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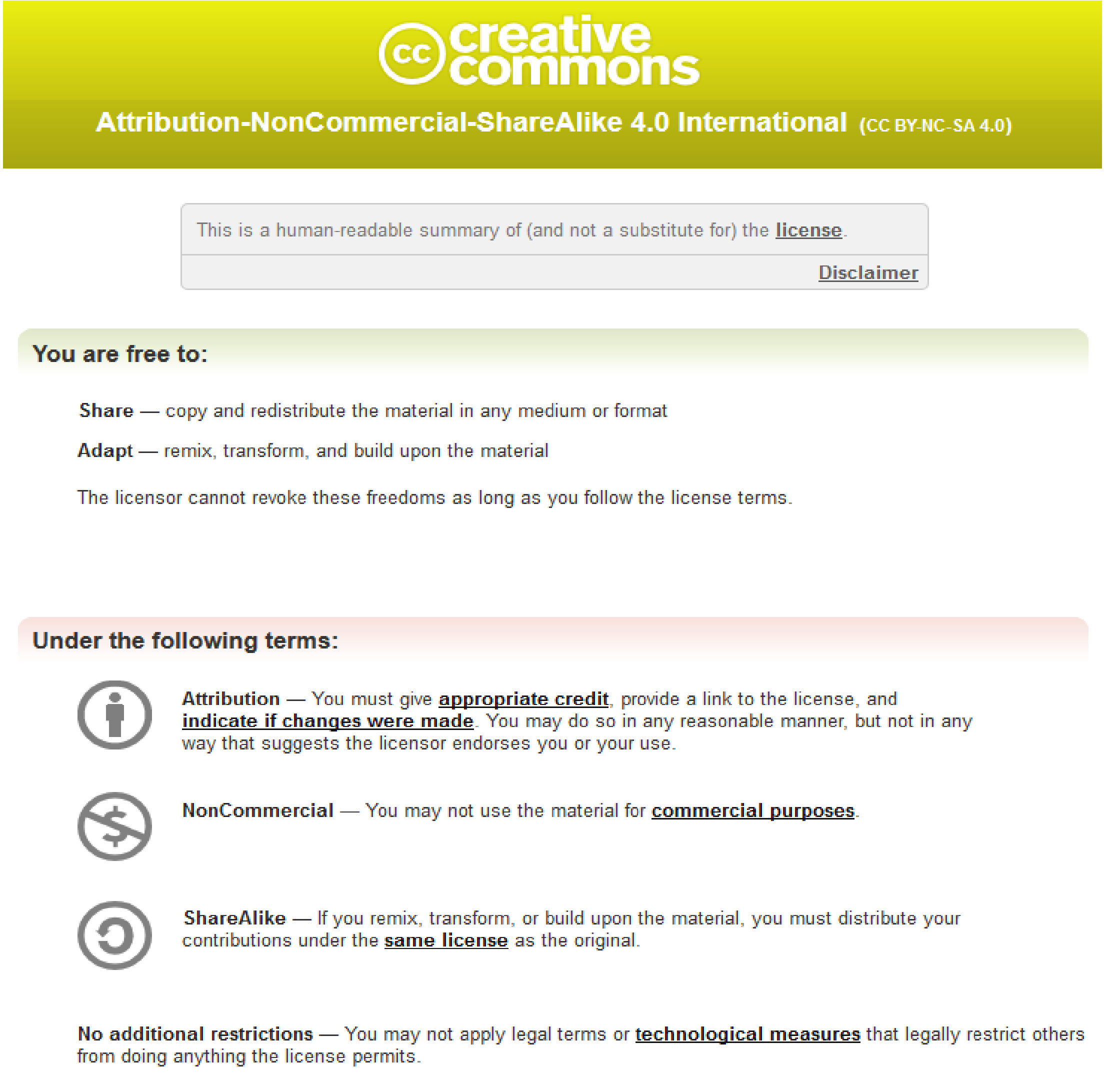

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Review

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. Higher incidence of lower back pain, leucocytosis, hypotension, thrombo-cytopenia, microhaematuria, oliguria, anuria, serious renal injury. Longer hospital stay. Case fatality rate higher	Milder symptoms, normal or low white blood cell count, longer fever history. Less need for haemodialysis. Higher incidence of liver injury related to disease severity. Higher rate of misdiagnosis. Case fatality rate lower

Table 2
Summary of the studies reviewed

Details	Study area & period	Methods	Results
Li CP et al., 2013 [11]	Heilongjiang province 2001-2009	Monthly climatic data including mean temperature, maximum temperature, minimum temperature, relative humidity and rainfall were used. The association with the incidence of HFRS was investigated by using the seasonal autoregressive integrated moving average (SARIMA) models. Southern oscillation index (SOI) was used as an indicator of ENSO.	Relative humidity with a one-month lag and a three-month lag, maximum temperature with a two-month lag, and southern oscillation index with a two-month lag were significantly associated with HFRS transmission. Other climatic variables, including monthly minimum temperature, rainfall, and monthly mean temperature, were not significantly associated.
Xiao H et al., 2013 [1]	Hunan province 2005 to 2009	Ecological niche models (ENMs) were used to evaluate potential geographic distributions of rodent species. Data on elevation, precipitation, temperature, precipitation seasonality and temperature seasonality were used. The relationship between rodent density and HFRS incidence was investigated.	The highest occurrence of HFRS was in districts with strong temperature seasonality, where elevation was $<$200m, mean annual temperature was around 17.5 °C, and annual precipitation was 1300-1600 mm. The number of HFRS cases was correlated with rodent density, and the incidence of HFRS cases in urban and forest areas was mainly associated with the density of *Rattus norvegicus* and *Apodemus agrarius*, respectively.
Xiao H et al., 2013 [3]	Hunan province 1991 to 2010	Wavelet analyses were performed by using monthly reported time series data of HFRS cases to detect and quantify the periodicity of HFRS. A generalized linear model with a Poisson distribution and a log link model were used to quantify the relationship between climate and HFRS cases.	There was a significant association of HFRS incidence with moisture conditions and the Multivariate El Niño-Southern Oscillation Index (MEI). Annual incidence of HFRS was positively correlated with annual precipitation and annual mean absolute humidity. Monthly HFRS cases were significantly correlated with precipitation with a lag of 5 months.
Xiao H et al., 2013 [12]	Hunan province 2004 to 2011	An auto-regressive integrated moving average model (ARIMA) with explanatory variables was used to examine the independent contribution of climatic variables and food supply to rodent density. Monthly normalized difference vegetation index (NDVI) and temperature vegetation dryness index (TVDI) for rice paddies were also used.	Relative rodent density of the HFRS host was significantly correlated with monthly mean temperatures, monthly accumulative precipitation, TVDI and NDVI with lags of 1-6 months. There was an inverse correlation between TVDI and rodent density.
Xiao H et al., 2013 [28]	Hunan province 2005 to 2010	Variables relating to climate (monthly rainfall, mean temperature, relative humidity, and air pressure), environment, rodent host distribution and disease occurrence were collected and analysed using a time-series adjusted Poisson regression model. The multivariate ENSO index (MEI); and NDVI values, absolute humidity, mean temperature and rodent density were also used.	Density of the rodent host and multivariate El Niño Southern Oscillation index had the greatest effect on the transmission of HFRS with lags of 2–6 months. Mean temperature, rainfall, absolute humidity, MEI, and NDVI value for rice paddies, orchards, forest land and residential areas were significantly correlated with the monthly notified number of HFRS cases with a lag time of 1–6 months.
Lin H et al., 2013 [19]	Shandong province 2006 to 2011	This study examined the effect of meteorological factors (daily mean temperature, relative humidity and rainfall) on the occurrence of HFRS using a generalized additive model adjusted for day of the week and public holidays, long-term trends and seasonal patterns.	When daily temperature was $<$ 17 C, a positive association was found with HFRS occurrence, with excessive risk (ER) for a 1 C increase on the current day being 2.56% (95% CI: 0.36% to 4.80%). An inverse association was found when daily temperature was $>$17 °C. Inverse associations were also observed for relative humidity and rainfall.
Liu J et al., 2012 [24]	Shandong province 1977 to 2001	A symmetric bidirectional case-crossover design was used to examine the effect of monthly mean temperature and precipitation on the risk of HFRS, with the hazard period being the 3 calendar months preceding the month when the case was diagnosed, and the control period being the same calendar month of the year before, and the year after, the hazard period. The mean temperature and precipitation for each month was grouped into low, moderate and high. Analysis was done using conditional logistic regression.	Temperatures of 10-25 °C and moderate precipitation (10-120 mm) in the current month was the most favourable condition for HFRS incidence. During the previous 3 months of a HFRS case being diagnosed, a monthly mean temperature level $>$25oC, compared to the monthly mean temperature of 10–25oC was significantly associated with a lower risk of HFRS. Cold weather 2 months before significantly decreased the number of cases. Lack of precipitation and excessive precipitation in the month the case occurred were both associated with lower risk of HFRS.
Xiao H et al., 2011 [29] [Article in Chinese]	Hunan province 2000 to 2009	A climate-based forecasting model for HFRS transmission was established using the Cochran-Armitage trend test. Cross-correlations analysis was used to assess the time-lag period between climatic factors (including monthly average temperature, relative humidity, rainfall and Multivariate El Niño-Southern Oscillation Index) and monthly HFRS cases. A time series Poisson regression model was used to analyse the influence of climatic factors on HFRS transmission.	Monthly average temperature (1-month lag period), relative humidity (3-month lag period) rainfall (6-month lag period) and Multivariate Elño-Southern Oscillation Index (3-month lag period) were closely associated with monthly HFRS cases.
Liu X et al., 2011 [21]	Liaoning province 2004 to 2009	Annual and seasonal fluctuation of HFRS cases was examined. Principal component analysis was constructed by using climate data (temperature, relative humidity, accumulative precipitation, air pressure, wind velocity and monthly sunshine duration). A principal components regression model (PCR) was used to quantify the relationship between climate factors and transmission of HFRS. The PCR model was compared to a general multiple regression model.	A declining temporal trend of annual HFRS incidence was identified. HFRS cases peaked in spring and winter. The monthly trends of HFRS were significantly associated with local temperature, relative humidity, precipitation, air pressure, and wind velocity of the different previous months. Relative humidity factors affected HFRS negatively.

Table 2 (*Continued*)

Details	Study area & period	Methods	Results
Fang LQ et al., 2010 [7]	Shandong province 1973 to 2005	A spatiotemporal analysis of human HFRS cases was undertaken. Seasonal incidence maps and velocity vector maps were produced to analyse the spread of HFRS over time, and a panel data analysis was conducted to explore the association between HFRS incidence and climatic factors (monthly average temperature, relative humidity, and monthly cumulative precipitation) incorporating Granger causality tests and a panel Poisson model with fixed effects. Univariate analysis and multivariate analysis were performed.	The variations in HFRS incidence were significantly associated with local precipitation, humidity, and temperature. The spread of HFRS may have been accompanied by seasonal shifts of Hantaan virus dominated transmission to Seoul virus -dominated transmission over the past three decades. Monthly cumulative precipitation with 1-month lag, monthly average relative humidity with 1-month lag and monthly average temperature with 2-month lag were significantly associated with HFRS incidence.
Zhang WY et al., 2010 [27]	Inner Mongolia 1997-2007	Cross-correlations assessed crude associations between climate variables, (rainfall, land surface temperature, relative humidity, and the multivariate El Niño Southern Oscillation index) and monthly HFRS cases over a range of lags. Time-series Poisson regression models were used to examine the independent contribution of climatic variables to HFRS transmission.	Cross-correlation analyses showed that rainfall, land surface temperature, relative humidity and El Niño Southern Oscillation were significantly associated with monthly HFRS cases with lags of 3-5 months. There was a peak of HFRS cases in winter. HFRS was consistently and strongly associated with temperature, precipitation, relative humidity, and El Niño Southern Oscillation index.
Guan P et al., 2009 [15]	Liaoning province 1990 to 2006	A Structure Equation Model (combination of multiple regression and factor analysis) was used based on climatic variables (monthly air pressure, temperature, precipitation and relative humidity), virus-carrying index and incidence of HFRS. Pearson's correlation was performed to quantify the relation-ships between climatic variables, reservoir data and the monthly incidence of HFRS.	Temperature, precipitation, relative humidity and virus-carrying index were positively related to the monthly HFRS incidence with a lag of 3, 3, 3 and 1 month, respectively, while air pressure had a negative correlation with the incidence with a lag of 3 months. Climate and reservoirs affect the incidence of HFRS. Most cases were acquired in winter to spring.
Luo CW et al., 2009 [25] [Article in Chinese]	Heilongjiang province 1984 to 2007	The correlation between meteorological factors (maximum temperature, minimum temperature, mean temperature, mean relative humidity and rainfall) and rat density and the incidence rate of HFRS was investigated. Statistical analysis involved Spearman rank correlation and multiple-stepwise regression.	The analysis showed a significant correlation between the mean temperature, mean relative humidity and rainfall in the past six months and the incidence rate of HFRS in the current month. The rat density was significantly and positively correlated with the incidence rate of HFRS, and the highest correlation was observed in the data 1, 2 and 3 months prior.
Yan L et al., 2007 [8]	Rural areas in China with population <1,000/km2 1994-1998	A landscape epidemiologic approach, combined with geographic information system and remote sensing techniques, were used as well as univariate and multivariate logistic regression.	HFRS incidence was associated with elevation, normalized difference vegetation index, precipitation, annual cumulative air temperature, semi hydromorphic soils, timber forests, and orchards. Few cases occurred in areas that were extremely hot or cold and none in arid areas. Incidence was highest in frigid temperate zones followed by warm temperate zones. There was an increased risk in areas with lowest elevation. The highest incidence occurred in semi-humid areas with medium precipitation.
Lin H et al., 2007 [22]	Liaoning province 2000 and 2005	GIS-based spatial analyses were conducted to detect spatial distribution and clustering of HFRS incidence at the county level, and the difference between the cluster areas and non-cluster areas was analyzed. A spatial scan statistic was applied to identify clusters of HFRS. T-test analysis was conducted on the average relative humidity and forestation between cluster areas and other areas.	Relative humidity and forestation in the cluster areas were significantly higher than in other areas. There was strong evidence of clusters, but the underlying mechanism is unknown. The relatively higher risk areas were in the eastern and western mountainous regions with a humid or semi-humid climate and an annual average precipitation of 650–1,200 mm and 500 – 600 mm, respectively.
Liu J et al., 2006 [26] [Article in Chinese]		Case-crossover design was applied to analyse the time series data of incidence rates of HFRS and meteorological variables in different seasons. Analysis was undertaken using conditional logistic regression.	The important seasonal factors varied. Spring: relative humidity, wind velocity, air pressure, minimum temperature, total rainfall. Summer: mean temperature and precipitation of the same month, relative humidity, sunlight hours and mean wind velocity of the preceding three months. Autumn: relative humidity and total hours of sunlight, wind velocity, and mean temperature. Winter: relative humidity, total rainfall, hours of sunlight, wind velocity and total rainfall.
Wu RJ et al., 2005 [33] [Article in Chinese]	Jiangsu province 1990 to 2002	The correlation between HFRS incidence and meteorological factors was examined using correlation analysis and multiple regression models.	Humidity, sunlight, precipitation, average temperature and lowest temperature were important factors relating to HFRS incidence.
Bi P et al., 2005 [9]	Anhui province 1971-1992	The relationship between monthly Southern Oscillation Index (SOI) and monthly incidences of HFRS was investigated using Spearman's correlation.	There was a negative relationship between the monthly average of SOI and monthly incidences of HFRS. Most HFRS cases developed in autumn-winter.
Bi P & Parton KA 2003 [30]	Anhui province 1970-1976 China 1970-1975	The relationship between the annual SOI and incidence of HFRS was investigated using Spearman's correlation.	Inverse correlation between the SOI and the incidence of HFRS in China, stronger correlation in Anhui province.
Bi P et al., 2002 [18]	Anhui province 1980-1996	Spearman's rank correlation and multiple regression analyses were used to assess the independent effects of climatic factors, the density of mice, autumn crop production and occupational variables on the transmission of HFRS.	Most cases acquired in autumn-winter. Seasonal mean minimum temperature, the autumn density of mice and autumn crop production were positively correlated with the seasonal incidence of HFRS; mean air pressure, rainfall and the SOI were inversely associated.

Table 2 (*Continued*)

Details	Study area & period	Methods	Results
Bi P et al., 1998 [14]	Anhui province 1961-1977 1983-1995	Spearman's rank correlation analysis and multiple linear regression analyses were used to estimate the relation between seasonal rainfall, density of mice, occupational factors, and occurrence of the disease.	Peaks during the autumn and winter. The density of *A. agrarius*, the difference in river water level, crop production, lower levels of precipitation and less inundation of farmland, were significantly associated with the incid-ence rate of HFRS (the relative contribution of autumn crop production was almost 3x greater than other variables).

incidence[3,15,21,24–27] others a negative relationship[7,9,14,18,19] or no association at all.[11]

Generally, plentiful rainfall is a risk factor for an HFRS outbreak in forthcoming months.[24] Low-lying regions and wetlands with moist soil are ideal habitats for mice and present an increased risk for disease transmission.[8,9,14] Closely related to rainfall and associated with HFRS is the Normalised Difference Vegetation Index, an indicator of the amount of green vegetation in an area.[1] Furthermore, studies have shown a link between autumn crop production and annual incidence of HFRS.[14,18]

However, flooding can be detrimental to host populations, causing a reduction in rodent population by destroying micro-environments including nests.[3,18] Consequently, an inverse relationship can exist between rainfall and rodent density where areas of low lying farmland have been inundated with water[14] resulting in reduced opportunities for rodent-human contact.[18]

By contrast, lack of rainfall and dry conditions are also associated with lower incidence as drought usually results in a reduction in rodent populations.[24] Indeed, a negative association with host density was shown in a study incorporating a Temperature Vegetation Dryness Index (TVDI), as higher TVDI values represent dry conditions and thus food shortage.[12] Moderate precipitation (10-120 mm) would seem to be the most favourable condition for the occurrence of HFRS.[8,24] Whilst these studies concentrate on rainfall in rural areas, there is a lack of information about the influence of rainfall on rodent populations in urban areas, where the reservoir has different ecological characteristics.

3.2. *Temperature*

It is difficult to compare findings for temperature given the range of metrics and methodologies used. Variables from different studies included mean, minimum, maximum ambient temperature and land surface temperature (incorporating monthly, annual or daily observations) at various lag periods between 1 and 6 months. Land surface temperature directly influences the distribution and abundance of *A. agrarius* populations,[27] whereas ambient temperature considers impacts on both mice and human behaviour. Associations between temperature and HFRS incidence were both positive[11,15,18,21,25–28] and negative.[7] Also found was an association between temperature and rodent density[11,12] but no significant association with incidence.

Few cases have been found to occur in areas that are extremely hot or cold.[8] Liu et al (2012) reported that mild temperatures of 10-25 °C are most favourable for rodent breeding and breeding rates for both *A. agrarius* and *R. norvegicus* decrease with temperatures outside of this range.[24] A threshold temperature of 17°C was identified in a study by Lin et al (2013) below which there was a positive association with HFRS, yet with higher temperatures there was an inverse association.[19] Similarly, Xiao (2013) found the highest occurrence when temperatures were around 17.5°C.[1]

3.3. *Humidity*

Humidity (relative or absolute) was also used as an indicator in several studies and most found a positive association with HFRS incidence.[3,11,15,27–29] Liu et al (2006) identified that relative humidity was an important factor in all four seasons.[26] The highest incidence of disease was reported to be in semi-humid areas[8] or in mountainous regions with a humid or semi-humid climate.[22] Inverse associations of humidity with incidence have also been reported.[7,19,21]

3.4. *Global climate patterns: SOI and MEI*

The El Niño Southern Oscillation (ENSO) is a systematic ocean-atmosphere oscillation pattern of climate variability that has a marked effect on climate in China.[9,11,28] An indicator of ENSO is the Southern Oscillation Index (SOI) which is the normalised atmospheric pressure difference between sea level pressures between Tahiti and Darwin, Australia.[9] Several studies used SOI to measure possible associations with HFRS incidence as it may be more appropriate than using other variables such as averaged rainfall or temperature data when analysing data for large regions. SOI is generally positive during the cold La Nina period and negative during the warm El Nino.[9] Overall, it was found there was an inverse correlation between SOI and the density of mice[18] and consequent incidence of HFRS,[9,30] and that the negative association can occur after a 2 month lag period.[11]

Some studies used the Multivariate El Niño-Southern Oscillation Index (MEI) as an alternative indicator of the global climate pattern. MEI is based on the six main observed variables over the tropical Pacific: i.e. sea-level pressure, zonal and meridional components of the surface wind, surface air temperature, sea surface temperature and total cloudiness fraction of the sky.[3] MEI was found to be an important predictor of the intensity of HFRS[28] and although one study showed there was a negative relationship with incidence and MEI at a lag of 3 months,[29] 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%.[3,27,28]

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.[21] 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.[24]

It is generally thought that precipitation, followed by air temperature, is the most important meteorological element influencing the endemic intensity of the disease.[24] 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.[24] Rainfall has an influence on vegetation growth and thus on the density of rodents and hantavirus infectivity,[3,28] whereas the gestation period and sexual maturation of rodents may be modified by temperature leading to changes in the population dynamics.[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).[6] Spatiotemporal differences also exist in the pathogen carrying rate of the rodents and virulence of the viruses.[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.[28] This occurs because the commercial immunological test kits to identify hantaviruses do not discriminate between the HTNV and SEOV antigens.[5] 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.[9] Comprehensive preventive 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.[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.[15,21] There has also been improved surveillance, public education about HFRS, and environmental management strategies.[6,10,13,21] 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.[12,13] However, it is difficult for quantitative studies of climate-disease associations to account for these factors in statistical models.[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 socioeconomic circumstances comprise 93% of all HFRS cases.[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.[3,18] As food supply is an important predictor of the rodent population,[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.[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.[15,27]

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.[4,15] 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"[6(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 (*R. rattus, R. flavipectus*) that may be the cause of HFRS in areas such as Zhejiang province.[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.[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.[17] 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[9,11,30] with higher incidence occurring with El Niño events when SOI becomes negative.[9] Recent research has shown that due to greenhouse warming, extreme El Niño events will increase in frequency, doubling from about one event every 20 years to one every 10 years.[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,[1,11,21] and some reports suggest the figures are higher.[1] There has also been an increase in incidence in some areas[19] and new epidemic areas have emerged.[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.[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 unpack 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.

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