Review

Transmission of Haemorrhagic Fever with Renal Syndrome in China and the Role of Climate Factors: A Review

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A B S T R A C T

Haemorrhagic fever with renal syndrome (HFRS) is a rodent-borne disease that poses a serious public health threat in China. HFRS is caused by hantaviruses, mainly Seoul virus in urban areas and Hantaan virus in agricultural areas. Although preventive measures including vaccination programs and rodent control measures have resulted in a decline in cases in recent years, there has been an increase in incidence in some areas and new endemic areas have emerged. This review summarises the recent literature relating to the effects of climatic factors on the incidence of HFRS in China and discusses future research directions. Temperature, precipitation and humidity affect crop yields, rodent breeding patterns and disease transmission, and these can be influenced by a changing climate. Detailed surveillance of infections caused by Hantaan and Seoul viruses and further research on the viral agents will aid in interpretation of spatiotemporal patterns and a better understanding of the environmental and ecological drivers of HFRS amid China’s rapidly urbanising landscape and changing climate.

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1. Introduction

Haemorrhagic fever with renal syndrome (HFRS) is a serious zoonotic disease occurring mainly in China, where 30,000-60,000 cases are reported annually. Symptoms include fever, headache, back pain, abdominal pain, hypotension, multisystemic haemorrhage and acute renal failure. The five clinical stages of HFRS are: febrile, hypotensive, oliguric, diuretic, and convalescent. The fatality rate in the 1960s was around 14% but has since fallen due to advances in treatment. Those who survive the disease can develop chronic renal impairments. China’s incidence of HFRS is the highest in the world, accounting for 90% of global cases. More than 1 million cases were reported between 1950 and 1995 and 91,000 cases reported during the five years to 2009. Although prior to 1950 the disease had been reported in only 2 provinces, it has since spread across the country. It has now been noted in all 31 provinces and is endemic in 28 of these.

The etiologic agents of HFRS are single-stranded RNA viruses of the genus Hantavirus. Of the seven serotypes of hantaviruses in China, it is mainly Seoul virus (SEOV) and Hantaan virus (HTNV) that cause HFRS, the latter being responsible for up to 70% of cases. Amur virus has also been identified in a limited number of patients. The main natural reservoir hosts of SEOV and HTNV are the brown Norway rat (Rattus norvegicus) and the striped field mouse (Apodemus agrarius) respectively. Transmission of the viruses to humans is mainly due to inhalation of aerosolised urine or faeces, contact with the saliva of infected rodents or via contaminated food, necessitating close contact between humans and rodent hosts. Whilst there is a predominance of HTNV in the north-east of China and SEOV in the south western areas of the country, both reservoir hosts are found in nearly all provinces. The A. agrarius rodent is found mainly in forested regions and...
fields, whereas *R. norvegicus* is abundant in urban areas (Table 1). For the latter, studies have shown that viral shedding of SEOV is most common in large, mature male rats and that well-established rat populations pose the greatest risk to human health.4

Many cases occur in people living in poor housing conditions and most often affected are male farmers aged between 30 and 50 years, as well as forest workers and soldiers.2,13 Crops provide a food source for rodents, and where traditional farming methods are in use, there are numerous opportunities for humans to be exposed to the virus, particularly during harvest time when farmers reside in close proximity to the fields.1,10,14 In these rural areas where HTNV is most likely the cause, symptoms are more severe than HFRS caused by SEOV.2,4,15 One recent study showed the case fatality rate for a cohort of HTNV-infected HFRS patients was 6.3%, but 0% for those with SEOV infection (Table 1). For survivors, the humoral immune response to hantaviruses confers life-long immunity to re-infection.16

Climatic conditions are one of the many factors that can affect rodent population dynamics, and the consequent risk of virus exposure in humans.5,7,17 Although HFRS cases can occur at any time there is generally a bimodal seasonal case distribution, with a rapid peak in winter and a longer lasting peak in spring.6,7,10,15 Autumn to winter peaks are associated with infections transmitted by *A. agrarius*,14,18,19 and are associated with harvest season, whereas summer and spring peaks occur for infections where *R. norvegicus* is the source.6,7,20

In some provinces preventive measures including vaccination programs and rodent abatement strategies have been put in place in recent years, resulting in a dramatic decline in cases.6,10 Nevertheless, HFRS remains a serious public health threat on mainland China.2,10,15,21,22 A better understanding of virus ecology and epidemiology of the disease is therefore required to curb the likely occurrence of future epidemics. Amid predictions of rising global temperatures and more extreme weather events, it is important to understand the influence of variables such as temperature, rainfall and humidity on disease incidence. The purpose of this review is to summarise the recent literature relating to the effects of climatic factors on the incidence of HFRS in China, to determine how HFRS ecology may change in a future climate and to identify new research directions.

2. Methods

To establish the climate factors affecting the transmission and incidence of HFRS in China, a search of the recently published scientific literature was conducted based on previous methods.23 Following the selection of appropriate literature, reports of associations between HFRS and meteorological and climatic factors were appraised to make an initial identification of the important drivers of HFRS incidence.

### 2.1. Search strategy

The electronic databases PubMed and Scopus were used to search for relevant literature with the abstract or full text in English. Combinations of the following key terms were used for the search strategy: ‘China’, ‘Haemorrhagic fever with renal syndrome’, ‘Hemorrhagic fever with renal syndrome’, ‘climate’, ‘weather’, ‘climate change’, ‘climate variability’, ‘temperature’, ‘rainfall’ and ‘humidity’. Titles and abstracts were screened for relevance and full texts were obtained if the article met the inclusion criteria below. Reference lists were then scanned for additional articles not previously identified. The ‘Google’ search engine was also searched to source relevant grey literature.

### 2.2. Inclusion criteria

Studies were included if they met the following criteria:

1. Investigated the effects of climatic factors or meteorological variables (e.g. temperature, rainfall, humidity, South Oscillation Index) on the incidence and transmission of HFRS
2. Related to HFRS in China
3. Were published in the years between 1993 and 2013
4. The article (or abstract) was published in English

### 3. Results

An initial search generated 34 articles. Of these, 16 did not meet the inclusion criteria. Three additional articles were sourced from citation snowballing of reference lists. The final 21 articles are summarised in Table 2. The study sites of articles reviewed included the provinces of Inner Mongolia in the north; Heilongjiang and Liaoning in the north-east; Shandong, Anhui and Jiangsu in the east; and Hunan in central China. Study designs and methodologies were highly varied and rarely replicated. Approaches included seasonal autoregressive integrated moving average models, generalized linear models, generalized additive models, multiple linear regression analyses, auto-regressive integrated moving average models, Poisson regression models, case-crossover designs, principal components regression models, ecological niche models, spatiotemporal analysis, structure equation models, Pearson’s correlation, and Spearman rank correlation. This spectrum of methodologies makes comparisons between studies highly problematic. Overall however, the findings show that climate factors including rainfall, temperature and humidity have a definitive but variable, influence on HFRS incidence.

#### 3.1. Rainfall

Findings in regard to rainfall/precipitation were inconclusive with some studies showing a positive relationship with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main causal agents of HFRS in China</th>
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<tbody>
<tr>
<td><strong>Main reservoir host</strong></td>
<td>Hantaan virus (HTNV)</td>
</tr>
<tr>
<td>Microenvironment</td>
<td>Apodemus agrarius</td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td>Rural (fields)</td>
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<tr>
<td>Greater predisposition to oedema and haemorrhage.</td>
<td>Milder symptoms, normal or low white blood cell count, longer fever history.</td>
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<td>Longer hospital stay.</td>
<td>Higher incidence of liver injury related to disease severity.</td>
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<td>Case fatality rate higher</td>
<td>Higher rate of misdiagnosis.</td>
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<td>Case fatality rate lower</td>
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<tr>
<td>Details</td>
<td>Study area &amp; period</td>
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<tr>
<td>Li CP et al., 2013 11</td>
<td>Heilongjiang province 2001-2009</td>
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<td>Xiao H et al., 2013 3</td>
<td>Hunan province 2005 to 2009</td>
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<td>Xiao H et al., 2013 3</td>
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<td>Xiao H et al., 2013 28</td>
<td>Hunan province 2005 to 2010</td>
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<tr>
<td>Lin H et al., 2013 13</td>
<td>Shandong province 2006 to 2011</td>
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<td>Liu J et al., 2012 24</td>
<td>Shandong province 1977 to 2001</td>
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<td>Xiao H et al., 2011 20</td>
<td>Hunan province 2000 to 2009</td>
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<td>Liu X et al., 2011 21</td>
<td>Liaoning province 2004 to 2009</td>
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<td>Details</td>
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<td>Fang LQ et al., 2010</td>
<td>Shandong province</td>
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<td>Zhang WY et al., 2010</td>
<td>Inner Mongolia</td>
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<td>Guan P et al., 2009</td>
<td>Liaoning province</td>
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<tr>
<td>Luo CW et al., 2009</td>
<td>Heilongjiang province</td>
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<tr>
<td>Yan L et al., 2007</td>
<td>Rural areas in China with population &lt;1,000/km2</td>
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<td>Lin H et al., 2007</td>
<td>Liaoning province</td>
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<td>Liu J et al., 2006</td>
<td>[Article in Chinese]</td>
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<td>Wu RJ et al., 2005</td>
<td>Jiangsu province</td>
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<td>Bi P et al., 2005</td>
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<td>Bi P &amp; Parson KA 2003</td>
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<td>Bi P et al., 2002</td>
<td>Anhui province</td>
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incidence of HFRS was found to be positively associated with low temperatures, high relative humidity and rainfall in several studies. Liu et al. (2006) identified relative humidity as an important factor in all four seasons. The highest incidence of disease was reported to be in semi-humid areas or in mountainous regions with a humid or semi-humid climate. Inverse associations of humidity with incidence have also been reported. There is an inverse correlation between SOI and the density of mice and consequent incidence of HFRS. The negative association between SOI and the risk of HFRS incidence has also been reported. Some studies used the Multivariate El Niño-Southern Oscillation Index (MEI) as an alternative indicator of the global climate pattern. MEI was found to be an important predictor of the intensity of HFRS and although one study showed there was a negative relationship with incidence and MEI at a lag of 3 months, others showed a 1 unit rise in MEI (at lags of 4-6 months) was associated with increases in HFRS cases of between 55% and 66%.

4. Discussion

It is clear from the studies under review that weather and climate are indirectly associated with the incidence of HFRS. However, findings can be inconsistent. China is a vast and topographically heterogeneous country and the literature shows varied findings given the range of climate zones and geographical characteristics of the study regions. Factors relating to the breeding patterns and survival of the rodent hosts (e.g. the elevation, soil type, and abundance of vegetation), land use and human activities also vary across geographical and climate regions.

It is generally thought that precipitation, followed by air temperature, is the most important meteorological element influencing the endemic intensity of the disease. Abundant precipitation and warm temperatures are ideal conditions for the plentiful growth of crops and help boost rodent populations. These conditions can be indicators of an HFRS outbreak in the forthcoming months. Rainfall has an influence on vegetation growth and thus on the density of rodents and hantavirus infectivity, whereas the gestation period and sexual maturation...
of rodents may be modified by temperature leading to changes in the population dynamics.\textsuperscript{7,27}

At this point it is important to take a moment to contextualise the findings and discuss the complexities of this dichotomous disease. Firstly, HFRS involves two rodent hosts with quite different habitats (one rural, one urban) transmitting two phylogenetically distinct viruses (although genetic re-assortment does occur between SEOV and HTNV).\textsuperscript{3} Spatiotemporal differences also exist in the pathogen carrying rate of the rodents and virulence of the viruses.\textsuperscript{9} Inherent issues arise from the fact that quantitative studies of weather-disease associations are generally undertaken using datasets of HFRS incidence that record cases of confirmed hantavirus disease but do not distinguish between HTNV or SEOV infections.\textsuperscript{28} This occurs because the commercial immunological test kits to identify hantaviruses do not discriminate between the HTNV and SEOV antigens.\textsuperscript{3} Although segregating the viral ecologies is problematic at present, making assumptions about the effects of climate on HFRS with no due consideration of the two separate viruses can be misleading at best and erroneous at worst.

Furthermore, several other factors need to be considered before causal links can be attributed solely to changes in weather patterns. These include occupational factors, urbanisation in China in the past three decades, and the socio-economic status and immunity of the population at risk, together with their knowledge of the disease.\textsuperscript{9} Comprehensive preventive measures and control measures have been implemented in the last 20-30 years as authorities have recognised the need to address the high rate of disease.\textsuperscript{20} Two main approaches have been used: programs to control rodent populations (deratization around residential areas); and large scale vaccination programs targeting the high-risk age group of 16–60 year olds with a vaccine protecting against both HTNV and SEOV.\textsuperscript{15,21} There has also been improved surveillance, public education about HFRS, and environmental management strategies.\textsuperscript{6,10,11,21} These preventive measures, together with improved living conditions, have had a significant influence, and overall there has been a dramatic decline in the number of cases.\textsuperscript{12,21} However, it is difficult for quantitative studies of climate-disease associations to account for these factors in statistical models.\textsuperscript{21}

A clear understanding is required of the unique epidemiological factors associated with HFRS. Identifying those at risk depends on whether the disease is likely to be acquired in rural or urban areas by contact with field mice or brown rats respectively. For both situations however, socio-cultural and socio-economic issues affect vulnerability. In fact, people living in low socio-economic circumstances comprise 93% of all HFRS cases.\textsuperscript{3}

In rural areas there is a higher risk for people living near, or working on, cultivated land where murine hosts are prevalent. Occupational factors are therefore important considerations with workers and peasants being vulnerable.\textsuperscript{3,18} As food supply is an important predictor of the rodent population,\textsuperscript{12} times of greater crop production are associated with higher incidence rates of HTNV infections, with peak incidence coinciding with the autumn harvest season when farmers work (and often sleep) in the fields.\textsuperscript{14} Furthermore, in rural areas and elsewhere, there have been increases in the numbers of tourists, travellers, migrant workers and deployed troops who are likely to be a susceptible, unvaccinated population who may lack health awareness of the disease.\textsuperscript{10,27}

The rapid development of China’s urban construction will affect the incidence of SEOV infections as greater numbers of rats and people cohabitating in cities provides more opportunities for human-rodent interaction. Hence the risk of HFRS will increase with urbanization and urban poverty.\textsuperscript{15} This risk may be modified however, if standards of living increase. One report states that “SEOV has become the largest threat for public health in China and may bring even more potential threats to humans as rat species become more widespread along with globalization of the economy”\textsuperscript{35}(p. 1200) Additionally, recently reported research has shown that novel genetic variants of Gou virus, closely related to HTNV, have been found in other rat species (\textit{R. rattus, R. flaviview}) that may be the cause of HFRS in areas such as Zhejiang province.\textsuperscript{20} Hence, authorities need to be vigilant in the surveillance of infected rodent populations.

4.1. Climate change

The effects of climate change on HFRS are unclear. It is expected that surface air temperature over China could increase markedly, more so in winter and spring than in other seasons, and particularly in the north. Precipitation is also expected to increase in most areas.\textsuperscript{31} Reports suggest changes in climate could affect hantaviruses through impacts on the host rodent populations, via their breeding patterns, micro-environments and geographical distribution.\textsuperscript{14} With rising temperatures, cooler areas may become conducive to rodent breeding and breeding seasons may be extended. This has the potential for a major impact on the number and scale of outbreaks in China and emergence of the disease into previously unaffected areas.

Several studies found an inverse correlation between SOI and incidence of HFRS\textsuperscript{11,20} with higher incidence occurring with El Nin\~{o} events when SOI becomes negative.\textsuperscript{9} Recent research has shown that due to greenhouse warming, extreme El Nin\~{o} events will increase in frequency, doubling from about one event every 20 years to one every 10 years.\textsuperscript{32}

However, for reasons mentioned above, caution is required when prognosticating about the impacts of climate change as there is a clear need to distinguish the effects on the ecology of the causal agents. It is plausible for example, that changing weather patterns will have a greater effect on rodent populations in rural areas than in cities. Indeed, climate change will be just one of the factors likely to influence HFRS in the future, along with increased numbers of people at risk, wider vaccination programs, better surveillance and improved preventive measures.

In conclusion, HFRS remains a significant public health issue in China. Despite considerable preventive measures being in place, there are still 20,000 to 50,000 new cases annually.\textsuperscript{1,11,21} and some reports suggest the figures are higher.\textsuperscript{1} There has also been an increase in incidence in some areas\textsuperscript{19} and new epidemic areas have emerged.\textsuperscript{13} The studies under review have shown that despite spatial differences in findings, changes in temperature, rainfall and humidity are linked to changes in disease rates. Climatic conditions influence crop yields, human and rodent activities, and opportunities for viral exposure in susceptible populations. Variation in meteorological conditions will affect incidence, and these variations will be tempered by public health measures to address the high rates of this disease in communities. Although it is difficult to predict the effects of climate change and warmer temperatures, the transmission of HFRS may be affected in a number of ways including effects on crop production, shifting the geographical range of the reservoir, increasing the rate of rodent reproduction and shortening the incubation period.\textsuperscript{18} Authorities therefore need to be vigilant in public health measures such as vaccination programs, improving public awareness and rodent control initiatives in rural and residential areas.

4.2. Further Directions

Research needs to continue to identify potential disease-causing hantavirus variants in rodent populations. Furthermore, public health education programs need to raise health consciousness in not only people residing and working in high-risk areas, but also in tourists, travellers and migrant workers in agricultural
employment. A better understanding of the environmental and ecological drivers of HFRS is required to unpick the factors underpinning the extensive expansion of the disease from a few provinces in the middle of last century, to most of China at present. How the changing face of China with its rapid transformation of agricultural to urban landscapes will affect the incidence of HFRS, is at present unknown and requires close scrutiny over coming years.

Research on the effect of climate change on the two major virus types is scant at present as specific data have not been available to date. Detailed surveillance and recording cases caused by HTNV and SEOV (or other hantaviruses) separately would aid epidemiological advances in knowledge regarding the effects of climate variability and disease transmission. This would also help to better identify changing spatiotemporal patterns, the effectiveness of interventions and to clarify weather-incidence associations of this serious zoonotic disease.

Conflict of interest: The authors declare no conflicts of interest.

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