Vital Surveillances

Hemorrhagic Fever with Renal Syndrome and Diversity and Distribution of Hantaviruses — China, 2014–2023

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ABSTRACT

Introduction: Hemorrhagic fever with renal syndrome (HFRS) caused by hantavirus remains a significant threat to human health in China. The incidence of HFRS, distribution, and evolution dynamics of hantavirus are influenced by factors such as ecological environment, climate, and rapid development; therefore, timely evaluation is essential for the prevention and control of HFRS.

Methods: The spatial, seasonal, temporal distributions, and spatiotemporal analysis of reported HFRS cases in China from 2014 to 2023 were performed using Excel 2019, ArcGIS, and SaTScan software. Rodents were trapped at national surveillance sites for HFRS. Genomic sequences of hantaviruses were obtained from lung tissues and aligned with reference genomic sequences using MAFFT. Phylogenetic analysis was performed using MEGA11.0.

Results: In the past decade, the incidence rate decreased from 1.01/100,000 to below 0.4/100,000; however, areas with hantavirus transmission were expanding. Diversity and distribution of hantaviruses were documented across 22 provincial-level administrative divisions, with 12 genotypes of Hantaan virus and 9 genotypes of Seoul virus identified circulating in China.

Conclusion: Significant progress has been made in HFRS control and prevention in China, with declining incidence rates. However, affected areas are expanding, and diverse hantaviruses are widely distributed, creating a risk of incidence rebounding that should not be ignored. More targeted strategies are needed to address potential new and complex challenges that lie ahead.

Hantaviruses belong to the *Orthohantavirus* genus, family *Hantaviridae*, which can cause two syndromes in humans: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (*1*). HFRS is endemic in China and remains a serious threat to public health (*1*). Three hantaviruses capable of causing HFRS in humans have been identified in China: Hantaan virus (HNTV), Seoul virus (SEOV), and Puumala virus (*2*). Hantavirus transmission from rodents to humans reached its peak between 1984 and 2000, with the highest incidence in 1986, when 993,433 cases and 2,044 deaths were reported across 29 provincial-level administrative divisions (PLADs). This represented an incidence rate of 11.06/100,000 and an average case fatality rate of 2.02% (*3*). Since the 1980s, the Chinese government has implemented a national HFRS prevention and control program, and in 2007, inactivated vaccines against HNTV and SEOV were included in the national expanding immunization program (EPI). These efforts have yielded significant progress, with the incidence rate declining substantially and stabilizing at a relatively low level between 0.60 and 1.01/100,000 from 2007 to 2021 (*4*). However, the geographic areas affected by HFRS continue to expand, with viruses maintaining active transmission among rodent populations even in regions with few or no reported human cases (*5*). The potential for HFRS resurgence remains a significant concern (*6*).

Hantaviruses that cause HFRS typically circulate in small rodents inhabiting human dwellings and surrounding environments (*7*). Human infection can occur whenever susceptible individuals come into contact with infected rodents or their contaminated urine and droppings, with transmission influenced by various natural and social factors (*8*). To understand the current HFRS situation, we analyzed the epidemiological characteristics of reported cases and the diversity and distribution of hantaviruses in China from 2014 to 2023.

METHODS

Descriptive Analysis

Data on HFRS cases in China from January 1, 2014 to December 31, 2023, were obtained from the National Notifiable Disease Reporting System (NNDRS) based on date of incidence. Descriptive epidemiologic analyses were conducted using Excel (version 2019, Microsoft Corporation, Redmond, USA) and ArcGIS (version 10.8.1, ESRI Inc, RedLands, USA) software.

Spatiotemporal Analysis

Spatiotemporal and seasonal analyses were performed using SaTScan software (version 10.1.2; Information Management Services, Maryland, USA) at county and month levels, respectively. The maximum scanning window was set to 50% of the total population. The maximum temporal clustering scale was set to 50% of the total study period, with a step size of one month, as described previously (*9*). A cluster of HFRS cases in the selected region was considered significant when $P \leq 0.05$. Areas at risk were identified by comparing the observed number of cases within each window to the expected number using a Poisson model. Demographic data stratified by age and sex were obtained from the National Bureau of Statistics of China (accessed on January 5, 2024).

Sequencing and Phylogenetic Analysis

Rodents were trapped at national surveillance sites for HFRS in China. Hantavirus genomic RNA was detected in rodent lung samples using real-time RT-PCR (*10*), and genomic fragments were amplified using RT-PCR and sequenced using Sanger sequencing. Published genomic sequences of hantaviruses with collection dates and regions were obtained from GenBank for phylogenetic analysis. Phylogenetic trees were constructed using the neighbor-joining (NJ) method implemented in MEGA11.0 (*11*). Topologies were evaluated by bootstrap analysis of 1,000 iterations.

RESULTS

A total of 91,388 cases were reported from 31 PLADs in China between 2014 and 2023, with an average incidence rate of 0.65/100,000. The incidence rate fluctuated between 0.37 and 0.86 per 100,000 persons, peaking in 2018 (0.86/100,000) and reaching its lowest level in 2022 (0.37/100,000) (Figure 1A). Cases were reported across all age groups, with 72.21% aged 15–59 years, 2.57% ≤14 years, and 25.22% ≥60 years (Figure 1B). The proportion of cases ≥60 years increased from 20.26% in 2014 to 31.96% in 2023, while cases aged 15–59 years decreased from 77.77% to 64.28%, and cases ≤14 years slightly increased from 1.97% to 3.74%. Regional variations were evident in age distribution, with a high proportion of cases ≤14 years in Sichuan (12.86%) and Jiangxi (8.05%), and a high proportion of cases ≥60 years in Hubei (35.72%) and Jiangsu (31.07%) (Figure 1B). Regarding occupational distribution, farmers still constituted the majority of cases, though their proportion showed a downward trend to 64.59% in 2023, while the proportion of cases involving individuals performing household chores and unemployed persons increased to 11.88% in 2023.

A total of 9 PLADs reported average annual incidence rates higher than the national average, including Shaanxi, Heilongjiang, Shandong, Liaoning,

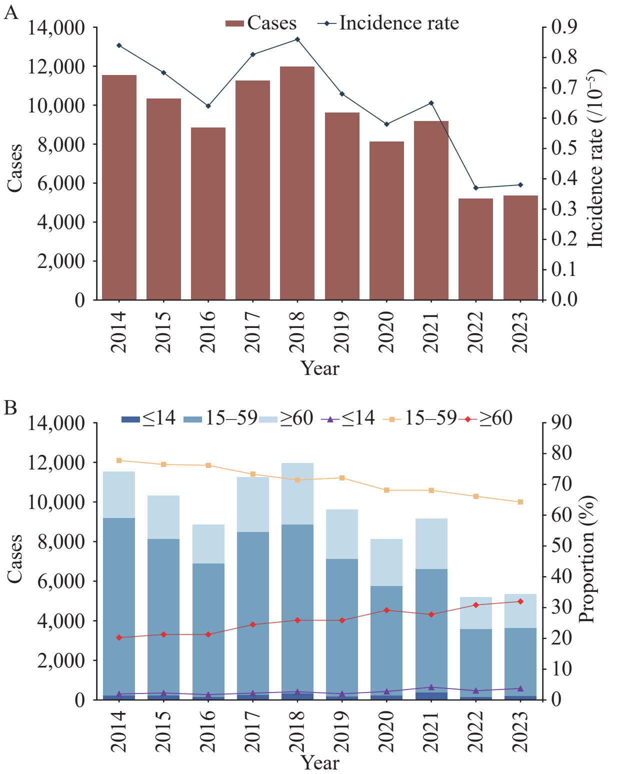

FIGURE 1. The reported cases of HFRS from 2014 to 2023 in China. (A) The number of national annually reported cases and incidence rate of HFRS; (B) The age distribution and proportion of age groups of the annually reported cases.

Abbreviation: HFRS=hemorrhagic fever with renal syndrome.

Hunan, Jilin, Jiangxi, Fujian, and Hubei. Among these, Shaanxi (16,164 cases), Heilongjiang (10,820 cases), Shandong (9,309 cases), Liaoning (7,864 cases), and Hunan (5,620 cases) accounted for 54.47% (49,777/91,388) of the total cases. Over the past decade, HFRS cases were reported from 2,106 of the 2,891 county-level administrative regions in China, with 1,865 counties reporting fewer than 100 cases each. Of these, 828 counties reported cases in 8–10 years, accounting for 92.26% of total cases (84,310/91,388), with 149 counties among them reporting fewer than five cases annually; 485 counties reported cases in 4–7 years, with annual case numbers ranging from 1–24, accounting for 5.91% (5,405/91,388) of total cases; 793 counties reported cases in 1–3 years, with annual case numbers ranging from 1–5, accounting for 1.83% (1,673/91,388) of total cases. The proportion of counties with fewer than five annual cases increased from 62.31% to 76.96%. These results demonstrate significant regional variations in hantavirus transmission from rodents to humans, with a decreasing number of high-incidence counties. Spatiotemporal cluster analysis identified 337 counties with high risk of hantavirus transmission, 113 counties with medium risk of HFRS clusters, and 283 counties with potential risk of case clusters.

Nationally, reported cases exhibited two annual peaks. The spring–summer peak occurred between April and July, contributing 31.25% of cases, while the fall–winter peak occurred between October and January of the following year, with October to December accounting for 47.82% of total cases. The seasonal distribution of HFRS varied by region, with cases primarily concentrated in November–December [relative risk (*RR*): 2.40, log-likelihood ratio (LLR): 6618.60, *P*<0.001]. Most PLADs showed a bimodal distribution, except for Xinjiang, Qinghai, Xizang, and Hainan, where only occasional sporadic cases were reported. Shaanxi (November–December, *RR*: 6.19, LLR: 6156.35, *P*<0.001), Shandong (October–December, *RR*: 2.85, LLR: 1204.21, *P*<0.001), and Heilongjiang (November, *RR*: 3.59, LLR: 1275.45, *P*<0.001) primarily experienced winter onset, while Hebei (January–June, *RR*: 2.00, LLR: 236.16, *P*<0.001), Guangdong (January–June, *RR*: 1.89, LLR: 151.42, *P*<0.001), Fujian (January–June, *RR*: 1.50, LLR: 67.10, *P*<0.001), and Yunnan (March–August, *RR*: 1.50, LLR: 53.55, *P*<0.001) primarily experienced spring and summer onset.

Laboratory surveillance data of hantaviruses were collected and analyzed. Complete genomes of 47 strains of SEOV and 11 strains of HTNV were obtained in this study. Additionally, published genomic sequences of 2,032 strains of SEOV and 1,972 strains of HTNV were screened from GenBank. The obtained sequences were compared with selected reference sequences from 150 strains of SEOV and 136 strains of HTNV. Phylogenetic analysis identified 12 genotypes of HTNV (HTNV1–12) and 9 genotypes of SEOV (SEOV1–9) circulating across 22 PLADs in China, with significant regional variation (Table 1 and Supplementary Figure S1, available at https://weekly.chinacdc.cn/).

DISCUSSION

Hantaviruses can infect and cause serious disease in humans worldwide. The spillover transmission of hantavirus from rodents to humans is highly efficient, presenting significant challenges for HFRS prevention and control (*12*). After decades of implementing comprehensive prevention and control measures in China, the incidence of HFRS has decreased to a low level (<0.4/100,000), the number of counties reporting cases has been reduced by approximately one-fourth (<1,000), and the majority of these counties report fewer than 5 cases annually. However, 337 counties still remain at high risk for HFRS clusters, suggesting the potential for rapid incidence rebounds. Therefore, active targeted measures based on risk analysis should be developed for the prevention and control of HFRS in these "hotspots".

The proportion of cases aged 16–60 has decreased, while the proportion of cases among individuals over 60 years has increased. The impact of the EPI should not be overlooked, as vaccination primarily targeted populations aged 16–60. The shift in case distribution from middle-aged to elderly people likely reflects the ongoing urbanization, industrialization, and changing demographics of agricultural workers in China over recent decades (*13*). The seasonal distribution of HFRS cases is typically related to rodent distribution patterns. The fall–winter peak of incidence is generally attributed to *Apodemus agrarius*, while the spring–summer peak is primarily associated with *Rattus norvegicus* (*14*). The changing seasonal distribution patterns of HFRS over the past decade reflect shifts in rodent habitats, at-risk populations, and patterns of human exposure to infected rodents in China.

The identification of 9 co-circulating genotypes of SEOV and 12 genotypes of HTNV in China demonstrates a more extensive diversity of hantaviruses

TABLE 1. Geographic distribution of the identified genotypes of HTNV and SEOV in China.

PLAD	Genotype	
	SEOV	HTNV
Beijing	SEOV3	
Tianjin		HTNV4
Hebei	SEOV1, SEOV2, SEOV3	
Shanxi	SEOV1	
Liaoning	SEOV1, SEOV3	HTNV6
Jilin	SEOV3, SEOV4	HTNV2, HTNV6
Heilongjiang	SEOV3, SEOV8	HTNV2, HTNV6
Jiangsu	SEOV1	HTNV5, HTNV7, HTNV9
Zhejiang	SEOV1, SEOV3, SEOV5	HTNV8
Anhui		HTNV1, HTNV5, HTNV9
Fujian	SEOV3, SEOV5, SEOV7	
Jiangxi	SEOV1, SEOV2, SEOV5	HTNV12
Shandong	SEOV1, SEOV3	HTNV2, HTNV5
Henan	SEOV1	HTNV4, HTNV5
Hubei	SEOV2	HTNV9, HTNV10
Hunan	SEOV2, SEOV7	HTNV5, HTNV10
Guangdong	SEOV7	HTNV5
Hainan	SEOV7	
Sichuan		HTNV5, HTNV7
Guizhou		HTNV3, HTNV4, HTNV6, HTNV9
Yunnan	SEOV7, SEOV9	HTNV1, HTNV5
Shaanxi		HTNV4, HTNV5

Abbreviation: PLAD=provincial-level administrative division; HTNV=Hantaan virus; SEOV=Seoul virus.

than previously reported (*15*). This diversity complicates laboratory detection and pathogenic assessment of hantaviruses. When coupled with increasingly convenient transportation and frequent regional interactions, these factors may lead to heightened risks of potential recombination and the emergence of viral variants.

In this study, the epidemiological analysis of HFRS was based on reported cases, which may underestimate the true severity of the HFRS epidemic. Nevertheless, China has achieved significant progress in HFRS prevention and control over the past decades. The ecological environment, living conditions, and public health service systems have undergone substantial changes in China. More targeted strategies are needed to address potential new and complex challenges, including evidence-based education and training for professional personnel, gap analysis of specialized HFRS support at the county level, and increased public awareness of infection risk factors.

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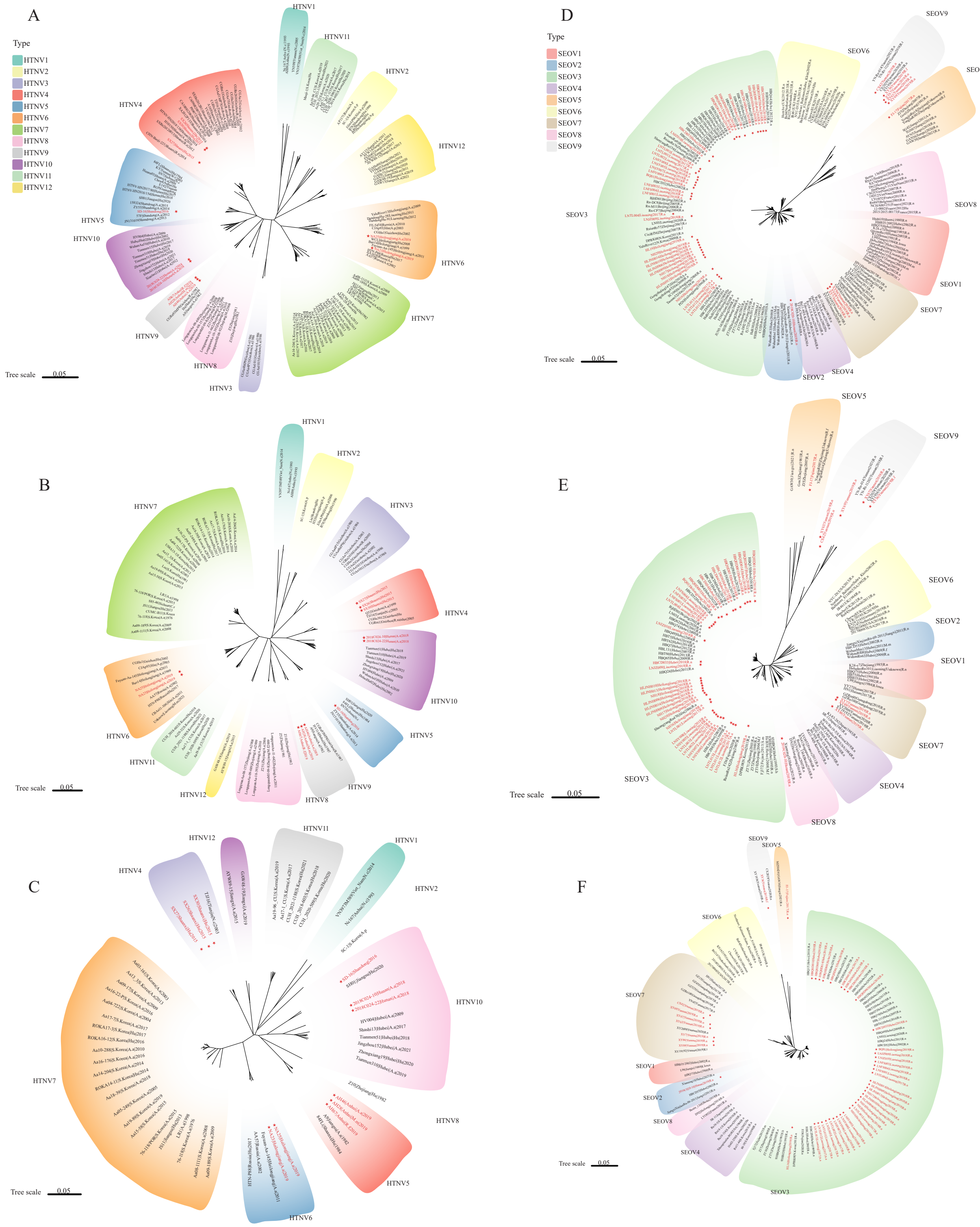
SUPPLEMENTARY MATERIAL



SUPPLEMENTARY FIGURE S1. Phylogenetic analysis of the complete coding sequences of the S (A), M (B), and L (C) segments of hantaviruses circulating in China.

Note: The sequences labeled with red lines and red stars were obtained in this study.