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Review

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

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ABSTRACT

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.


## 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.[1] Symptoms include fever, headache, back pain, abdominal pain, hypotension, multisystemic haemorrhage and acute renal failure.[2–4] The five clinical stages of HFRS are: febrile, hypotensive, oliguric, diuretic, and convalescent.[5] The fatality rate in the 1960s was around 14%[6] 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.[1,3,7,8] More than 1 million cases were reported between 1950 and 1995[9] and 91,000 cases reported during the five years to 2009.[2] Although prior to 1950 the disease had been reported in only 2 provinces,[6] it has since spread across the country. It has now been noted in all 31 provinces[10] and is endemic in 28 of these.[8,11]

The etiologic agents of HFRS are single-stranded RNA viruses of the genus *Hantavirus.* Of the seven sero/genotypes of hantaviruses in China,[6] 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.[8] The main natural reservoir hosts of SEOV and HTNV are the brown Norway rat (*Rattus norvegicus*) and the striped field mouse (*Apodemus agrarius*) respectively.[6] Transmission of the viruses to humans is mainly due to inhalation of aerosolised urine or faeces, contact with the saliva of infected rodents,[4,6,12] 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,[10] both reservoir hosts are found in nearly all provinces.[6] The *A. agrarius* rodent is found mainly in forested regions and

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fields, whereas *R. norvegicus* is abundant in urban areas[1] (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[6] 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[5] (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.[3,17] 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*,[9,14,18,19] 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 1**
Main causal agents of HFRS in China

| | Hantaan virus (HTNV) | Seoul virus (SEOV) |
|---|---|---|
| Main reservoir host | *Apodemus agrarius* | *Rattus norvegicus* |
| Microenvironment | Rural (fields) | Urban (homes) |
| Clinical manifestation[5] | Greater predisposition to oedema and haemorrhage.<br>Higher incidence of lower back pain, leucocytosis, hypotension, thrombo-cytopenia, microhaematuria, oliguria, anuria, serious renal injury.<br>Longer hospital stay.<br>Case fatality rate higher | Milder symptoms, normal or low white blood cell count, longer fever history.<br>Less need for haemodialysis.<br>Higher incidence of liver injury related to disease severity.<br>Higher rate of misdiagnosis.<br>Case fatality rate lower |