance and prevention and once again calls into question the preparedness towards zoonoses originating from the wild [55], a topic that has been of interest to scientists for several years now [56, 57].

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None to declare.

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