Hantaviruses and climate change

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Abstract

Most hantaviruses are rodent-borne emerging viruses. They cause two significant human diseases, haemorrhagic fever with renal syndrome in Asia and Europe, and hantavirus cardiopulmonary syndrome in the Americas. Very recently, several novel hantaviruses with unknown pathogenic potential have been identified in Africa and in a variety of insectivores (shrews and a mole). Because there is very limited information available on the possible impact of climate change on all of these highly dangerous pathogens, it is timely to review this aspect of their epidemiology. It can reasonably be concluded that climate change should influence hantaviruses through impacts on the hantavirus reservoir host populations. We can anticipate changes in the size and frequency of hantavirus outbreaks, the spectrum of hantavirus species and geographical distribution (mediated by changes in population densities), and species composition and geographical distribution of their reservoir hosts. The early effects of global warming have already been observed in different geographical areas of Europe. Elevated average temperatures in West-Central Europe have been associated with more frequent Puumala hantavirus outbreaks, through high seed production (mast year) and high bank vole densities. On the other hand, warm winters in Scandinavia have led to a decline in vole populations as a result of the missing protective snow cover. Additional effects can be caused by increased intensity and frequency of extreme climatic events, or by changes in human behaviour leading to higher risk of human virus exposure. Regardless of the extent of climate change, it is difficult to predict the impact on hantavirus survival, emergence and epidemiology. Nevertheless, hantaviruses will undoubtedly remain a significant public health threat for several decades to come.

Keywords: Climate, hantavirus, insectivore, rodent

Introduction

Although discovered more than 30 years ago, hantaviruses are still considered to be ‘emerging viruses’ because of their increasing significance as human pathogens. These zoonotic viruses cause two human clinical syndromes but are not known to cause disease in their rodent reservoir hosts. Haemorrhagic fever with renal syndrome (HFRS) is a significant medical problem in Asia and Europe, whereas hantavirus cardiopulmonary syndrome (HCPS) is responsible for significant morbidity and mortality in both North and South America.

Both diseases are acute febrile infections that are usually acquired through the inhalation of aerosols or dust particles contaminated with virus containing rodent excreta, which is often encountered in rodent-infested buildings, such as log cabins or farm buildings, when they are being cleaned. The initial symptoms of infection are very similar and include an abrupt onset of high fever, malaise, myalgia, back and abdominal pain, and other influenza-like symptoms. HFRS is mainly characterized by renal failure and haemorrhages varying from small petechiae to severe internal bleeding and the disseminated intravascular coagulation syndrome. On the other hand, pneumonia and cardiovascular dysfunction are characteristic of HCPS. Common factors of hantavirus infections are an increased permeability of the microvascular endothelium and thrombocytopenia. Hantaviruses do not cause significant pathological effects, suggesting that immune mechanisms rather than direct viral cytopathology can explain the complex pathogenesis of HFRS and HCPS. Currently, it is assumed to be a multifactoral process and includes T-cell mediated endothelial damage, immune effectors, cytokines and chemokines, as well as a β3-integrin (used by pathogenic hantaviruses as receptors) dysfunction-mediated increase of vascular permeability [1–4].
Approximately 150,000 HFRS cases are estimated to occur worldwide annually. More than 90% of them are reported from China, the far-eastern parts of Russia, and Korea where the most severe cases, with case fatality rates reaching 15%, are recorded [5]. The type species of the genus Hantavirus (family Bunyaviridae), is Hantaan virus (HTNV). Although HFRS has been recognized since the 1930s, the causative virus eluded discovery until 1976 when it was finally isolated from its rodent reservoir, the striped field mouse, Apodemus agrarius, trapped near the Hantaan river in South Korea [6]. Seoul virus (SEOV), as it became known, is the only hantavirus known to be distributed worldwide because of the global dispersal of its natural host, rats (Rattus rattus, Rattus norwegicus). The most commonly recognized European hantavirus is Puumala virus (PUUV), which causes a mild form of HFRS, usually called nephropathia epidemica (NE) and is transmitted to humans by the reservoir host, bank voles (Myodes glareolus). On the other hand, severe cases of HFRS are also reported in Europe, mostly in the Balkan region. These are caused by Dobrava–Belgrade virus (DOBV) [2].

Prior to 1993, human disease as a result of hantaviruses was not recognized in the Americas. However, an outbreak of an acute pulmonary distress syndrome in the south-west of the USA led to the discovery of a new hantavirus transmitted to humans by rodents collected in Muerto Canyon. Several names (Four Corners virus, Muerto Canyon virus and Sin Nombre virus) were initially proposed for the virus but, because Muerto Canyon was situated in the Four Corners regions and was the sacred burial ground for Navajo Indian chiefs, the name Sin Nombre virus (SNV), meaning without a name, was chosen. The disease was first called hantavirus pulmonary syndrome but, subsequently, the name hantavirus cardiopulmonary syndrome was proposed because death in fatal cases is caused by cardiac failure rather than pulmonary oedema [7]. The rodent host for SNV is the common deer mouse (Peromyscus maniculatus). The disease has a case fatality rate of up to 50%. Other related, so called ‘New World hantaviruses’ were soon discovered in other American rodents [8]. In South America, Andes virus (ANDV) is the most important causative agent of HCPS. ANDV is so far the only hantavirus with reported human-to-human transmission [9–11].

Hantaviruses form a separate genus within the Bunyaviridae family, one of the largest viral families with over 300 viruses. They are enveloped viruses with a single-stranded RNA genome of negative polarity that is divided into three segments. The striking difference from other bunyaviruses is that hantaviruses are not transmitted by arthropod vectors (i.e. are not arboviruses). This important ecological aspect makes hantaviruses substantially distinct from other bunyaviruses when considering climate change impacts. Hantaviruses are very strictly associated with their natural reservoir hosts, mainly rodents, but, as recently reported, also insectivores (i.e. shrews and moles). This strict association is reflected also in their phylogeny; rodent-associated hantaviruses form three major evolutionary clades, which correspond to the three Muridae subfamilies of their natural hosts. HTNV, SEOV and DOBV are examples of Murinae-associated hantaviruses; PUUV belongs to the Arvicolinae-associated hantaviruses, whereas SNV and ANDV are members of Sigmodontinae-associated hantaviruses. The obvious similarities of hantavirus and rodent phylogenies led to the hantavirus-rodent co-evolution and co-speciation concept [12]. However, recent phylogenetic analyses and evolutionary rate calculations [13,14], as well as recent findings of insectivore-associated hantaviruses, suggest that this concept will have to be re-evaluated.

### New Members of the Genus

More than 30 years after the isolation of the prototype HTNV and more than 10 years after the surprising and quite alarming discovery of hantaviruses that cause HCPS in the USA, two more important milestones have been passed over the past 2 years. The first was the discovery of hitherto unknown endemic hantaviruses in Africa and the second was the discovery of a variety of novel, phylogenetically very distinct hantaviruses in nonrodent hosts, shrews and, most recently, a mole. It is unlikely that there is a connection between the recent discoveries of hantaviruses in Africa and in insectivores and the ongoing climate changes. Nevertheless, such novel possibilities have to be taken into consideration when evaluating the possible impacts of climate change on hantaviruses.

Several studies in African populations have shown the presence of antibodies that cross-react with Eurasian hantaviruses, although the final proof of occurrence of indigenous hantaviruses in African rodents was missing. Africa therefore remained Terra incognita on the hantavirus geographic map until 2006 when the first genetic evidence of the presence of hantaviruses in Africa was reported. The first African hantavirus, named Sangassou virus (SANGV), was found in the African wood mouse (*Hylomyscus simus*) trapped in a forest habitat in Guinea, West Africa and belongs to the group of Murinae-associated hantaviruses [15]. A second African hantavirus came soon after and its discovery was even more surprising than the first one. Very divergent hantavirus sequences were found in Therese’s shrew (*Crocidura...*)
thecus), again trapped in Guinea. In phylogenetic analyses, Tanganyka virus (TGNV), as the virus was named, is only distantly related to other hantaviruses, reflecting the fact that it was found in a shrew instead of a rodent [16]. The discovery of novel viruses always raises the question of their public health importance. Although HFRS or HCPS are not recognized diseases in Guinea, or Africa in general, the pathogenic potential of SANGV, TGNV, and probably other, yet undiscovered African hantaviruses, should not be underestimated. In Africa, where medical health care conditions are relatively limited, hantavirus-associated disease may be confused with other severe diseases or may be unrecognized. In our ongoing investigation, we have identified hantavirus-specific antibodies in Guinea residents, indicating that African hantaviruses are able to infect humans (Klempa B, Koivogui L, Sylla O, Koulemou K, Auste B, Krüger DH, Fichet-Calvet E, Meulen J, unpublished data).

Ironically, the first hantavirus ever isolated was the shrew-associated Thottapalayam virus (TPMV) isolated from an Asian house shrew (Suncus murinus) in India in 1971 [17]. However, its relatedness to hantaviruses was not recognized until many years later [18,19]. TPMV was then for decades considered to be the single exception of a hantavirus with a nonrodent reservoir. At about the time of the discovery of the shrew-associated hantavirus (TANGV), several other unique isolates of hantavirus were being made. These included the detection of Camp Ripley virus in the northern short-tailed shrew (Blarina brevicauda) [20], Ash River virus in the masked shrew (Sorex cinereus), Jemez Springs virus in the dusky shrew (Sorex monticolus) in the USA [21]; Cao Bang virus (CBNV) in the Chinese mole shrew (Anourosorex squamipes) in Vietnam [22]; and Seewis virus in the Eurasian common shrew (Sorex araneus) in Switzerland [23]. Most recently, the spectrum of hantavirus hosts was further extended to moles when Asama virus was found in the Japanese shrew mole (Urotrichus talpoides) trapped in Japan [24].

Several important scientific observations resulted from the discovery of the shrew-borne hantaviruses. They were found in widely separated geographical regions throughout the world, even in countries considered atypical for hantaviruses, such as Switzerland or Guinea. Second, insectivores and mice are so divergent in evolutionary terms, it can be confidently predicted that other groups of mammals will carry hantaviruses. Nothing is known about the pathogenicity of the shrew-borne hantaviruses at the moment. However, they share such low amino acid sequence similarities with rodent-associated hantaviruses that there is probably no serological cross-reactivity with the 'old' hantaviruses (as shown for TPMV) [25]. This fact almost certainly explains why they have remained undetected for such a long period of time using current hantavirus-specific diagnostic tools.

Possible Consequences of Climate Change

Based on the hantavirus mode of transmission and circulation in nature, it is reasonable to assume that climate change might influence hantaviruses through impacts on hantavirus reservoir host populations. Outbreaks of hantaviral disease have been associated with changes in rodent population densities. The changes that affect rodent population dynamics are often weather/climate related. The best example is the US Four Corners outbreak in 1993, which was preceded by a dramatic increase in rainfall associated with the 1992–1993 El Niño. This led to increased rodent food resources and a focal 20-fold increase in the rodent population, followed by invasion of buildings by rodents, and an increased risk of human disease [8,26,27].

It is difficult to avoid speculation when discussing the possible climate change impacts. The spectrum of impacts may vary from no impact at all to dramatic changes in size and frequency of hantavirus outbreaks, changes in hantavirus species spectrum, and geographical distribution. Nevertheless, some recent changes in rodent populations and hantavirus infections associated with climate change have been reported from Europe. Interestingly, in different geographical parts of Europe, global warming appears to have opposite effects on the most common European hantavirus, PUUV, and its reservoir host M. glareolus.

In western and central European regions, periodic high bank vole abundance has been related to mast years, with high seed production of oak and beech. Mast years are induced by summer conditions, especially by elevated average temperatures. It is generally believed that high seed production in the autumn improves winter survival of rodents and is associated with early breeding in spring, resulting in high densities in early summer, which then gives rise to PUUV-associated NE outbreaks. In Belgium, such outbreak years originally occurred in a 3-year cycle but, recently (i.e. subsequent to 2001), this has changed to a 2-year cycle and the overall incidence of PUUV infections has increased. Similar tendencies were also observed in other western and central European countries [28]; for example, in Germany, the two highest numbers of hantavirus cases were observed in 2005 and 2007 [29,30]. This correlates with the fact that shorter mast year intervals and increasing mast crops have been observed in recent years [31]. Recent studies evaluated the relationship among tree seed production, climate and NE incidence in Belgium and showed that high summer and autumn...
temperatures, 2 years and 1 year, respectively before NE occurrence, relate to high NE incidence [32,33]. It is therefore quite obvious that elevation of the average temperatures in Europe as a part of the global climate change scenarios might lead to a significant increase in PUUV as a public health threat, at least in western and central Europe.

In Scandinavia, where the majority of PUUV-associated NE cases within Europe currently occur, recent observations associated with climate change are in striking contrast to those reported above. Northern voles and lemming populations are known for their 3–4-year population cycles with high amplitudes. These cycles allow PUUV to spread efficiently in the rodent population, resulting in human NE outbreaks in the autumn and early winter during the high density years [34]. However, in recent years, the characteristic of high-amplitude cycles has gradually changed towards annual fluctuations. Moreover, a long-term decline in vole population density has been observed, mainly characterized by decreased vole survival rates in winter. The reasons for the decreased vole wintering success are considered to be the result of specific changes in climatic patterns normally referred to as the North Atlantic Oscillation (NAO), which leads to mild and wet winters. Although it might appear illogical, warm and wet winters do not favour rodent population density increases in this part of Europe. This is because the shorter period of protective snow cover combined with more frequent freezing and thawing periods produces an ice rather than snow cover [35,36]. Because the NAO phenomenon is believed to be affected by global warming [37], the current decline in vole densities can also be considered as an early effect of global warming [35]. This effect will most likely lead to the decrease of PUUV infections in Scandinavia in the long-term future. Interestingly, however, it appears to be having an opposite effect at present. A recent large PUUV outbreak in humans in Sweden in January of 2007 was linked to the high rate of invasion of buildings by voles, probably because of the missing protective snow cover during the unusually warm winter [38].

The observed changes in vole population density and PUUV incidence in west and central Europe and Scandinavia comprise examples of how climate change will influence hantaviruses through effects on the entire ecological system, including rodents. It can be generally concluded that, especially in regions of moderate climate, an increased risk of human disease will be mediated by higher rodent densities associated with higher food availability and wintering success. Moreover, changes in geographical distribution of distinct rodent species might bring hantaviruses to new regions. For example, striped field mice (A. agrarius) are currently invading new regions in central Europe [39–42]. Although this invasion has yet not been linked to climate change, it might have important epidemiological consequences because A. agrarius is the carrier of DOBV in central Europe.

Furthermore, the indirect effects on rodents, and thus the risk of human exposure to hantaviruses, can be attributed to changes in human behavior. For example, changing agricultural practices, human population movements, deforestation, re-afforestation, land reclamation, irrigation projects, etc. all might create conditions that increase the risk of human exposure to hantaviruses. Additionally, contact rates with as yet unidentified hantaviruses may also increase. This could be particularly pronounced in Africa because it is now recognized that hantaviruses are abundant in Africa and there is an enormous diversity of African rodents and insectivores. One can therefore anticipate many new hantaviruses with unpredictable pathogenic potential emerging during the next decades.

Increasing intensity and frequency of extreme climatic events, such as floods, droughts or hurricanes, represent extremely important contributory factors in the context of climate change and its impact on hantavirus disease in humans. A 30-year study of a desert rodent community affected by two major floods demonstrated that extreme climatic events can decimate resident populations, alter species composition and interspecific interactions, influence invasion dynamics and thereby result in a rapid, wholesale reorganization of the community [43]. If hantavirus reservoir hosts form part of the affected community, dramatic changes in hantavirus incidence and species spectrum can be expected. Different hantavirus species could assume dominance, together with their natural host, whereas others could be eliminated from the affected geographical region. In such situations, currently unrecognized hantaviruses and reservoir hosts could replace the eliminated species. For example, shrews and the recently recognized shrew-associated hantaviruses, currently of unknown pathogenic potential, might be better adapted to the new climatic conditions. The recent increase in field rodents in houses and other buildings in Sweden, accompanied by a significant PUUV outbreak [38], provides another example of the potential impact of extreme climatic change events.

It is interesting to note that, regardless of the extent to which changes in hantavirus distribution and incidence arise, they will remain restricted to specific geographical regions as a result of the strict association of hantaviruses with their rodent/insectivore reservoir host species and their zoonotic mode of virus transmission. However, one scenario could lead to a major global public health threat. If the consequence of climate change in South America favoured the long-tailed pygmy rice rat (Oligoryzomys
longicaudatus), this could lead to a significant increase in the frequency of human infections by ANDV, with potentially alarming results. As far as we know, ANDV is the only hantavirus for which person-to-person transmission has been documented [9–11]. Moreover, ANDV is associated with high mortality rates (>40%) [1]. A recent prospective study showed that viral RNA could be detected in peripheral blood cells for up to 2 weeks before the onset of symptoms or the appearance of anti-hantavirus antibodies [11] and the infectious virus was isolated from a seronegative, asymptomatic child 2 days before he developed HCPS [44]. Thus, the virus could be spread by asymptomatic patients to other parts of the world. However, the currently accepted opinion is that, should such a situation arise, an influenza-like pandemic scenario is highly unlikely because human-to-human transmission of ANDV appears to be very inefficient, occurs mainly within households, and requires relatively intimate interpersonal contact [11].

**Concluding Remarks**

Hantaviruses are emerging viruses that cause two serious human zoonoses. The intention of this review is not to provide a list of catastrophic, highly speculative scenarios but, instead, to draw attention to the recent findings and trends relating to hantaviruses that should be considered in the perspective of climate change. Global warming will affect hantaviruses through their natural reservoirs, rodents and insectivores. Recent trends, as observed in western and central Europe and Scandinavia, indicate that, from the public health point of view, these influences can have negative as well as positive effects. The most obvious negative consequences for humans will be increasingly frequent and will result in larger hantavirus outbreaks. On the other hand, a continuous decline in certain rodent population densities, as recently observed in Scandinavia, might lead to a significant decrease in hantavirus incidence in humans.

Changes in the geographical distribution of the rodent carriers could deliver hantaviruses to new geographic regions and changes in species composition might cause yet unrecognized hantaviruses to become dominant and thereby epidemiologically important. We could even experience novel hantavirus diseases. Particularly, the African and insectivore-associated hantaviruses may be concealing considerable potential in this respect.

It is difficult to predict how extensive the climate change effects will be. Nevertheless, hantaviruses will remain a significant public health threat in the near future, emphasizing the need for further hantavirus research, especially focusing on pathogenesis, diagnostics, and antiviral and vaccine development.

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**Transparency Declaration**

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Hantaviruses and climate change

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