



## Research Models for Rodent-Borne Hemorrhagic Fever Viruses: Arenaviruses and Hantaviruses

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### Introduction

Rodentia make up about half of the mammal population and have a negative impact on humans in at least two ways: they destroy massive amounts of food each year and they are carriers of infectious disease, spreading over 20 viruses and >40 bacteria and parasites directly and indirectly. Rodents consume 5%–17% of the rice harvest in Asia alone. According to some estimates, this amount of food could feed almost 200 million people. Rodents perform both indirect and direct roles in the spread of infectious illness. Rodents, like other mammals, can act as short-term carriers, amplifying infectious pathogens that are then transmitted to humans *via* intermediates, primarily arthropod vectors.

Amplification of viruses like Yellow Fever and Crimean Congo Hemorrhagic Fever, which are conveyed to humans *via* mosquitos and ticks after the insects feed on infected rodents, are examples of such indirect roles in virus dissemination (among other animals). Rodents can play a direct role in the spread of infectious viruses to humans by acting as the infectious agents sole viral reservoirs (or carriers) in nature. Infectious agents are propagated and maintained in perpetuity within these carrier rodent populations by vertical (parent to offspring) and/or horizontal transfer (adult to adult). Infectious illnesses are transmitted to humans by direct contact with rodent secretions and excreta from these carrier populations. Increases in rodent vector populations, which are frequently due to increased food sources as a result of favorable weather conditions, can result in measurably higher cases of viral disease in human populations. Rodents are important reservoirs for two viral families: Arenaviridae and Hantaviruses (family Bunyaviridae).

### Arena Viruses

Arena viruses are single-stranded ambience RNA viruses with two segments, Short (S) and Large (L), each encoding a 10.7 Kbp genome with five proteins. The Nucleo Protein (NP) and the glycoproteins GP1 and GP2 are encoded by the S segment. The receptor binding protein (and target of neutralizing antibodies) GP1 and the membrane fusion protein GP2 are the receptor binding protein (and target of neutralizing antibodies) and the membrane fusion protein, respectively. The RNA-dependent RNA polymerase and the Z protein are encoded by the L segment. Based on the initial geographical region of virus isolation and serology, this family is split into two

broad complexes: Old World (OW) and New World (NW). Several of the more than 20 identified arena virus species can cause disease in humans. The most common arena virus is Lymphocytic Choriomeningitis Virus (LCMV), which was first discovered by Armstrong and Lillie and can infect mice (*Mus musculus*) as well as pet rodents like hamsters and guinea pigs. LCMV infection in humans is usually mild and asymptomatic, with death being an uncommon occurrence. This review will not be focused on it. We do want to point readers that, despite its rarity, LCMV can cause HF illness in humans. However, in this analysis, we concentrate on arena viruses, which are more typically responsible for HFs and have a far higher risk of causing deadly disease in people.

Lassa virus, an OW arena virus that causes Lassa fever, is the most well-known human pathogen among them. Lassa virus infects between 100 and 300 thousand people per year, mostly in the Manna River region of West Africa (Liberia, Guinea, and Sierra Leone), but also in Nigeria and Mali. HFs is also caused by a number of NW arena viruses. Clades A, B, and C make up the NW complex, however only those from clade B are pathogenic to humans. The most common infection in this group is Junin Virus (JUNV), which is the cause of Argentine HF (AHF). Human sickness is also caused by the Machupo Virus (MACV), Guanarito Virus (GTOV), and Sabia Virus (SABV) in Bolivia, Venezuela, and Brazil, respectively.

Bolivian HF, Venezuelan HF, and Brazilian HF are caused by the viruses MACV, GTOV, and SABV. Arena viruses that are harmful to humans have only recently emerged. Chapare Virus (CHPV) in Bolivia and Lujo Virus (LUJV) in Southern Africa are two examples. In addition, the White Water Arroyo Virus (WWAV), a NW arena virus, has been linked to human disease in North America.

Originally assumed to be spread by arthropod vectors (mites), further research has revealed that rats play an important role in the natural maintenance of arena viruses. Individual arena virus species establish a chronic infection in a single rat species in certain geographical regions, albeit this is not always the case. Human exposure to *Mastomys natalensis*, a persistently infected rat species, causes LF. Humans contract JUNV after coming into contact with *Calomys musculinus*. GTOV is transferred by two rodent species: *Sigmodon alstoni* and *Zygodontomys brevicauda*, and MACV are spread to humans through contact with *Calomys callosus*. SABV's host has yet to be identified. Exposure to rat excreta and secretions (urine and saliva) causes human infection, which is spread *via* aerosols, skin abrasions, and most likely ingestion.

The extent to which these viruses affect human populations is determined by rodent habitat choices. *Mastomys natalensis*, the LASV host, is widely dispersed in Sub-Saharan Africa, putting a large number of people in the region at risk of infection. NW arena viruses are mainly considered agricultural worker illnesses, with the exception of MACV. This can be explained by the fact that MACV-infected *Calomys callosus* are more closely related with human habitation than other NW arena viruses that infect rodents that are more commonly seen in rural areas. Tacaribe Virus (TACV), a NW arena virus, was first isolated from bats, implying that bats may also serve as arena virus carrier populations. Recent research suggests, however, that bats are not capable arena virus carriers and are only afflicted for a short time.

## Hantaviruses

Hantaviruses (genus Hantavirus, family Bunyaviridae) are single-stranded, negative-stranded RNA viruses with three segments: Small (S), Medium (M), and Large (L). The Nucleoproteins (N) is encoded by the S segment, the glycoproteins is encoded by the M segment, and the RNA-dependent RNA polymerase is encoded by the L segment. Some hanta viruses produce a Nonstructural (NSs) protein encoded by an alternative Open Reading Frame (ORF) within the S segment's N protein-coding region. Puumala virus, like two other non-hantavirus members of the Bunyaviridae family, Rift Valley fever virus and La Crosse virus, expresses this NS protein, which suppresses type I interferon and nuclear factor kappa B (NF- $\kappa$ B) activity, potentially allowing greater viral replication in the absence of interferon. However, the role of this NS protein in HPS-causing hanta viruses is poorly understood, as deletion of the ORF has no effect on the N protein's ability to regulate IFN responses.

Hemorrhagic Fever with Renal Syndrome (HFRS) and its milder version, Nephropathies Epidemica (NE), are all hantavirus diseases, as are Hantavirus Pulmonary Syndrome (HPS) and Hantavirus Cardiopulmonary Syndrome (HCPS). In both disorders, hantaviruses primarily infect micro vascular endothelial cells, causing vascular leakage through changing the endothelium's barrier characteristics. The endothelium in the kidney (predominant with NE and HFRS-causing hantaviruses) and the lungs becomes unable to manage tissue fluid accumulation due to this non lytic infection (predominant with HPS-causing hantaviruses). Hantaviruses that cause old world HFRS include Hantan Virus (HTNV), Dobrava Virus (DOBV), and Seoul Virus (SEOV), all of which have a case fatality rate of up to 15% and a significant level of morbidity. DOBV and HTNV have been linked to severe cases of HFRS, while SEOV has been linked to intermediate disease. The etiological agent of NE, Puumala Virus (PUUV), has a case fatality rate of 1%. HTNV is found in China, Russia, and Korea, DOBV in the Balkans, and PUUV in northern Europe, specifically

Belgium, Finland, France, the Netherlands, Norway, Sweden, and Russia. SEOV, which is spread by domestic rats, has a global reach because to international shipping. SEOV, dubbed tchoupitoulas virus after its discovery in New Orleans, Louisiana, was found in brown rats caught in the 1980s and again more recently. Andes Virus (ANDV) and Sin Nombre Virus (SNV), which have a 35% case fatality rate, are two of the most prominent new world HPS-causing hanta viruses. ANDV is primarily found in Argentina and Chile in South America, whereas SNV was the term given to the virus that caused the four corners area outbreak in the United States in 1993.

Each of these hanta viruses has its own rodent reservoir, with Old World hantaviruses carried by infected *Myodes*, *Rattus*, and *Apodemus* mice, and New World hantaviruses carried by infected *Sigmodontinae* rodents. Hantaviruses are commonly misunderstood to be transmitted only by rodents, whereas in reality, they infect a wide range of tiny mammals, not just rodents. Hantaviruses have also been isolated from shrews [Thottapalayam Virus (TPMV); Asian house shrew (*Suncus murinus*); order Soricomorpha], moles [Nova Virus (NVAV); European mole (*Talpa europaea*); order Soricomorpha], and bats [Magboi Virus (MGBV); slit-faced bat (*Nycteris hispida*); order Chiropteran]. One crucial distinction to be made among these hanta viruses is that only those isolated from rodent species have been linked to human disease. Most hantavirus-related human sickness is thought to be caused by inhaling aerosolized excreta or secretions from infected rodents, or, in the case of ANDV, by direct person-to-person contact with infected people. Furthermore, documented virus transmission through an animal bite has been reported, albeit infrequently. Although there have been no confirmed examples of human hantavirus sickness caused by hantavirus ingestion, animal model data suggests that this is still a possibility. To prevent or treat HFRS or HPS, there are presently no FDA-approved vaccinations, post exposure prophylactics, or therapies.