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Hantaviruses—Globally emerging pathogens

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ABSTRACT

Hantaviruses are emerging zoonotic viruses which cause human disease in Africa, America, Asia, and Europe. This review summarizes the progress in hantavirus epidemiology and diagnostics during the previous decade. Moreover, we discuss the influence of ecological factors on the worldwide virus distribution and give an outlook on research perspectives for the next years.

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1. Introduction

Hantavirus disease is a zoonosis. The causative viruses, collectively belonging to the genus *Hantavirus* of the *Bunyaviridae* family, are harbored by small mammals as reservoir hosts and transmitted to men. In humans, they cause febrile disease, usually named “Hemorrhagic Fever with Renal Syndrome” (HFRS) for disease in Asia and Europe and “Hantavirus Cardiopulmonary Syndrome” (HCPS) in the Americas with case fatality rates of up to 35–50% [67,48,45,18]. The pathogenesis of hantavirus disease is characterized by changes in blood coagulation, vasodilatation and disturbances in the barrier function of the capillaries, resulting in extravasation of blood and inflammatory processes in the affected organs. Since pathogenesis is highly similar and clinical appearance is overlapping between both syndromes, comprehensive terms as “hantavirus disease” or “hantavirus fever” have been suggested to denote the disease [12,92].

Virus transmission to humans occurs via inhalation of aerosolized rodent urine, saliva, and feces, rarely by rodent bites. In the environment, virus particles remain infectious for several weeks – depending on factors as humidity, temperature, and association with protective proteins [22]. An overview about the risk factors of hantavirus infections was very recently compiled by Watson et al. [98]; the most prominent factors are involvement

in outdoor activities, such as rural- and forest-related activities, peridomestic rodent presence, exposure to potentially infected dust, and outdoor military training. Humans are usually considered to be dead-end hosts who do not transmit the virus further. However, indubitable human-to-human transmission of Andes hantavirus was reported in Argentina and Chile [99,63,9,53,14].

According to the presence of infected animal hosts and their contacts to humans, occurrence of hantavirus disease can be observed in different climatic zones including subtropics and tropics. Hantaviruses are considered to belong to the group of emerging viruses; this has mainly to do with the frequent identification of novel hantaviruses and their role as human pathogens. There are different trends in the development of case numbers; whereas in China – the country with most HFRS cases per year worldwide – the number of patients seems to decrease because of the vaccination approaches in this country [23], the number of cases in Europe and particularly Germany shows a clear increase over the last years [70,46].

Here, we will refer to the progress in hantavirus epidemiology and diagnostics during the previous decade (see also Box 1) with a particular focus on infections in tropical areas.

2. Epidemiology

2.1. Africa

Africa is clearly the continent with the most recent scientific progress in terms of hantavirus epizootiology and epidemiology. Ten years ago, no indigenous African hantaviruses were known, while today, approximately 10 hantaviruses have been identified not only in rodents but also shrews and even bats in Africa.

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Box 1: Most important (clinically relevant) developments during the last 10 years

- Progress on diagnostic methods: Recombinant viral antigens for use in serology (ELISA, Western blot), Commercial kits for rapid diagnosis using immune chromatography, Real time PCRs
- Deeper information on molecular epidemiology of hantaviruses and their occurrence in different reservoir hosts
- New insights into the molecular processes of viral replication and the pathophysiology of hantavirus infection
- Decrease of the number of clinical cases in countries with immunization programs

Several seroepidemiological studies in African humans suggested the presence of hantaviruses in Africa much earlier (for a comprehensive review, see [100]). However, the first African hantavirus, named Sangassou virus (SANGV), was found in the African wood mouse (*Hylomyscus simus*) trapped in a forest habitat in Guinea first in 2006 [36]. Meanwhile, several other rodent- as well as shrew-borne hantaviruses were identified in sub-Saharan Africa.

The African continent has also played an important role in the recent change in the dogmatic view on hantaviruses as rodent-borne viruses. Not only due to several shrew borne-viruses, but also because the very first bat-borne hantaviruses were found in Africa (reviewed in [100]). All of these newfound shrew- and bat-borne hantaviruses were identified only through molecular detection of viral RNA in wild-living animals.

SANGV, so far the only African hantavirus isolated on cell culture, was used in the most recent seroepidemiological studies in Guinea which utilized a comprehensive battery of serological assays (enzyme-linked immunosorbent assay, immunofluorescence assay, Western blot analysis, neutralization assays) to ensure specificity [38,40]. Initial studies demonstrated a hantavirus seroprevalence of about 1–2% was observed among the human population of Guinea and the South African Cape Region, respectively [38,100]. Moreover, hantavirus antibodies were retrospectively detected in 3 (4.4%) of 68 patients with fever of unknown origin from Sangassou village in Guinea. In one pediatric patient suffering from typical HFRS symptoms, the presence of SANGV-specific IgM antibodies was shown and in a serum sample taken one year later neutralizing anti-SANGV IgG antibodies were detected [38].

These data indicate that hantavirus infections may be an underestimated medical problem in Africa. Further studies are clearly necessary but are hampered by the lack of appropriate antigens from African rodent-, shrew-, and bat-borne hantaviruses. Recent advances in next-generation-sequencing technologies and gene synthesis will probably enable researchers to overcome these difficulties in the near future.

2.2. The Americas

About 4000 HCPS cases have been reported in the Americas since 1993 caused by thirty hantavirus strains. [18]. In North America Sin Nombre virus (SNV) is the most prominent hantavirus causing cardiopulmonary syndrome [34] while Andes virus (ANDV) is the most important pathogenic hantavirus in South America. In Central America, Choclo virus (CHOV), harbored by *Oligoryzomys fulvescens*, causes HCPS in Panama [97], a country belonging to the tropical/subtropical zone. Other recognized pathogenic hantaviruses and their associated reservoir hosts are listed in Table 1.

In South America, the diversity and distribution of hantaviruses are highly complex. In phylogenetic analyses, the majority of the South American hantavirus strains fall into three major

Table 1
Hantaviruses reported to be pathogenic for humans.

Continent/virus	Recognized reservoir host
Africa Sangassou virus (SANGV) ^a	<i>Hylomyscus simus</i>
America Sin Nombre virus (SNV) Monongahela virus (MNGV) New York virus (NYV) Bayou virus (BAYV) Black Creek Canal virus (BCCV) Andes virus (ANDV) Maciel virus (MACV) Bermejo virus (BMJV) Araraquara virus (ARQV) Juitituba virus (JUQV)	<i>Peromyscus maniculatus</i> <i>Peromyscus maniculatus</i> <i>Peromyscus leucopus</i> <i>Oryzomys palustris</i> <i>Sigmodon hispidus</i> <i>Oligoryzomys longicaudatus</i> <i>Necromys benefactus</i> <i>Oligoryzomys chacoensis</i> <i>Necromys lasiurus</i> <i>Oligoryzomys nigripes</i> <i>Calomys callidus</i> <i>Calomys laucha</i> <i>Oligoryzomys moojeni</i> <i>Oligoryzomys fornesi</i>
Laguna Negra virus (LANV) Castelo dos Sonhos virus (CASV) Anajatuba virus (ANJV)	
Asia Hantaan virus (HTNV) Amur/Soochong virus (AMRV/SOOV) Seoul virus (SEOV) Thailand virus (THAIV) ^a	<i>Apodemus agrarius</i> <i>Apodemus peninsulae</i> <i>Rattus norvegicus</i> <i>Bandicota indica</i>
Europe Puumala virus	<i>Myodes glareolus</i> <i>Apodemus flavicollis</i> <i>Apodemus ponticus</i> <i>Apodemus agrarius</i>
Dobrava-Belgrade virus	<i>Microtus arvalis</i> <i>Rattus norvegicus</i>
Tula virus (TULV) Seoul virus (SEOV)	

^a So far only serological evidence reported.

monophyletic groups called Andes, Laguna Negra, and Rio Mamore clades [58]. However, numerous hantavirus names are described in the literature suggesting existence of many unique hantaviruses although their taxonomical status is unclear or if they are even highly similar to the established hantavirus species. In this review, for the scope of clarity, we use the names as they were originally reported without judging the taxonomical status of the reported viruses (Table 1, Fig. 1).

Studies in Brazil showed that Araraquara virus (ARQV), harbored by *Necromys lasiurus* [90], seems to be one of the most virulent hantaviruses, leading to HCPS with 50% case fatality rate [17]. ARQV's rodent host developed an opportunistic behavior, adapting to human anthropogenic changes, further increasing ARQV public health concerns [89,72]. Similarly, Castelo dos Sonhos virus (CASV) is harbored by *Oligoryzomys moojeni*, a rodent that lives in an extensively deforested area of lumber commerce and cattle breeding at the northern Amazon [54].

The eco-epidemiology of hantaviruses depends on the micro-habitat of its reservoir [58]. Thus, landscape composition, climate and seasonality, as well as human agricultural activity and environmental degradation, are important factors of hantavirus epidemiology. In the southwest of North America outbreaks of HCPS cases have been shown to correlate with weather and especially precipitation [34]. The ecology of SNV in the 1993 outbreak at Four Corners showed that an increased precipitation augmenting food availability increased hantavirus reservoir populations [34]. Longitudinal studies with *Peromyscus maniculatus* and SNV also revealed that the decrease in species richness and the preponderance of males are factors that contribute to virus maintenance [8].

An increased prevalence of ARQV infection in its natural-reservoir *Necromys lasiurus* correlated with environmental degradation and the dry winter season in Brazil. Human environmental change (e.g. increased grassland) favored the abundance

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