



The evolution and emergence of hantaviruses

Edward C Holmes^{1,2} and Yong-Zhen Zhang²

Hantaviruses are a major class of zoonotic pathogens and cause a variety of severe diseases in humans. For most of the last 50 years rodents have been considered to be the primary hosts of hantaviruses, with hantavirus evolution thought to reflect a process of virus-rodent co-divergence over a time-scale of millions of years, with occasional spill-over into humans. However, recent discoveries have revealed that hantaviruses infect a more diverse range of mammalian hosts, particularly Chiroptera (bats) and Soricomorpha (moles and shrews), and that cross-species transmission at multiple scales has played an important role in hantavirus evolution. As a consequence, the evolution and emergence of hantaviruses is more complex than previously anticipated, and may serve as a realistic model for other viral groups.

Addresses

¹ Marie Bashir Institute for Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Biological Sciences and Sydney Medical School, The University of Sydney, Sydney, NSW 2006, Australia

² State Key Laboratory for Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Zoonoses, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Changping, Beijing, China

Corresponding author: Holmes, Edward C
(edward.holmes@sydney.edu.au)

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Introduction

Hantaviruses (family *Bunyaviridae*, genus *Hantavirus*) are archetypal emerging viruses with the capacity to cause substantial morbidity and mortality in humans. All hantaviruses share a negative-sense RNA genome of approximately 12,000 nucleotides in length that is arranged into large (L), medium (M), and small (S) segments, and contained within an enveloped virion [1]. The most serious disease manifestations of hantavirus infection in humans are Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS), which have mortality rates of up to 15% and 40%, respectively [2,3].

Hantaviruses are an important and on-going public health issue in countries such as China [4^{**}], and lead to more sporadic outbreaks in Europe [5,6^{*}] and the Americas [7], including a high profile episode among campers in Yosemite National Park, California, in 2012 [8^{**}].

Rodents have long been considered to be the primary reservoir hosts of hantaviruses. The etiologic agent of HFRS, Hantaan virus (HTNV), was discovered in 1978 [9], with the striped field mouse (*Apodemus agrarius*) identified as its likely reservoir host. Subsequent studies revealed the presence of rodent reservoirs for such viruses as Puumala virus (PUUV), which circulates in the bank vole *Myodes glareolus* [10], Seoul virus (SEOV) which is found in Norway rats (*Rattus norvegicus*) [11], Dobrava virus (DOBV) which resides in the yellow-necked mouse (*A. flavicollis*) [12], Sin Nombre virus (SNV) from *Peromyscus maniculatus* [13], and Andes virus (ANDV) from *Oligoryzomys longicaudatus* [14], all of which have resulted in human disease. That hantaviruses were relatively commonly sampled from rodents, and exhibited a generally host-specific relationship, led to the theory that hantaviruses and rodents had co-diverged over time-scales of many millions years [15]. Indeed, the theory of virus-host co-divergence has been central to identifying additional novel hantaviruses. While key elements of this theory still hold true, perhaps the most important finding of recent studies in hantavirus ecology and evolution is that these infectious agents are carried by a more diverse range of mammalian species, particularly bats, moles and shrews, and that their evolutionary history has also been characterized by relatively frequent host jumping (i.e. cross-species transmission) [16^{**},17^{**},18]. Despite the rapid increase in the number of known hantaviruses following more intensive sampling, a trend mirrored in many other viral families, the taxonomic status of these new viruses is largely unresolved [19] and awaits confirmation by the International Committee on Taxonomy of Viruses (ICTV).

Herein, we will outline recent work on the biodiversity of hantaviruses and discuss the evolutionary and ecological processes that have shaped this diversity. Our central hypothesis is that we are likely still scratching the surface of hantavirus biodiversity, itself produced by a complex interplay between cross-species transmission and co-divergence over long evolutionary time-scales. In doing so we suggest that hantaviruses provide an ideal data set by which to understand fundamental aspects of RNA virus evolution and emergence.

Expanding knowledge of hantavirus biodiversity

Perhaps paradoxically given that hantaviruses have generally been considered to be viruses of rodents, the first hantavirus isolated — Thottapalayam virus (TPMV) — was found in the Asian house shrew (*Suncus murinus*) in India [20]. However, it was not until the last decade that the importance of Soricomorpha as potential hosts for diverse hantaviruses came into focus, and to date more than 20 hantaviruses have been described in Soricomorpha species worldwide (Figure 1). Examples of hantaviruses in shrews include Tanganya virus (TGNV) which was identified in *Crocidura theresae* sampled in Guinea [21], Camp Ripley virus (RPLV) which was found in *Blarina brevicauda* in the USA [22], and Seewis virus (SWSV) that was detected in *Sorex araneus* from Switzerland [23]. The first hantavirus identified in a mole was Asama virus (ASAV) detected in *Urotrichus talpoides* from Japan [24]. More recent examples include Rockport virus (RKPV) isolated from the eastern mole (*Scalopus aquaticus*) in the USA [25], Bowé virus (BOWV) sampled from Doucet's musk shrew (*Crocidura douceti*) in Guinea [26], and Nova virus (NVAV) isolated from the European common mole (*Talpa europaea*) [27].

A similar bounty of hantaviruses is now being documented in bats [28*]. The first report of a bat hantavirus was that of HTNV isolated from *Rhinolophus ferrum-equinum* and *Eptesicus serotinus* in South Korea [29]. A variety of other bat hantaviruses have been identified since this time. For example, an analysis of bat species in China revealed the presence of Huangpi virus (HUPV) in *Pipistrellus abramus* bats and Longquan virus (LQUV) in *Rhinolophus* spp. (horseshoe) bats [17**]. Interestingly, LQUV was found in three species (*Rhinolophus affinis*, *R. onoceros*, and *R. sinicus*) from the same geographic locality, highlighting the importance of host jumping on a local scale. Still in Asia, Xuan Son virus (XSV) was found in *Hipposideros pomona* bats from Vietnam [30], while in Africa Magboi virus (MGBV) was isolated from *Nycteris hispidus* bats in Sierra Leone [31], and Mouyassué virus (MOUV) was detected in *Neoromicia nanus* bats from Côte d'Ivoire [32]. As well as these seemingly bat-specific viruses, the rodent-borne Araraquara virus (ARQV) was detected in two bat species (*Diphylla ecaudata*, *Anoura caudifer*) in Brazil [33], again reflecting the action of cross-species virus transmission. The case of ARQV also shows how the same virus can be shared among multiple host species, thereby countering the old notion that each hantavirus was restricted to a specific host [6*].

The clear conclusion from recent surveys of hantavirus biodiversity is that Soricomorpha and bats are important and natural reservoirs for hantaviruses, and may eventually turn out to be as common viral hosts as rodents. Importantly, however, no bat or Soricomorpha associated hantaviruses are known to infect or cause disease in

humans (Figure 1). Bats are of special interest as there has been considerable attention devoted to understanding why these animals seemingly harbor such a diverse array of viruses [34–37]. Although there are suggestions that the immune systems of bats may function in a way that is different to that of other mammals and enables them to carry, persistently, a multitude of viruses [38*,39–41], it is also possible that the high viral diversity in bats at least in part reflects aspects of their ecology: that they often live in large and dense populations, with wide geographical distributions [42]. This will increase the number of susceptible hosts that fuels viral transmission. This 'ecological' theory for viral biodiversity receives more support from the observation that rodents are also seemingly a rich source of viruses, including hantaviruses, and also frequently live in large and dense populations. In turn, the emergence of hantaviruses in human populations can often be traced to changing ecological interactions between humans and rodents, such as the establishment of new agricultural practices including food and grain storage, and fluctuations in species diversity [6*,43]. Whatever the true cause(s), it seems certain that additional bat and rodent hantaviruses will be identified, as well as those from other mammalian taxa only poorly sampled to date. Indeed, we are clearly only scratching the surface of viral biodiversity for animal RNA viruses as a whole [44,45], and work in this area will be greatly enhanced by recent advances in metagenomics and high-throughput sequencing [46*].

Origin and evolutionary history of the hantaviruses

One of the most important consequences of our new knowledge of hantavirus biodiversity and ecology is a refined understanding of the patterns and processes of evolutionary change in these viruses.

The 'classic' model of hantavirus evolution was that they co-diverged with rodent hosts on a time-scale of millions of years. In particular, the general congruence between the phylogenies of the viruses and their rodent hosts, especially within the *Muroidea*, provided powerful support for the theory of long-term co-divergence [47,48]. Importantly, even with the discovery of hantaviruses in a wider range of mammalian taxa, it is striking that rodent hantaviruses still cluster according to whether their hosts are members of the family *Cricetidae* and subfamily *Murinae*, an observation that is compatible with co-divergence [1,49]. In addition, the close phylogenetic relationships among some hantavirus taxa across large geographical areas, and where related hosts are infected, similarly suggests an ancient evolutionary process. The presence of *Microtus*-borne hantaviruses in both the Old World and the New World serves as a good example [50*].

On top of this back-bone of virus-host co-divergence we can add increasingly frequent examples of cross-species

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