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Emerging Viruses in Latin America

Contemporary Virology

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Introduction

Emerging microbial pathogens were responsible for the large epidemics of the past, and they continue causing outbreaks, epidemics, and pandemics around the world. Several infectious agents, such as dengue, chikungunya, malaria, and tuberculosis, are endemic in Latin America, negatively impacting public health in several countries in the region (Yeh et al. 2021). The microbial diversity in Latin America (Calisher 2013) is responsible for the continuous emergence of novel human pathogens.

Emerging viruses can cause self-limiting outbreaks when they infect isolated populations. However, in an increasingly interconnected world, these outbreaks can progress to regional epidemics, or even to pandemics, as we recently experienced with SARS-CoV-2 and COVID-19.

Historically, epidemics have been a constant scourge of humanity since the time when the first cities began to be established around the year 7500 B.C. in the fertile valleys of Mesopotamia, on the banks of the Nile River, and in the valleys of the Indus and Yellow rivers in Asia, among others. New pathogens, especially those coming from animals (zoonoses), managed to establish themselves in these populations, causing epidemics when they reached the critical mass needed to maintain the circulation of the new pathogen without depleting the population of susceptible individuals. It has been estimated that the minimum population density needed to sustain epidemics varied according to the pathogen, although it's thought to be in the order of 200,000 people (Dobson and Carter 1966).

Pathogens that are newly introduced among humans find populations without previous immunity and can cause widespread epidemics and pandemics. These pathogens establish a balance between their pathogenicity and the possibility to continuously circulate endemically in the human population. In the past, when cities grew in number and size, and communications were established between them, pathogens spread more widely and led to the first major epidemics and pandemics (McNeill 1976). With the increase in the world's population and its exposure to new pathogens, the danger of new epidemics and pandemics is real (Morens et al. 2004, 2008; Morens and Fauci 2013; Esparza and Vizcaino 2021).

The determinants for the emergence or reemergence of infectious diseases are several (Centers for Disease Control 2018). Perhaps the main one is the growth of the human population which has led to increasing urbanization and encroachment into new environments, with a consequent risk of "spilling over" of infectious pathogens from animals to humans. According to the World Health Organization, approximately 60% of known infectious diseases and 75% of emerging diseases are zoonotic in origin. Climate change has also impacted the spread of disease, best exemplified by the expanded distribution of vector-borne diseases. Global travel and trade also contribute to the worldwide spread of infectious diseases.

Most of the epidemics and pandemics in the recent past (influenza, HIV/AIDS, Ebola, dengue, chikungunya, Zika fever, COVID-19) have been caused by viruses, and it is reasonable to expect that additional viral agents could be incriminated in future outbreaks, epidemics, and pandemics.

The International Committee on Taxonomy of Viruses (ICTV) recognizes 4404 different virus species in all hosts, eukaryotes, and prokaryotes, with more than 200 virus species documented in humans. Theoretical calculations, based on the potential number of eukaryotic species on earth, place the estimated size of the virosphere (the total number of virus species on earth) in the order of 87 million eukaryotic viruses distinct enough to be considered different species (Geoghegan and Holmes 2017). Of course, not every existing eukaryotic virus has the potential to zoonotic spillover, which would depend on the distribution and intensity of infection in reservoir hosts, its release from the host, its survival and dissemination, its exposure to humans, and, lastly, the susceptibility of the human host (Plowright et al. 2017).

In this regard, it is instructive to remember the Rockefeller Foundation Virus Program that between 1951 and 1970 established virus isolation laboratories in seven different tropical countries (including Port of Spain in Trinidad and Tobago, Belem in Brazil, and Cali in Colombia) to increase the knowledge about arthropod-borne viruses and the involvement of these agents in human diseases (Theiler and Downs 1973). Using basic laboratory techniques, such as neutralization, complement fixation, and inhibition of hemagglutination, the program increased the number of recognized arborviruses from around 30 in 1951 to 300 in 1970. With the availability of modern technology, especially DNA and RNA sequencing, novel efforts are aiming to expand our knowledge of the virosphere, including the global hotspots that could originate emerging zoonotic diseases (Allen et al. 2017; Carroll et al. 2018).

This book, edited by Flor H. Pujol and Alberto E. Paniz-Mondolfi, compiles an important collection of articles written by distinguished Latin American scientists, discussing different aspects of emerging viruses in the region. The articles represent examples of the expertise existing in Latin America, essential to understanding the potential emergence and spread of viruses in the region and to prepare for confronting future viral threats.

The first chapter, by Grillet and Vincenti-González, reviews the impact of deforestation on the emergence of zoonotic viruses in South America, where the two most threatened tropical forests are the Amazon and the Atlantic Forests.

The following three chapters describe the South American hemorrhagic fevers caused by Hantaviruses and Arenaviruses. Mattar et al. (Chap. 2) describe the Hantaviruses that cause the hantavirus pulmonary syndrome, a group of viruses whose primary reservoirs are Sigmodontinae rodents. Cases have been diagnosed in all of South America, except Ecuador, with more than 43 genotypes reported. Various hantaviruses are distributed in the Americas: Sin Nombre Virus (USA), Black Creek Canal (USA), Choclo (Panamá), Calabazo (Panamá), Maripa (French Guiana), Andes (Argentina, Chile, Uruguay), Bermejo (Argentina), Laguna Negra (Paraguay, Bolivia), Mamore (Bolivia), Lechiguanas (Argentina), Juquitiba (Brazil), and Araraquara (Brazil), among others.

Hantavirus hemorrhagic fevers are life-threatening clinical syndromes, with a 15–30% fatality rate, characterized by an insidious onset of nonspecific signs followed by hemorrhagic manifestations and shock. Hantaviruses have clinical manifestations and histopathological findings similar to other hemorrhagic fevers such as dengue, Zika fever, yellow fever, malaria, encephalitis, leptospirosis, and rickettsia, making the differential diagnosis. Given the diversity of rodent species in the Latin America region, it can be predicted that more hantaviruses viruses will be discovered, and that some will cause human diseases with a high impact on public health.

Paniz-Mondolfi et al. (Chap. 3) report that in the western plains of Venezuela, cases of both hantavirus cardiopulmonary syndrome and hemorrhagic fever with renal syndrome are caused by the hantaviruses Caño Delgadito and Maporal. Additional research is needed to confirm the etiological diagnosis and to devise effective preventive strategies.

Silva-Ramos et al. (Chap. 4) review the epidemiology, pathology, clinical manifestations, and therapeutic approaches associated with the most prevalent South American arenaviruses: Guanarito, agent of the Venezuelan hemorrhagic fever; Sabiá, causing the Brazilian hemorrhagic fever; Machupo and Chapare, which cause hemorrhagic fever in Bolivia; and Junín, agent of Argentine hemorrhagic fever. These viruses have zoonotic origins and are primarily transmitted through contact with infected rodents, although person-to-person transmission can occasionally occur, especially in nosocomial settings. Their transition into infectious agents in humans coincided with environmental changes and shifts in agricultural practices, leading to explosive increases in host rodent populations. The spectrum of infections caused by these pathogens varies, ranging from self-limited febrile illnesses to severe hemorrhagic fever, with each virus presenting unique clinical manifestations.

The next two chapters bring us up to date on two viruses that were initially isolated in the early 1950s in Trinidad and Tobago by The Rockefeller Foundation Virus Program and are now emerging as potential threats in Latin America. Lednicky at al. (Chap. 5) review the situation with the Mayaro virus, a mosquito-borne alphavirus endemic in the tropical forest in Central and South America. While most Mayaro virus infections are usually asymptomatic, it can sometimes manifest as a debilitating arthritogenic disease, with symptoms like those encountered in severe cases of Chikungunya fever. Navarro et al. (Chap. 6) discuss the Oropouche virus, an arbovirus member of the genus Orthobunyavirus. The virus is maintained in a

transmission cycle involving midges as the arthropod vector and multiple vertebrates as potential wildlife hosts. Currently, the true public health impact of Oropouche fever remains poorly understood.

The next four chapters discuss COVID-19 in Latin America. Jaspe et al. (Chap. 7) describe how Latin America faced the challenge of genetically characterizing the variants of SARS-CoV-2. Although the World Health Organization recommended genomic surveillance through whole-genome sequencing, some countries with limited sequencing capacities adopted alternative rapid strategies, such as real-time PCR using variant-specific probes, or partial viral genome sequencing to effectively conduct genomic surveillance. These approaches allowed the Latin American region to describe the emergence, distribution, and evolution of the SARS-CoV-2 variants in real time.

Ascanio et al. (Chap. 8) review the phylogenomic of SARS-CoV-2 isolated from Venezuelan migrants residing in Colombia, shedding light on critical aspects of the virus's circulation in this context. Ramirez et al. (Chap. 9) describe how, in early 2021, Colombia detected a new variant, B.1.621, which quickly became the dominant strain in the country. After circulating for seven months, the World Health Organization labeled this Mu (B.1.621) variant as a "variant of interest," underscoring the need for genomic monitoring, continued vaccination, and booster shots to guard against new variants. Gaete-Argel et al. (Chap. 10) describe the development of an HIV-based SARS-CoV-2 pseudotype approach to assess neutralizing antibodies against SARS-CoV-2 in patients and immunized individuals. This system could represent an invaluable tool to characterize the humoral immunity against SARS-CoV-2 and other emerging viral pathogens in countries lacking access to appropriate biosafety facilities.

The last four chapters of the book exemplify basic science approaches to study emerging viruses in Latin America. In Chap. 11, Noya et al. discuss the use of synthetic peptides as a source of antigens for the detection of antibodies against infectious diseases. This approach could be of great value for the immunodiagnostic of future epidemics and pandemics.

Chapter 12, by Castillo et al., provides evidence suggesting that differences in the traffic of the non-structural protein NS1 of dengue virus exist between virus-infected mammalian and mosquito cells. This finding could have important implications for the understanding of the biology of the virus.

In Chap. 13, Palacios-Rápalo et al. present current findings about different FDA-approved drugs with activity against important emerging viruses in Latin America. They argue that repositioning drugs with antiviral activity can be a first line for treating emerging viral diseases.

Lastly, in Chap. 14, Peñaflor Téllez et al. discuss the replicative cycle of caliciviruses, showing that they depend on cellular factors for efficient replication. Recognizing viral and cellular molecules involved in calicivirus replication may help to develop antiviral therapies against human norovirus, an important calicivirus increasingly recognized as a leading cause of acute gastroenteritis worldwide.

These contributions represent relevant examples of the expertise existing in the Latin American region, essential for understanding the potential emergence and spread of viruses in the region and for preparing to confront future viral threats.

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José Esparza

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Chapter 2
Public Health Importance of Hantavirus Hemorrhagic Fevers in Colombia and South America

Salim Mattar, Jairo Chevel, Alfonso Calderon, Camilo Guzman, Anggie Ortiz, Ameth Salim Mattar, Alejandra Garcia, Liliana Sanchez, and German Arrieta

2.1 Introduction

Vector-transmitted hemorrhagic fevers (HFs) are a reason for emergency consultation, mainly in tropical countries. Among hemorrhagic fevers are those transmitted by rodents, such as *Hantavirus*, arenavirus, leptospirosis, and yersiniosis. They are distributed worldwide and have a high morbidity and mortality epidemiological burden. Over the past 50 years, there has been a spectacular emergence and reemergence of epidemics of vector-borne hemorrhagic diseases caused primarily by viruses believed to be under control, such as dengue, Zika, chikungunya, yellow

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fever, equine encephalitis, Saint Louis virus, arenavirus, *Hantavirus*, or other viruses that have extended their geographical distribution borders such as West Nile and Rift Valley fever. Hemorrhagic fevers caused by bacteria and parasites such as *Leptospira*, *Rickettsia*, and malaria have also reemerged (Guzmán et al. 2017; Mattar et al. 2013; Parra Barrera et al. 2023).

Hantaviruses and arenaviruses are natural viruses of rodents. In the last 5 decades, four South American hemorrhagic fevers caused by arenaviruses have emerged. All have similar clinical manifestations with hantaviruses, and the fatality rate is between 15% and 30%. Hantavirus infections have been increasingly recognized in South America since the description in 1993 of hantavirus pulmonary syndrome. Given the diversity of rodent species in the Americas region, it is possible to predict that more viruses will be discovered, and some will cause human diseases with a high impact on public health (Enria and Pinheiro 2000).

Various studies have demonstrated changes in global epidemiology, especially in the tropics. Population growth, urbanization, human activities, and climate change contribute to a continuous fluctuation in the epidemiology of vector-borne hemorrhagic fevers in the tropics. Hemorrhagic fevers caused by bacteria or viruses share many characteristics, making a clinical diagnosis difficult (Mattar et al. 2013, 2017). In the case of some viral hemorrhagic fevers, person-to-person transmission can occur through direct contact with blood, infected secretions, and even sexual transmission. Infectious agents are transmitted mainly by arthropods, rodents, and bats (Mattar et al. 2017). In hantavirus and arenavirus infections, the animal reservoirs are usually wild rodents; however, pets, domestic livestock, urban mice, monkeys, and other primates can also act as intermediate hosts. Viral hemorrhagic fever describes a life-threatening clinical syndrome characterized by an insidious onset of nonspecific signs followed by hemorrhagic manifestations and shock (Enria and Pinheiro 2000; Guzmán et al. 2017; Mattar et al. 2017). A combination of capillary leak syndrome and hemorrhagic diathesis also characterizes hemorrhagic fever syndrome. The clinical manifestations and histopathological findings are similar and make differential diagnosis problematic.

This chapter aims to show the public health importance of hantavirus hemorrhagic fevers in Colombia and South America.

2.2 Hemorrhagic Fevers Common in the Tropics Transmitted by Arthropods and Rodents

The etiological agents of hemorrhagic fevers (HFs) affect humans on all continents. Some of the arboviruses can cause heart failure and hemorrhagic manifestations. In the case of hantaviruses, arenaviruses, and leptospirosis, the animal reservoirs are generally rodents, some wild and others synanthropic (Mattar et al.

2013, 2017). Domestic livestock, monkeys, bats, and primates may also serve as intermediate hosts for these agents. Population growth, urbanization, human activities, and even climate change contribute to a continuing shift in the epidemiology of many arbovirus- and rodent-borne HFs. Hemorrhagic fevers share many common clinical features (Fig. 2.1). Infectious agents transmitted by arthropods, such as mosquitoes and ticks, cause many viral hemorrhagic fevers. Some viral hemorrhagic fevers and human-to-human transmission can occur through direct contact with infected patients with blood or secretions. It was recently shown that the Andes hantavirus can be transmitted from person to person (Martínez et al. 2020).

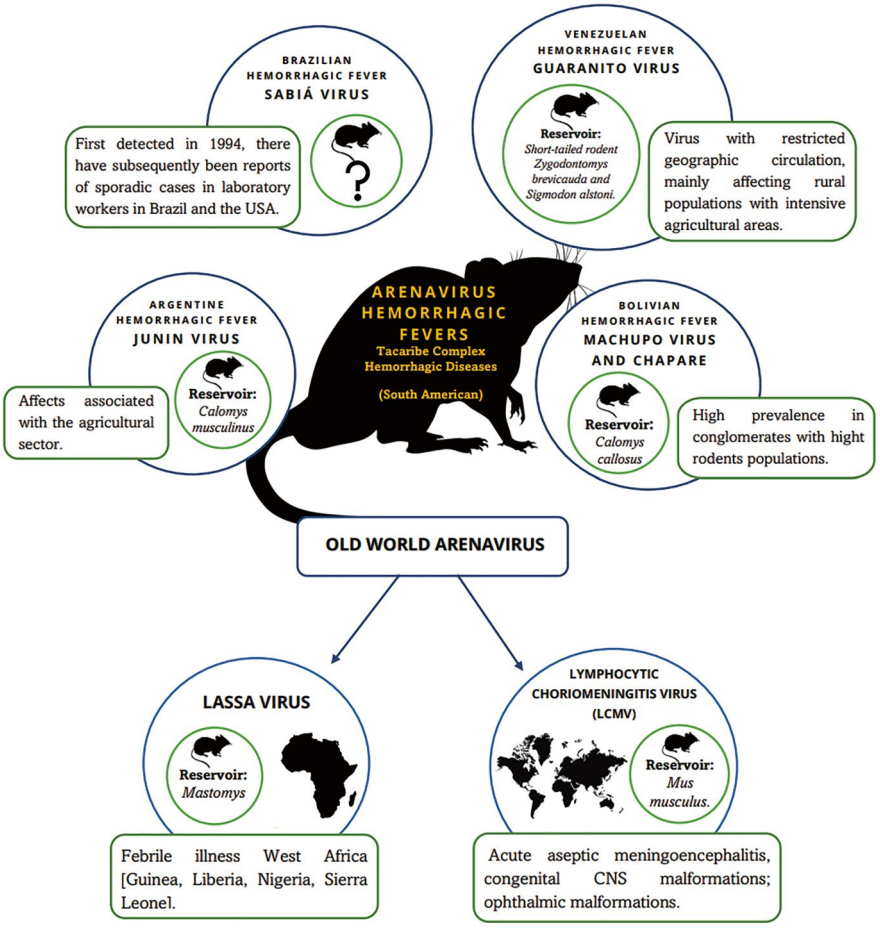

Fig. 2.1 Hemorrhagic fevers caused by arenavirus

2.2.1 *Arenavirus Hemorrhagic Fevers*

Since one of the differential diagnoses must be made with *Hantavirus*, arenaviruses that are also transmitted by rodents deserve essential mention. Four members of the Tacaribe complex of arenaviruses cause HF in humans: the Junín, Machupo, Chapare, Guanarito, Sabiá, and Juquitiba viruses (Mattar et al. 2011; Salazar-Bravo et al. 2002; Soto and Mattar 2010). Besides, there are the Old-World arenaviruses, the lymphocytic choriomeningitis virus (LCMV) in the Americas and the Lassa virus circumscribed in Africa (Fig. 2.1).

The Junín virus is the agent of Argentine hemorrhagic fever. The disease affects men more, probably due to the occupational risk associated with agricultural work. The mouse *Calomys musculinus* is recognized as the primary host of the Junín virus (Soto and Mattar 2010).

The Guanarito virus, the agent of Venezuelan hemorrhagic fever, mainly affects rural populations. Venezuelan hemorrhagic fever has been described near the Portuguese province in northwestern Venezuela, an area of intensive agriculture. In 1989, irregular cases of Venezuelan hemorrhagic fever were probably misdiagnosed as dengue before its detection as a distinct hemorrhagic disease. In Colombia, the circulation of the Guanarito virus was demonstrated in people from rural areas of the Caribbean department of Córdoba. The reservoir of the Guanarito virus is a short-tailed rodent called *Zygodontomys brevicauda* and *Sigmodon alstoni* (Mattar et al. 2011; Salazar-Bravo et al. 2002; Soto and Mattar 2010).

Regarding Bolivian hemorrhagic fever, the Machupo virus is considered the etiological agent discovered in 1962 during an outbreak of viral hemorrhagic fever. Outbreaks of Bolivian hemorrhagic fevers have occurred in cities and towns, probably related to factors that favored rodents' invasion of human homes. Outbreak control through good practices was achieved by implementing intensive rodent education and trapping programs. The reservoir of the Machupo virus is a sunset mouse called *Calomys callosus*. In 2019, an outbreak of FH was described in Bolivia with a new etiological agent called Chapare virus (Silva-Ramos et al. 2021).

Regarding Brazilian hemorrhagic fever, the Sabiá virus is recognized as the etiological agent. The Sabiá virus was detected in 1994 in a Brazilian patient who was believed to have yellow fever, at which time he was diagnosed with viral hemorrhagic fever. Subsequently, cases of human disease caused by the Sabiá virus have been reported. The reservoir of this virus is unknown, but it is assumed to be a South American rodent. Sporadic cases of Sabiá virus infections have been reported among laboratory workers in Brazil and the United States (Soto and Mattar 2010).

In addition to the South American hemorrhagic viruses described above, the main Old-World arenaviruses are lymphocytic choriomeningitis virus (LCMV) present in the Americas and the Lassa virus. LCMV has a global spread, which coincides with the geographic dispersal of its primary host, the ever-present house

mouse *Mus musculus*. LCMV causes acute aseptic meningoencephalitis and congenital CNS and ophthalmic malformations (Mehl et al. 2023; Soto and Mattar 2010). Recently, in Germany, the reappearance of LCMV (lineages I and II) in wild house mice (*Mus musculus domesticus*) and of LCMV lineage I in a sick golden lion tamarin (*Leontopithecus rosalia*) from a zoo in Germany was reported. The mouse population at this site suggests an outbreak following a recent introduction from two different sources or long-term persistence in the local house mouse population but with an apparent low prevalence (Mehl et al. 2023). Lassa fever is a significant cause of illness in West Africa; between 100,000 and 300,000 cases and numerous deaths related to the Lassa virus are projected. Cases are mainly reported in hyperendemic or endemic foci in West African countries: Guinea, Liberia, Nigeria, and Sierra Leone. Recent Lassa outbreaks occurred during the COVID-19 pandemic in some African countries (CDC 2022).

2.3 Hantavirus

Hantaviruses in the Americas cause hantavirus pulmonary syndrome (HPS) in humans; the primary reservoirs of these viruses are rodents of the *Sigmodontinae* subfamily (Guzmán et al. 2017; Moore and Griffen 2023). In Cuba and other Caribbean islands, such as Grenada, Barbados, and Trinidad and Tobago, cases of *Hantavirus* in rodents and humans have been reported (Adesiyun et al. 2011; Groen et al. 2002; Kumar et al. 2016; Rovida et al. 2013; Sharma et al. 2019). In Fig. 2.2 are depicted the hantaviruses in the Americas and the reservoir involved.

In Central America, Nicaragua, Costa Rica, and Panama, hantaviruses have been found in humans and rodents (Armien et al. 2004; Yih et al. 2019). In South America, cases of hantavirus pulmonary syndrome have been diagnosed in Colombia, French Guiana, Brazil, Peru, Bolivia, Argentina, Chile, Paraguay, and Uruguay, with numerous viral genotypes identified in humans and rodents (Fig. 2.2). In Colombia between 2004 and 2006, using Sin Nombre virus (SNV) antigens, the first serological studies carried out in the Colombian Caribbean were published, which reported the circulation of *Hantavirus* in humans (Máttar and Parra 2004) and in rodents (Alemán et al. 2006). Later, in 2011, the genetic identification of a new hantavirus was carried out in rodents from Urabá, Antioquia, Colombia (Londoño et al. 2011). In 2012, another study demonstrated human infection using hantavirus antigens from the South American Maciel and Araraquara strains (Guzmán et al. 2013). In Córdoba, an area of the Colombian Caribbean, a study of undifferentiated tropical fevers reported four cases of patients infected by *Hantavirus* and two cases of dengue and *Leptospira* coinfections with *Hantavirus* (Mattar et al. 2017). In 2023, in the same department of Córdoba, a patient coinfected with malaria and *Hantavirus* was found (Tique-Salleg et al. 2023).

Fig. 2.2 Description of the principal hantaviruses and reservoirs in the Americas. The reservoir (when known) for each virus is given after its name

2.3.1 Biological Characteristics of Hantaviruses

The viruses of the *Bunyaviridae* family are divided into five genera: *Orthobunyavirus*, *Phlebovirus*, *Nairovirus*, *Tospovirus*, and *Hantavirus*. All of these families, except for hantaviruses, are arboviruses (arthropod-borne viruses) and have cycles of wild transmission between wild vertebrate hosts or plants (tospoviruses) and hematophagous arthropods (Schmaljohn 2007). Members of each genus differ by the mode of replication, other molecular characteristics, and the lack of antigenic relationships between members of different genera.

Hantaviruses have a 71–149 nm (average diameter of 112 nm) and present glycoprotein projections on their surface Gn and Gc fixed to a lipid bilayer approximately 7 nm thick, thus forming the viral envelope (Albornoz et al. 2016). Electron microscopy studies show that most viral particles are spherical; however, elongated shapes are commonly found in infected tissues. Hantaviruses comprise a

single-stranded RNA genome of negative polarity and are tri-segmented, located in a helical capsid. The three RNA segments, L, M, and S, have different sizes and functions. The L (large) or "large" segment encodes the L protein (247 kDa-dependent viral RNA polymerase). The M (medium) or "median" segment encodes the 58 and 68 kDa glycoproteins Gn and Gc (Albornoz et al. 2016). The S (small) segment encodes the 50 kDa nucleocapsid protein called N. The total genomic RNA size range for hantaviruses is 11,845 nucleotides (nt) and 12,317 nt for the unnamed virus (SNV). They have four structural proteins: a nucleocapsid protein N, which constitutes the major antigen of hantaviruses and is the cause of cross-reactions between the different viruses (genus-specific antibodies), which complement fixation and immunofluorescence and ELISA can detect. The glycoproteins (Gn) and (Gc) are in the virion envelope. Both are specific antigens that have hemagglutinating capacity and induce the formation of neutralizing antibodies in infected animals. The last protein, L, is attributed to RNA polymerase activity (Moreno et al. 2014).

Regarding *Hantavirus* immunity, high titers of neutralizing antibodies in plasma have been found in survivors of the disease against the type of *Hantavirus* that prevails in the patient's region. At the same time, there were no substantial titers against the heterologous agent of other hantaviruses. In the group of participants, neutralizing antibody titers could be detected after infection up to 11 years after the disease. Titers of up to 1:1600 could be detected. These results suggest that plasma from patients surviving hantavirus infection is a potential source of neutralizing antibodies and could be used as a therapeutic alternative for patients with acute illness or as a prophylactic intervention for people who may have been exposed to the virus (Valdivieso et al. 2006).

On the other hand, it is interested in the relationship between lipopolysaccharide (LPS) or endotoxin and the severity of hantavirus disease (Douglas et al. 2019). The Gram-negative bacteria shed endotoxin during their normal growth; studies have been conducted to establish the association of endotoxin levels with the severity of hantavirus disease based on hospitalization and disease severity (Douglas et al. 2019). Serum endotoxin levels are associated with hantavirus and hospitalization and disease severity ($p < 0.01$). Studies observed hantavirus replication in the intestine of patients, the gastrointestinal tract as a possible entry route for infection, and evidence of microbial translocation and its impact on the severity of hantavirus disease. There is believed to be a significant correlation between serum endotoxins and the severity of hantavirus disease and hospitalization in hantavirus-infected patients (Douglas et al. 2019).

Bunyaviridae's replication begins with the virus's attachment to the target cell. Some studies have described that this binding process would be mediated by the interaction of viral glycoproteins (Gn and Gc) with cellular integrins (Albornoz et al. 2016). Other researchers propose that a 50 kDa cellular protein would be directly involved in virus attachment to the cell (Cifuentes-Muñoz et al. 2014). Then, entry and undressing of the virus occurs, probably mediated by endocytosis and fusion of the viral membrane to endosomes (Albornoz et al. 2016). Subsequently, there is a primary transcription event in which the negative-sense viral RNA

produces the synthesis of messenger RNA (mRNA) using primers derived from the mRNA of the host cell and the polymerase associated with the virus (Moreno et al. 2014). Next, the M fragments' mRNA translation process is carried out in the ribosomes associated with the Golgi apparatus membrane. Glycosylation of the envelope proteins occurs here. It is currently known that Sin Nombre hantavirus's Gn and Gc glycoproteins can be expressed independently through a different start codon (Cifuentes-Muñoz et al. 2014). Subsequently, there is a synthesis of complementary positive-sense RNA, which serves as a template for the formation of viral RNA and the viral replication process. The packaging signals for hantavirus assembly are not well-known, but based on electron microscopy studies with Black Creek Canal viruses (Spiropoulou et al. 2003), they suggest that New World hantaviruses would assemble in cellular areas associated with the plasma membrane, in contrast to the Old World hantaviruses that would do it in the Golgi reticulum. Finally, the fusion of the plasma vesicles with the plasma membranes occurs and, consequently, the release of mature viral particles.

2.3.2 Hantavirus Reservoirs

The study of hantaviruses under the One Health vision is currently essential. A good model for the reservoirs was obtained in Northwest Argentina. Temperature, precipitation, and vegetation cover were the variables that contributed the most to the models. In total, 945 cases of HPS were recorded, of which 97.85% occurred in the highest-risk areas. It was estimated that 18% of the population of Northwest Argentina was at risk, and 78% of the cases occurred less than 10 km from the deforestation. Niche overlap occurred between *Calomys fecundus* and *Oligoryzomys chacoensis*. The study identified areas of potential risk for the transmission of HPS based on climatic and environmental factors that determine the distribution of reservoirs and the transmission of *Orthohantavirus* in Northwest Argentina (López et al. 2023).

2.3.3 Hantavirus Reservoirs Other than Rodents

It has been suggested that hantaviruses adapted to coexist with their reservoirs without causing harm, but new hosts, such as domestic animals and humans, can be highly pathogenic (Lee et al. 2014). The first *Hantavirus*, the *Thottapalayam virus*, was isolated from the Asian house shrew (*Suncus murinus*) in India in 1964 (Carey et al. 1971). Recent phylogenetic analysis suggests that hantaviruses first appeared in the order Chiroptera (bats) or Talpidae (moles) and Soricidae (shrews) before appearing in rodents (Guo et al. 2013). Bats, the only flying mammals, can travel great distances, and their extraordinary immune system also means they can harbor many pathogens. The circulation of chiropterans in rural and urban areas

in America may be of public health importance for studying viruses of the *Bunyaviridae* family.

In South America, hantaviruses have been detected in new reservoirs: in Brazil, in the lungs and kidneys of three species of marsupials (*Micoureus paraguayanus*, *Monodelphis ihering*, and *Didelphis aurita*). Also, in Brazil, *Diphylla ecaudata* and *Anoura caudifer* were found in bats; analyses of the partial S-segment sequences revealed that these hosts were infected with Araraquara virus strains (de Araujo et al. 2012). The Araraquara virus was detected in nine bat sera in different trophic groups, such as frugivores, carnivores, and hematophagous. Hantavirus was higher than rodents from the same region (Sabino-Santos et al. 2020). In another work with Old World bats, hantaviruses were only demonstrated in insectivorous bats (Guo et al. 2013). In deforested areas of the Amazon, hantaviruses were found in omnivorous bats *Phyllostomus hastatus* and the frugivorous *Dermanura gnoma* (Sabino-Santos et al. 2020).

Recent studies in bats from urban areas of Sao Paulo (Brazil), *Molossus*, long-tongued bat *Glossophaga soricina*, and Wagner's mastiff *Eumops glaucinus*, found specific IgG antibodies against the orthohantavirus nucleoprotein (Bueno et al. 2023).

In China, new hantaviruses have been described in bats and shrews; the Huangpi virus was found in *Pipistrellus abramus* (European shrew). The existence of four phylogroups of hantaviruses that infect a wide variety of mammalian hosts suggests possible transmission between species. The finding in various wild mammals suggests the critical role during the evolution of hantaviruses. The host jump demonstrates that co-divergence has played an essential role in the evolution of hantaviruses, making bats important natural reservoirs and that new hantaviruses may emerge in the future (Guo et al. 2013).

In China, the Laibin hantavirus was identified and transmitted by black-bearded bats (*Taphozous melanopogon*). Genomic analyses showed that Laibin is only distantly related to all bat-borne hantaviruses (Xu et al. 2015). In the European bat (*Nyctalus noctula*), a new provisional species of *Hantavirus*, the Brno virus, was identified, representing the first *Hantavirus* found in European bats (Straková et al. 2017). In Myanmar, *Hipposideros pomona* bats and *Hipposideros cineraceus* bats in Vietnam showed that more than one host species could harbor the Xuân Sơn virus (Arai et al. 2019) In Malaysia, in *Murina aenea* bats, sequence and partial genome segment analyses suggest that the identified virus may represent a new species of the *Mobatvirus* genus within the *Hantaviridae* family (Zana et al. 2019).

2.3.4 Epidemiology of Hantaviruses in the Americas

Hantaviruses and arenaviruses in the Americas have wild cricetid rodents (subfamilies Sigmodontinae, Arvicolinae, and Neotominae) as their reservoir (Montoya-Ruiz et al. 2014), except for the case of Tacaribe arenavirus isolated from a fruit bat of the genus *Artibeus* (Salazar-Bravo et al. 2002). The infection they establish in rodents is persistent and with little or no symptoms. Transmission to humans is

carried out through inhalation or contact of the mucous membranes with material contaminated with excreta from infected rodents, causing febrile syndromes that range from banal episodes to severe pulmonary symptoms with hemorrhagic manifestations (Navarrete et al. 2016). The clinical characteristics of hantavirus infection may differ depending on the species of virus that infects an individual; the indigenous viruses from Asia and Europe focus the most significant clinical damage on the kidney and those present in America, on the lung and heart (Jonsson et al. 2010) (Fig. 2.2). Analyzes of hantavirus epidemiological situations show that they are seasonal endemic diseases, which sometimes present as conglomerates of cases (clusters). Some observations indicate that patients infected by the Andes and Sin Nombre viruses can be transmitted from person to person through aerosolized particles. This phenomenon occurs during the febrile phase that characterizes the onset of the disease (OPS/OMS 2019; Padula et al. 1998).

HPS is not a new disease; in the United States, a retrospective study was carried out to establish the first cases of *Hantavirus*. The researchers examined stored lung tissue samples from people who had died from an unexplained lung disease. Some of these samples showed evidence of previous infection with SNV, indicating that the disease had existed before the first known 1993 outbreak. Cases of HPS were then discovered from tissue samples of people who had died of unexplained adult respiratory distress syndrome. Using this retrospective method, the first known case of HPS was that of a 38-year-old man who died in 1959 in Utah (CDC 2020).

The first described outbreak of hantavirus pulmonary syndrome (HPS) in the Americas occurred in 1993 in Four Corners, a geographical site where Arizona, Colorado, New Mexico, and Utah meet. A hantavirus was identified in that place, called the Sin Nombre virus (SNV) (Nichol et al. 1993). In addition, the virus was found in the rodent and natural host *Peromyscus maniculatus*. As of the end of 2021, 850 cases of hantavirus disease have been reported in the United States since surveillance began in 1993. These were laboratory-confirmed cases and included HPS and non-pulmonary hantavirus infection, with 556 cases occurring since 1993; 74% of patients were white, 17% were American Indian/Alaska Native, and 35% of reported cases were fatal. The mean age of the patients was 38 years (range, 5–88 years) (CDC 2023). In 2012, the US National Park Service reported nine confirmed cases of hantavirus infection in people who visited Yosemite National Park (Núñez et al. 2014).

In South America, the first *Hantavirus* associated with HPS was described in 1994 in Brazil (Silva et al. 1997) and was called Juquitiba; the reservoir is unknown. From 1993 to 2012, more than 1400 cases had been identified in 14 states of Brazil. These cases were caused by five strains of *Hantavirus*: Araucaria, Araraquara, Laguna Negra, Castelo dos Sonhos, and Anajatuba (Jonsson et al. 2010). These strains have as reservoirs the rodents *Oligoryzomys nigripes*, *Necromys lasiurus*, *Calomys* sp, *Oligoryzomys fornesi*, and *Oligoryzomys utiaritensis*, respectively.

In Argentina, the International Committee on Taxonomy of Viruses (ICTV) recognizes two species of *Hantavirus*: the Laguna Negra virus (LANV) and the Andes virus (ANDV), with numerous variants, present in different reservoirs and geographic locations (Iglesias et al. 2016). The province with the highest incidence is

Salta, next to Buenos. Currently, three different endemic areas are identified in Argentina: Northwest (Salta, Jujuy), Center (Buenos Aires, Santa Fe, and Entre Ríos), and South (Neuquén, Río Negro and Chubut) (Pantozzi et al. 2011). In the province of Buenos Aires until 2010, five genotypes were isolated: AND-Lechiguanas, AND-Bs.As, and AND-Plata, associated with cases of HPS and being reservoirs of rodents of the genus *Oligoryzomys* spp. and *Pergamino* (PRG) and *Maciel* (MAC) not associated with cases and whose reservoirs are *Bolomys obscurus* and *Akodon azarae*, respectively (Bellomo et al. 2009). Recent studies on ANDV transmission in Argentina demonstrate that a single introduction of ANDV from a rodent reservoir into the human population was possible. Transmission was possible through three symptomatic people who attended a crowded social gathering. After 18 cases were confirmed, public health officials imposed isolation of people with confirmed cases and quarantined potential contacts (Martínez et al. 2020). The median reproductive number was 2.12. The complete genome sequencing of the ANDV strain involved in the outbreak was performed with samples from 27 patients (Martínez et al. 2020). It showed that the strain present (Epuyén/18-19) was similar to the causative strain (Epilink/96) in the first outbreak in 1996 of person-to-person transmission of HPS caused by ANDV, which occurred in El Bolsón, Argentina. Clinical investigations involving patients with ANDV HPS revealed that patients with a high viral load and liver injury were more likely to spread the infection (Martínez et al. 2020).

The experimental animal model with Syrian hamsters confirms what was observed in El Bolsón and demonstrates that horizontal transmission of ANDV occurs efficiently in both inoculated hamsters and those infected by contact (Riesle-Sbarbaro et al. 2023).

In Chile, cases have been reported since 1995; the first outbreak occurred in Coyhaique in September 1977, which included two families with a fatality rate of 64%. Since then, it has occurred endemically with a marked seasonal increase that begins in late spring. Cases of SCPH have been confirmed from Valparaíso to Aysén, which frequently occur as regional outbreaks. The highest incidence, in decreasing order, corresponds to the regions of Aysén, Los Lagos, Araucanía, and Bío. Until September 2012, 786 cases had been reported in Chile. Eighty percent of the total accumulated cases of SCPH (Ministerio de Salud de Chile 2023) correspond to men, and the median age of the cases is 29 years. Living in rural areas continues to be the most crucial risk activity, with 49% of cases. Between 2017 and 2021, 261 cases were reported (Ministerio de Salud de Chile 2023).

In Bolivia, the first *Hantavirus* reported was the Río Mamoré virus (RMV), isolated from an *Oligoryzomys microtis* captured in 1964 (Silva-Ramos et al. 2021) (Fig. 2.2); this virus was not associated with human disease. In 1997, the Laguna Negra virus (LNV), whose host is *Calomys laucha*, was identified in a patient in Santiago, Chile, who had been on an extensive trip to Bolivia before presenting the disease (Johnson et al. 1997; Jonsson et al. 2010; Silva-Ramos et al. 2021) (Fig. 2.2).

In Uruguay, the first three cases of HPS were recorded in 2004, on the border with Brazil. The cases were associated with the Lechiguanas and Andes Plata strains, which have the rodent *Oligoryzomys fulvescens* as a natural reservoir.

However, one study found Juquitiba virus in the rodents *Oligoryzomys nigripes* and *Oxymycterus nasutus* (Delfraro et al. 2008; Jonsson et al. 2010) (Fig. 2.2).

In Paraguay, an HPS outbreak occurred in an agricultural community in the Chaco region in the spring and summer of 1995–1996 (Johnson et al. 1997). There was serological confirmation of six additional cases identified retrospectively in the region between 1987 and 1994. The case fatality rate during the outbreak was 12% (Insaurralde and Páez 2008) (Fig. 2.2). The Laguna Negra virus was identified as the etiological agent, and the mouse *Calomys laucha* was identified as the primary reservoir of this *Hantavirus*. In November 2011, two cases of *Hantavirus* caused by the Mamoré River hantavirus occurred in two rural communities in the Peruvian Amazon (Casapía et al. 2012). Both patients progressed to adult respiratory distress syndrome and refractory shock. One patient died, and the other recovered after 12 days. In both cases, the diagnosis was molecular.

Between 1999 and 2000, 12 cases of *Hantavirus* were reported in Panama. The *Hantavirus* identified in this country was called Choclo virus, and its natural host was determined to be *Oligoryzomys fulvescens* (Armien et al. 2004) (Fig. 2.2).

In 2008, the first human case of hantavirus was detected in French Guiana. The complete genomic sequence of Maripa virus was identified from a patient with hantavirus pulmonary syndrome (Matheus et al. 2023). The prodromal phase was characterized by fever (77.8%), myalgia (66.7%), and gastrointestinal symptoms (vomiting and diarrhea, 55.6%) that began, on average, 5 days before the illness, which was characterized by respiratory failure in all patients. Five patients died (55.6%), and the length of stay in the intensive care unit was 19 days (range, 11–28 days) for survivors (Matheus et al. 2023). The Maripa virus corresponds to a new variant of the Rio Mamoré virus species of the *Bunyaviridae* family, the *Hantavirus* genus. Until 2022, nine cases were confirmed by RT-PCR and IgM serology have been reported in French Guiana (Matheus et al. 2023).

In 2004, the first serological evidence of hantavirus circulation was reported in Colombia. A prevalence of hantavirus antibodies of 13.5% was found in workers in Caribbean rural areas of departments of Sucre and Córdoba (Máttar and Parra 2004). Later, in 2006, a prevalence of 2.1% was detected in 336 rodents captured in 11 municipalities in the department of Córdoba (Alemán et al. 2006). In 2012, a study demonstrated infection in humans using hantavirus antigens from the South American strains Maciel (Argentina) and Araraquara (Brazil) (Londoño et al. 2011). IgG antibodies were found in 10/288 (3.5%) human sera using the Maciel antigen and 21/288 with the Araraquara antigen (7.34%), with titers between 1/400 and 1/25,600. Of the seropositive IgG specimens, two (0.7%) resulted in titers of 1/400 of IgM anti-Araraquara hantavirus antibodies. This would mean that Colombian strains cross antigenically with these South American strains or that these viruses also circulate in Colombia. In 2012, hantavirus seropositivity was reported in rodents of the Murinae subfamily in the Sucre (Colombia) department, demonstrating the circulation of *Hantavirus* in rodents in northern Colombia (Máttar and Parra 2004; Soto and Mattar 2010). In Colombia, there are two cases of hantavirus infection. The first was a patient enrolled in a clinical trial for hemorrhagic fevers in the department of Córdoba (Mattar et al. 2014). Serum samples were collected from the

patient upon admission and discharge. The ELISA test was used with the SNV antigen, and the paired samples showed seroconversion of IgG and IgM. The finding of this first case of hantavirus infection in Colombia is consistent with the high seroprevalence found against *Hantavirus* in humans in the Caribbean region and the patient's exposure to rodents (Mattar et al. 2014). In another work carried out in the plains of eastern Colombia in the department of Meta, three cases of hantavirus infection were diagnosed. The disease was diagnosed by seroconversion of specific IgG antibodies against SNV in three people, two women and one male (Sánchez Lerma et al. 2015). The confirmed cases showed common characteristics: the average was 5 days from the onset of symptoms, fever >39 °C, myalgias, arthralgias, generalized fatigue, nausea, vomiting, diarrhea, headache, abdominal pain, and skin rash. Other findings included increased hematocrit, creatinine levels, and white blood cell counts (Sánchez Lerma et al. 2015). All patients had thrombocytopenia, significantly low platelet counts (98,000, 24,000, and 29,000), and mildly elevated liver enzymes. Chest X-rays were regular. The patients did not have pulmonary edema, only mild respiratory symptoms (Sánchez Lerma et al. 2015). The only two studies that have reported cases in Colombia are similar to those in Panama. In that country, 21% of patients diagnosed with HPS did not show pulmonary edema, and 44% had mild HPS with mild edema but without respiratory failure (Mattar et al. 2014; Sánchez Lerma et al. 2015).

The clinical presentation of hantavirus infection without pulmonary involvement has also been observed in the United States. In 2014, in response to atypical hantavirus cases, the United States expanded national reporting of laboratory-confirmed hantavirus infections to include HPS and non-pulmonary hantavirus infection, a disease with nonspecific viral symptoms, such as fever, chills, headache, head, and fatigue, but without cardiopulmonary symptoms. Reporting of non-pulmonary hantavirus cases began in 2015 (CDC 2023). This clinical presentation has been seen in Colombia and Panama (Mattar et al. 2014; Sánchez Lerma et al. 2015).

Both Central America and the Caribbean also have cases of hantavirus in humans, as well as evidence of infection in rodents. In Grenada, a prevalence of antibodies was found in 47 (27.5%) brown rats *Rattus norvegicus*, a known reservoir of Seoul Old World hantavirus. There were no significant differences related to the age and sex of the seropositive rats. Although there are no reports of hantavirus in humans in Granada, infection in reservoirs is a risk factor for disease transmission (Sharma et al. 2019). A work from the island of Barbados in the Caribbean demonstrated evidence of hantavirus exposure in both rats and humans (Groen et al. 2002; Kumar et al. 2016). The first documented evidence of hantavirus infection in Trinidad and Tobago was made in 236 people; 27 (11.4%) tested seropositive IgG for hantavirus infection. Among slaughterhouse workers, the infection frequency was 9.4% (6/64), compared to a seropositivity rate of 12.4% (18/145) and 11.1% (3/27) among livestock farm workers, office workers, and other people with minimal contact with animals, respectively. However, the differences were not statistically significant ($p > 0.05$). Age, sex, and race did not significantly affect the rate of hantavirus infection in the workers studied (Adesiyun et al. 2011). In Cuba, a European tourist

acquired a hantavirus disease (Rovida et al. 2013). In Nicaragua, hantavirus antibodies were found in mining workers (Yih et al. 2019).

2.4 Laboratory Diagnosis

In endemic areas, no clinical or laboratory signs are pathognomonic of hantavirus infection, so knowledge of local epidemiology and high clinical suspicion are necessary. Viral isolation of *Hantavirus* is complicated and, therefore, little used in current practice. Furthermore, this technique involves direct contact with the virus, which is highly infectious, so it should only be performed in category four biosafety level laboratories. Since 1993, RT-PCR (polymerase chain reaction coupled to reverse transcriptase) specific for hantaviruses has been created that can be used in category three laboratories and allow the diagnosis of the virus in the acute phase of the disease. However, the sensitivity of this test decreases in the convalescent phase (CDC 2023). In current practice, serology is the most used method for diagnosing the disease. Almost all patients with HPS have a positive IgM titer at the time of evaluation. In a patient with a compatible clinical picture, a positive ELISA or IFA IgM titer allows a presumptive diagnosis to be made, which must be confirmed.

2.4.1 Molecular Diagnosis of Hantavirus

Routine diagnosis of *Hantavirus* is made through serological tests; however, molecular tests are used to confirm acute infection. The polymerase chain reaction (PCR) is the gold standard for the molecular diagnosis of *Hantavirus*, and the S segment of the genome, mainly the nucleoprotein gene, is the most used because it is highly conserved (Nunes et al. 2019). For New World hantaviruses, RT-PCR and nested-PCR have been described (Moreli et al. 2004). Currently, real-time RT-PCR has reduced laboratory processing times. The latter can be performed using the sequence GCAGCTGTGTCTACATTGGAGAA (forward) TGGTTTTGAAGCCAGTTTTTTGA (reverse) and FAM AAACTC/ZEN/GCAGAACTCAAGAGA CAGCTGGC IwBFQ as a probe (Nunes et al. 2019). Molecular diagnosis is difficult due to the long prodrome of the infection, which does not allow easy detection of viremia; molecular diagnosis has application in postmortem specimens.

2.4.2 Differential Diagnosis

Hantavirus infection depends on the patient's infection phase. In the prodromal phase, the diagnosis presents differential viral states with nonspecific or febrile syndromes of undetermined origin. For the cardiopulmonary phase, in which

pulmonary and cardiac involvement is established, the diagnosis must be made considering the differentiation of pathologies that involve acute respiratory failure (Mattar et al. 2013). These pathologies are differential diagnoses in the prodromal and cardiopulmonary phases of HPS in immunocompetent patients. The period of hantavirus viremia is asymptomatic and lasts up to 7 days; the differential diagnosis must be made with severe atypical pneumonia (CDC 2023; Guzmán et al. 2017; Jonsson et al. 2010; Padula et al. 1998). In the early phase of infection, the complete blood count is the most helpful laboratory test to distinguish hantavirus infection (especially HPS) from atypical types of pneumonia caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* spp. Eighty-seven percent of patients with HPS have hemoconcentration, leukocytosis, and thrombocytopenia. Influenza pneumonia often occurs in outbreaks during the winter and has more upper respiratory symptoms and signs, including cough, sore throat, runny nose, and conjunctivitis (CDC 2020; Guzmán et al. 2017; Núñez et al. 2014; OPS/OMS 2019). In the pulmonary hemorrhagic phase, leptospirosis rarely presents with jaundice, kidney disease, or hemorrhagic manifestations in other tissues (CDC 2020; Guzmán et al. 2017; Núñez et al. 2014; OPS/OMS 2019). Rickettsiosis is characterized by a maculopapular rash, which can evolve into hemorrhagic papules that simulate other hemorrhagic fevers. In the laboratory, the leukocyte count is usually average. The diagnosis is based on the presence of an inoculation eschar (tick bite). Signs may be multisystem and may include pulmonary edema. Figure 2.3 shows the difficulty of differential diagnosis of hemorrhagic fevers (CDC 2023; Jonsson et al. 2010; Núñez et al. 2014; Padula et al. 1998; Pantozzi et al. 2011).

2.5 Clinical Presentation of Hantavirus Disease

Clinical manifestations can range from mild or asymptomatic to severe manifestations with large capillary leaks that lead to shock, multiorgan failure, and death. The following forms of presentation can be considered:

- Undifferentiated febrile syndrome of viral origin
- Hantavirus cardiopulmonary syndrome (HPS)
- Febrile hemorrhagic syndrome with renal involvement (FHSR)

The incubation period varies between 7 and 45 days. In some cases, the information available has allowed a better estimate, adjusting this period to 9 and 24 days. The undifferentiated febrile syndrome is prevalent in South America; the manifestations are similar in most viral, parasitic, or bacterial infections (Guzmán et al. 2017; Mattar et al. 2017). It presents with fever, general malaise, myalgias, and arthralgias lasting 3–7 days, sometimes with respiratory manifestations of the lower airway of mild to moderate severity and, less frequently, headache. Laboratory findings such as thrombocytopenia, leukopenia or leukocytosis, and anemia may be found (CDC 2023; Iglesias et al. 2016; Jonsson et al. 2010).

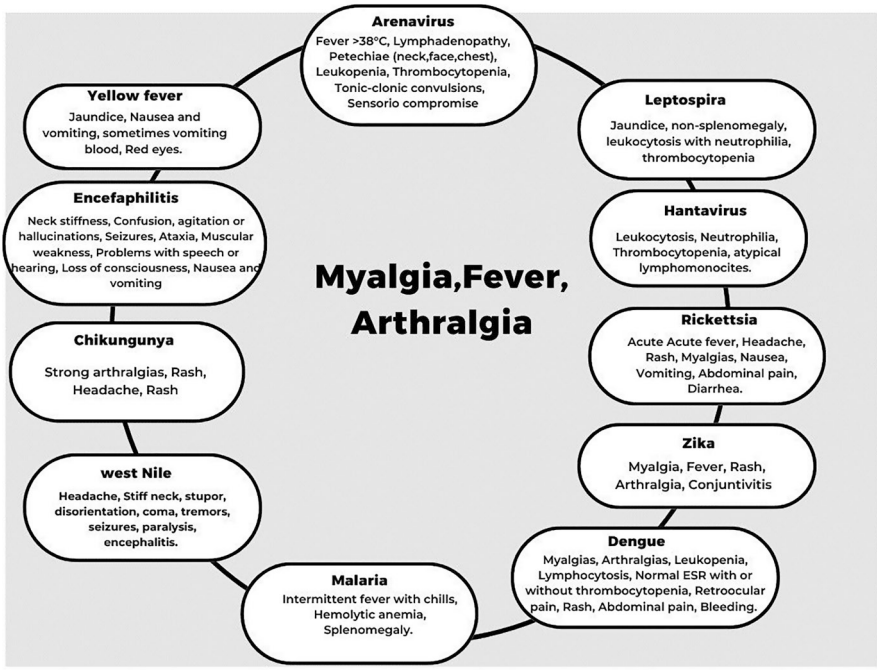

Fig. 2.3 Challenges of differential diagnosis of hemorrhagic fevers in the tropics

Coinfections are common in the Latin American tropics, such as malaria, dengue, leptospirosis (Guzmán et al. 2017; Mattar et al. 2017; Tique-Salleg et al. 2023), and recently with SARS-COV2. The symptoms may be more intense in coinfections, although progression to a severe clinical condition is not frequent. In the Colombian Caribbean region, cases of malaria-hantavirus coinfection have been described, where a clinical picture of moderate symptoms was observed without respiratory complications. Likely, the hantavirus genotypes circulating in the Caribbean do not produce severe clinical manifestations as in Panama (Armien et al. 2004; Tique-Salleg et al. 2023).

Hantavirus cardiopulmonary syndrome (HPS) can be divided into four phases: prodromal or febrile, cardiopulmonary, diuretic, and convalescence (Clement et al. 2012). The prodromal phase occurs after incubation and lasts from 3 to 5 days. At this stage, fever >38.5 °C, asthenia, chills, myalgia, severe abdominal pain, and, less frequently, nausea and vomiting occur. Headache, arthralgia, and diaphoresis may also appear. Upper respiratory symptoms are frequently absent at this stage, so it is essential to differentiate them from those caused by influenza, parainfluenza, adenovirus, and respiratory syncytial viruses (CDC 2023; Jonsson et al. 2010; Navarrete et al. 2016; OPS/OMS 2019). In children, fever tends to be constant and high. Abdominal pain may also suggest an acute abdomen, and myalgias are mainly located in the lower extremities. Although the physical examination, laboratory

examination, and chest X-ray may be expected, the complete blood count is the most helpful in this prodromal phase. Immunoblasts (atypical lymphocytes) may be evident among 10% >45% of the lymphocyte count. Leukocytosis (>12,000) with left shift and a leukemoid reaction may occur (CDC 2023; Jonsson et al. 2010). Thrombocytopenia and average or slightly increased erythrocyte sedimentation rate are essential in the differential diagnosis of leptospirosis. At the end of this prodromal phase, the cardiopulmonary phase begins, with nonproductive cough, tachypnea, dyspnea, and fine crackles that may be found on lung auscultation (Fig. 2.4) (Navarrete et al. 2016; OPS/OMS 2019; Vial et al. 2023).

Some patients develop hantavirus-associated cardiopulmonary syndrome, and signs of dyspnea, with tachypnea and hypoxemia, are associated with irritative cough (Clement et al. 2012; Navarrete et al. 2016). It is characterized by the presentation of pulmonary edema and shock that can progress rapidly between 4 and 24 h, with consequent respiratory distress (Baró et al. 1999; Lima et al. 2011). Although the host's immune response is essential, cytokines and other mediators act on the vascular endothelium of the alveolar-capillary membrane and the myocardium with increased myocardial interstitial edema and smaller diameter of myocytes with myocytolysis, triggering increased vascular permeability, which results in plasma extravasation and hypovolemia with hemoconcentration. Hypovolemia and heart failure can lead to shock with multiple organ failure followed by death. Echocardiography shows a significant reduction in ventricular ejection fraction (Yoshimatsu and Arikawa 2014). This state of shock is differentiated from septic shock by the presence of normal or increased peripheral resistance. Patients generally die from refractory shock, even if hypoxemia is adequately treated (CDC 2023). HPS is expected mainly in Argentina and Chile with infection by the Andes virus (ANDV), which presents a condition that may require renal replacement therapy in

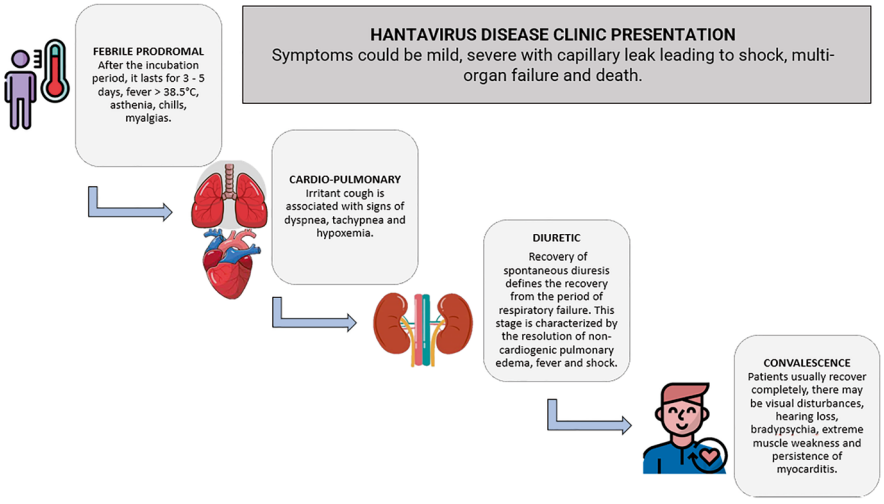

Fig. 2.4 Clinical presentation of hantavirus disease

addition to pulmonary manifestations, hemorrhagic symptoms, and deterioration in kidney function (Vial et al. 2023).

Laboratory findings in the cardiopulmonary phase are thrombocytopenia, hemoconcentration, normal leukocytes, or leukocytosis (leukocyte count >25,000/mm^3), with increased percentages of immature granulocytes and atypical lymphocytes in the peripheral blood smear; hypoprothrombinemia; increased partial thromboplastin time; increased nitrogen, increased LDH, CPK, liver enzymes, hyponatremia, and amylase; and metabolic acidosis (Lederer et al. 2013; Vial et al. 2023).

In the beginning, the chest X-ray showed signs of mild to moderate bilateral interstitial edema expression of non-cardiogenic pulmonary edema, conserving the shape and size of the cardiac silhouette. This infiltrate then progresses, producing alveolar edema, and in some cases pleural effusion occurs (Yoshimatsu and Arikawa 2014). The diuretic phase begins with the recovery of spontaneous diuresis. This defines the recovery from the period of respiratory failure and is characterized by the resolution of non-cardiogenic pulmonary edema, fever, and shock. The patient enters a polyuric phase where he eliminates several liters of urine daily, so adequate monitoring is necessary to avoid dehydration and electrolyte imbalances (Amada et al. 2014; Lederer et al. 2013). The convalescence phase can last up to 2 months. Although patients usually recover completely, there may be visual disturbances, hearing loss, bradypsychia, extreme muscle weakness, and the persistence of myocarditis (Vial et al. 2023).

2.6 When Should Hantavirus Pulmonary Syndrome with Respiratory Symptoms Secondary to Hantavirus Be Suspected?

This syndrome must be suspected in all patients with respiratory distress syndrome of unclear etiology in areas endemic for the disease (Amada et al. 2014), especially if it is accompanied by fever, marked leukocytosis, thrombocytopenia, and bilateral interstitial infiltrates. The differential diagnosis of this syndrome in South America includes malaria, strongyloidiasis, and leptospirosis.

2.6.1 Early Recognition of Severe Cases

Adequate triage is essential in the management of hantavirus disease. Patients with comorbidities such as kidney, and heart failure and diabetes have a higher mortality risk and should therefore be hospitalized. PAHO considers that an evaluation should be carried out that includes pulse oximetry, a blood count, and a chest X-ray. Patients with hypoxemia <90% and thrombocytopenia <130,000 mm^3 with or without leukocytes or interstitial infiltrates on radiography should be considered at high risk.

However, this approach has not been confirmed in prospective studies, so in epidemic conditions, observation of at least 24 h and a clinical reassessment must be performed on all patients (Vial et al. 2023). In cases with a clear suspicion, transfer to an institution where invasive mechanical ventilation is possible is a measure that can save the patients' lives and should be carried out once the diagnosis is suspected.

2.7 Febrile Hemorrhagic Syndrome with Renal Involvement (FHSR)

The syndrome is a characteristic clinical entity that manifests with fever, hypotension, and renal failure and may also manifest as mild glomerulonephritis and renal failure. Eurasian hantaviruses (Hantaan virus, Puumala virus, and Seoul virus [SEOV]) cause HFRS; SEOV has a worldwide distribution (Chand et al. 2020; Fitte et al. 2023). The febrile hemorrhagic syndrome, with renal involvement caused by *Hantavirus*, has not yet been described in South America. The severity and mortality of FHSR vary between 1% and 15% depending on the causative agent. Infections with Hantaan, Dobrava, and Amur viruses usually cause severe symptoms. Seoul virus generally causes a more moderate illness, while Puumala and Saaremaa virus infections are usually mild. It is characterized by a specific initial phase, high fever, disabling low back pain, and minor hemorrhagic signs. This condition may progress to hypotension and eventually to oliguric acute renal failure with active urinary sediment in proteinuria marked with casts and hematuria. These stages are usually more evident in severe disease and may not be seen in mild cases. The manifestations are abrupt; initial clinical signs include fever, chills, prostration, headache, and low back pain. Also, gastrointestinal signs include nausea, vomiting, and abdominal pain. The pain can sometimes be so severe as to resemble appendicitis. Patients may also present with conjunctival injection, photophobia, temporary impairment of vision, and petechial rash, which usually occurs on the palate or back. The first stage is the proteinuric stage. During this phase of the disease, hypotension may develop and may last for hours or days. In severe cases, this stage is usually followed by an oliguric phase and then a diuretic/polyuric phase as renal function improves. In severe cases, this phase can be observed in renal failure, some hemorrhage with disseminated intravascular coagulation, and hemorrhages in different organs (hemoptysis, hematuria, bleeding from the gastrointestinal tract). Patients who survive enter a polyuric phase where electrolyte alterations can be observed (Chand et al. 2020; Vial et al. 2023).

There are cases where renal involvement requiring transient hemodialysis due to Sin Nombre virus has been reported (Chand et al. 2020). Due to the serological cross-reactivity between SNV and SEOV, serological diagnosis is challenging. In these cases, the etiology must be resolved by PCR and massive sequencing, which is still expensive and only implemented in research laboratories. However, clinical recognition of renal signs and rapid detection of hantavirus infections can reduce

the risk of complications and fatal outcomes. Because hantavirus infection rarely manifests as kidney disease in the United States and South America, physicians may be less aware of HFRS. HFRS should be suspected in patients with acute renal failure, fever, bleeding, headache, and abdominal, back, and orbital pain. Epidemiological links such as living in rural areas and possible exposure to rodents in the last month can help in the presumptive diagnosis of hantavirus kidney infection. Doctors poorly recognize HFRS in South America, so its diagnosis should be routinely implemented. Thus, in South America, the clinical presentation of HFRS should be considered, and the differential diagnosis should be made with *Leptospira* and rickettsia (Alemán et al. 2006; Romero and Anjum 2023).

2.8 Treatment

Although hantavirus infection is potentially fatal, most patients present with moderate severity, requiring only supportive measures, adequate hydration, antipyretics, and anti-inflammatories (Lima et al. 2011). However, recognizing signs of severity indicates that the patient may benefit from more dynamic clinical management and strict monitoring in the intensive care unit. Multiple clinical trials have been carried out with antiviral medications, but an adequate benefit in reducing mortality has yet to be demonstrated. Vaccines are being developed in higher-risk populations to reduce the impact of infection. However, no specific vaccines or treatments are currently available for hantavirus diseases. On the other hand, reports suggest that human monoclonal antibodies could prevent or treat hantavirus infections (Engdahl and Crowe 2020).

2.8.1 Administration of Antiviral Drugs

Different experiments have been carried out with ribavirin in animal models with data of reduction in viral load and lethality of 45% when administered at the onset of symptoms compared to the control group. However, adequate effectiveness has yet to be observed in the clinical studies carried out with administering ribavirin at the beginning of the manifestations of hantavirus cardiopulmonary syndrome and febrile syndrome with renal involvement (Dheerasekara et al. 2020).

Lactoferrin was evaluated in an animal model of lactating mice to prevent FHSR. In combination with ribavirin, lactoferrin was required to prevent focus formation at concentrations of 40 and 160 mg/kg administered in two doses, resulting in 85% and 94% survival, respectively, when administered before exposure to the virus (Brocato and Hooper 2019).

Favipiravir is a pyrazine derivative, initially discovered for its anti-influenza properties. This component was first evaluated in vitro against bunyavirus and arenavirus, having and demonstrating activity against both virus families. Favipiravir

was evaluated in vivo in mouse models infected with SNV and ANDV. Oral administration twice a day, 100 mg/kg/day, reduces the detection of SNV serum viral RNA and SNV lung antigen. Likewise, administration twice a day, 100 mg/kg/day of favipiravir, resulted in 100% survival and reduced detection of ANDV RNA in blood and ANDV RNA and antigen in lungs. Consistent with other works, when the treatment was administered after the onset of viremia, it was not protective in mouse models with ANDV (Westover et al. 2016).

In hantavirus infections that infect endothelial cells, they induce a proinflammatory response. Therefore, it was considered that corticosteroid treatment would reduce shock and mortality. A study in Chile with high doses of methylprednisolone led Chilean medical centers to implement it as management. However, a subsequent phase II study for treating HPS with methylprednisolone did not confer clinical benefits (Dheerasekara et al. 2020). Immunotherapy with monoclonal and polyclonal antibodies in studies with ANDV-infected mice has shown they can inhibit HPS. In Chile, a multicenter, non-randomized study of human immune plasma for treating HPS caused by ANDV resulted in statistically moderate clinical benefits (Williamson et al. 2021).

2.8.2 Admission to Intensive Care

Support measures are vaguely mentioned in most tropical medicine texts when discussing tropical diseases that lack specific therapy. However, due to the global dengue epidemic, it has been demonstrated by different research groups that the aggressive management of tropical viral diseases through clinical protocols is associated with a reduction in mortality even without specific antiviral drugs (Guzmán et al. 2017). HPS produces a severe condition with respiratory compromise; the patient must be transferred to the intensive care unit, where they can receive, in addition to continuous monitoring, respiratory support, transfusions, and correction of metabolic and electrolyte imbalances (Jonsson et al. 2010).

The measures that have been associated with a reduction in mortality are (a) early transfer to the intensive care unit, (b) management of early intubation, (c) management of shock with a cautious infusion of fluids and early initiation of catecholamines (Dheerasekara et al. 2020), and (d) management of severe cardiogenic shock with extracorporeal membrane oxygenation (ECMO) (Lima et al. 2011). Some authors advise using broad-spectrum antibiotics until the exclusion of other pathologies that, such as leptospirosis or bacterial sepsis, cause similar respiratory symptoms. In the case of Andes virus infection associated with hemorrhagic syndrome and renal failure, transfusions and early hemofiltration initiation are crucial in managing these patients. During the polyuric phase, ICU monitoring is still helpful to ensure adequate fluid balance and correct electrolyte imbalances (Brocato and Hooper 2019).

2.9 Prevention

Contact with rodents and their excreta is the most critical risk factor for contracting hantavirus infection. Therefore, to prevent infection, it is crucial to carry out rodent control activities in the home and places where human activities occur. Rodent control should include the following:

- Eliminating food sources in and around the house
- Limiting places where rodents can enter the house
- Using traps
- Eliminating potential nesting sites around the house

Besides, ensure adequate ventilation of rooms or storage areas before entering, and use rubber gloves, disinfectants, and masks to avoid contact and aspiration of infected particles while cleaning (Zhang et al. 2010). Additionally, hantavirus vaccines are necessary to avoid infection in people at high risk.

2.10 Vaccines

In China, more than 1.5 million FHSR cases and more than 45,000 deaths (3%) were reported between 1950 and 2007. However, the incidence and mortality of FHSR have decreased, thanks to prevention measures and vaccination. In China and Korea, since 1995, inactivated vaccines against HTNV and SEOV have been used in areas where HFRS is highly endemic. Since 2003, purified bivalent vaccines for HTNV and SEOV inactivated with formaldehyde cultured in Vero cells have been used. The levels and favorable rates of HTNV-NP-specific IgM and IgG antibodies, as well as HTNV-neutralizing antibodies, increased significantly in the serum of vaccinated individuals. (Li et al. 2017). South Korea has widely used a formalin-inactivated HATN vaccine (Hantavax) for HFRS. Seroconversion and high specific antibody titers were demonstrated in humans with a recommended three-dose vaccination strategy (0 days, 1 month, and 12 months). Less than 50% of the sampled population produced neutralizing antibodies after the booster dose after 12 months (Cho and Howard 1999). A multicenter phase III clinical trial was conducted to evaluate the immunogenicity and safety of Hantavax (three-dose regimen at 0, 1, and 13 months) among healthy adults. Hantavax showed a boosting effect and immunogenicity that lasted 2 years with a three-dose schedule. The neutralizing antibody response was relatively poor with two primary doses; thus, booster vaccination at 2–6 months could be justified to provide timely protection to high-risk subjects (Song et al. 2016). However, a case-control study conducted in the Korean military showed no statistically significant efficacy even after three-dose vaccination.

In China, HTNV virus-like viral particle (VLP) vaccines adjuvanted with CD40L or GM-CSF were constructed using the HTNV M segment and the CD40L/GM-CSF

gene, cotransfected with a vector containing the S segment into cells. Chinese hamster ovary with dihydrofolate reductase (dhfr-CHO). GM-CSF-anchored CD40L or HTNV VLPs showed increased activation of macrophages and dendritic cells in vitro (Dong et al. 2019; Ying et al. 2016). These HTNV VLPs have provided stable long-term protection with a high titer of neutralizing antibodies in mice 6 months after immunization and HTNV-specific cellular immune responses through increased expression of IFN-g and CTL responses. Humoral and cellular immunity induced by VLPS adjuvanted with CD40L or GM-CSF was greater than unadjuvanted VLPs or inactivated HTNV vaccines in mice. European researchers have demonstrated high protection against PUUV using the core particle of the chimeric hepatitis B virus, which carries a 45-amino acid fragment of the PUU CG18-20 N strain inserted in the c/e1 region (Koletzki et al. 2000; Ulrich et al. 1999). Immunizations with VLPs carrying amino acids 75–119 of the PUU strain CG18-20 at the HBV core's C terminus have demonstrated a second minor protective region in the nucleocapsid protein. HBV core particles carrying the N-terminal 120 amino acids of the Dobrava, Hantaan, or Puumala nucleocapsid protein are highly immunogenic with or without adjuvant in B ALB/c and C57BL/6 mice (Schmaljohn et al. 1990).

A doubly recombinant molecular vaccine has been used by inserting the cDNA of the segments M and S genomic of HTNV into the vaccine virus. This recombinant vector vaccine effectively protected hamsters from infection with Hantaan and Seoul viruses but not against PUUV. In addition, this vaccine has been evaluated in phase I and phase II clinical trials. According to phase I results, neutralizing antibody titers increased against both the vaccine virus and HTNV with the second inoculation. A comparison of two vaccination routes has shown that deep inoculation effectively induced neutralizing antibodies in volunteers naive to the vaccine virus. However, subcutaneous inoculation was superior to deep inoculation in individuals immune to the vaccine virus (Maes et al. 2008; Schmaljohn et al. 1990).

The results of the phase II trial demonstrated that neutralizing antibodies against HTNV were detected in 72% of vaccine virus-naive volunteers and only in 26% of vaccine virus-immune volunteers (Brown et al. 2011; Chu et al. 1995). The nonreplicating adenovirus vector, expressing ANDV N, Gc, Gn, or Gn + Gc, elicited a robust immune response that protected hamsters against lethal ANDV infection and strong cytotoxic T lymphocyte responses (Safronetz et al. 2009).

Two clinical trials (phase I) using nucleic acid vaccines were conducted to test the efficacy and safety of M-segment DNA viruses HTNV and PUUV based on vaccine delivery technology. In both trials, the vaccines were considered safe and without serious adverse effects for human use. When vaccines were delivered by particle-mediated epidermal delivery (PMED), 30% and 44% of individuals developed neutralizing antibodies against HTNV or PUUV, respectively, in the single-vaccine group, and 56% of volunteers developed neutralizing antibodies against one or both viruses in the combined group (Boudreau et al. 2012; Hooper et al. 2014). However, the overall seroconversion rate <50% prevented further development. With the intramuscular electroporation delivery method, 56% and 78% of individuals developed neutralizing antibodies against HTNV or PUUV, respectively, in the

single-vaccine groups, and 78% of volunteers developed neutralizing antibodies against PUUV in the combined vaccine. Based on these results, it has been demonstrated that immunogenicity can be improved with advances in delivery technology (Jiang et al. 2015, 2018).

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