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Original Article

Epidemiology and changes in age distribution of hemorrhagic fever with renal syndrome in Shaanxi, China, from 2004 to 2023

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Abstract

Introduction: Hemorrhagic fever with renal syndrome (HFRS) is a serious viral disease in mainland China, and Shaanxi Province is one of the most severely affected areas. In order to reduce HFRS incidence, an inactivated bivalent vaccine against Hantaan virus (HTNV) and Seoul virus (SEOV) infections was developed and used in China since the 1990s.

Methodology: Descriptive epidemiological methods were used to analyze the spatial, temporal, and population distribution of HFRS along with changes in age distribution in Shaanxi Province from January 2004 to December 2023.

Results: A total of 34,265 HFRS human cases were reported in Shaanxi Province, including 25,737 males and 8,528 females. HFRS cases were geographically concentrated in the Guanzhong Plain. The local incidence of HFRS fluctuated remarkably over the past 20 years. The primary peak was from October to January. The proportion of HFRS cases in the 15–60 years age group showed a decreasing trend. However, the proportion of HFRS cases among the > 60 years age group increased by 150.94%, rising from 11.68% to 29.31%.

Conclusions: Data from a 20-year surveillance study shows that the proportion of HFRS cases in individuals over 60 years of age has increased significantly, which may potentially be due to vaccine coverage limitations. The results can be used to adjust the prevention and control measures of HFRS and to consider age-expanded vaccination strategies.

Key words: HFRS; hantavirus; vaccination; age incidence.

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Introduction

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne viral disease that results in acute nephropathy characterized by high fever and varying degrees of renal dysfunction and hemorrhagic manifestations [1]. A typical course of HFRS progresses through five distinct phases: febrile, hypotensive, oliguric, polyuric, and convalescent [2]. Worldwide guidelines recommend serological tests as the key and commonly used diagnosis method for HFRS [3]. The causative viruses are primarily transmitted to humans by contact with contaminated material; such as aerosols generated from urine, feces or saliva, infected food, or directly by rodents' bites [4]. HFRS is caused by several hantavirus species, including Hantaan virus (HTNV), Seoul virus (SEOV), Dobrava virus (DOBV) and Puumala virus (PUUV); which are RNA viruses of the family Hantaviridae and exhibit distinct geographical distributions and clinical severity patterns [2]. The fatality rate of HFRS ranges from less than 1% to 15% [5], with HTNV and DOBV infections demonstrating higher fatalities compared to SEOV or PUUV infections. HTNV and DOBV cause severe cases with a high mortality rate (5–15%), while SEOV and PUUV infections typically present as moderate disease with a case fatality rate of less than 1% [6,7].

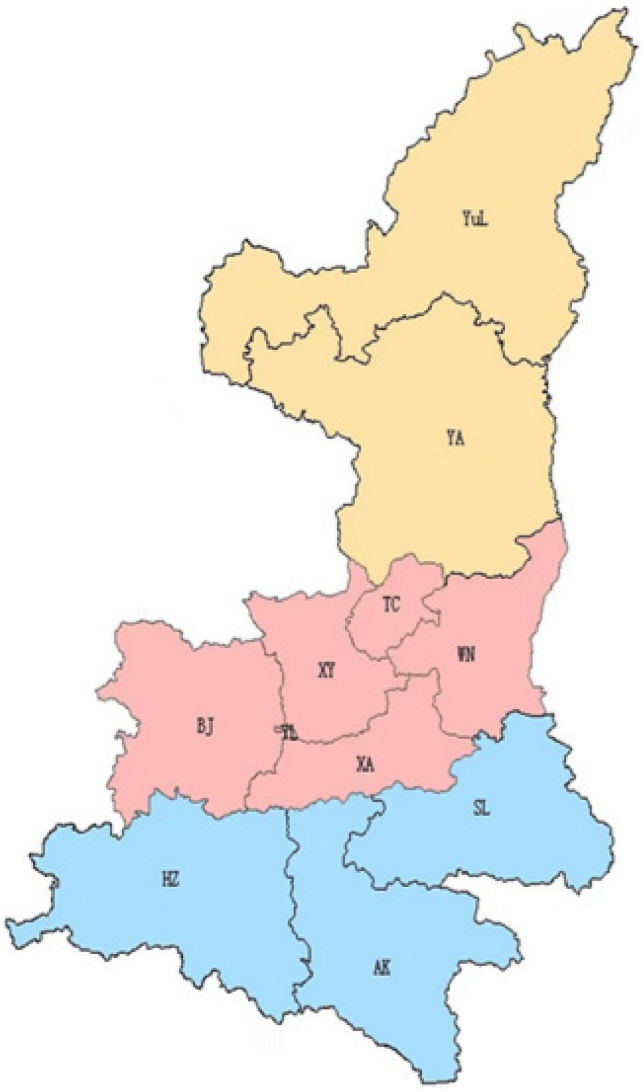
HFRS caused by PUUV or DOBV is highly endemic in Europe, Scandinavia, and Russia [8]. In China, HFRS is caused by infections with either HTNV (carried by *Apodemus agrarius*) or SEOV (carried by *Rattus norvegicus*), and HTNV infections remain more prevalent [4]. HFRS is a serious disease in mainland China, accounting for nearly 90% of reported cases worldwide [9]. During 1950–2007, a total of 1,557,622 HFRS cases and 46,427 fatalities (case fatality rate 3.0%) were reported in China [10]. The incidence and case fatality rate of HFRS have decreased in recent decades, because comprehensive preventive and management measures have implemented and played important roles in HFRS control. During the period 2004–2019, a total of 209,209 cases of HFRS and 1855 deaths were reported in China [11].

The occurrence and epidemics of HFRS are influenced by numerous environmental and social-economic factors, including meteorological factors, rodent density, and vaccination [7,12,13]. Vaccination is a well-established method for preventing infectious

diseases. Currently, no HFRS vaccines are approved for widespread use in Europe or the USA [14]. In Asia, Korea has used Hantavax® (developed from infected suckling mouse brain) for several years [7]. In order to reduce the incidence of HFRS, an inactive vaccine against HTNV and SEOV was developed and used in China since the 1990s [1]. These HFRS vaccines have demonstrated long-term safety through decades of use in Asia and the majority of observed adverse events were mild [15]. The seroconversion rates of Hantavax vaccine were reported to range from 23% to over 90% in previous studies [7]. In China, the protective effectiveness of the HFRS vaccine exceeds 90% at 6 years post-vaccination [16]. The Chinese government has implemented the HFRS-targeted expanded program on immunization (EPI) in several high-incidence provinces (Heilongjiang, Jilin, Liaoning, Shandong, Hebei, Shaanxi and Zhejiang) from 2008 [10]. Approximately 2 million doses of bivalent inactivated HFRS vaccine are used annually in China [17]. However, since the pharmacopoeia of People's Republic of China (2005) specified that the vaccines could only be used in persons between 16 and 60 years of age, the vaccine has been used only in this age group [18].

Shaanxi Province, located in western China, is one of the most severely affected areas. In 2010, 2011, 2012, 2017, and 2018, Shaanxi surpassed all epidemic areas with the highest HFRS incidence [11]. In this study, the epidemiology and trends of the reported HFRS cases in Shaanxi Province from 2004 to 2023 are described using age-stratified analyses (< 15, 15–60, > 60 years) to evaluate the changes in age distribution.

Figure 1. The map of Shaanxi Province.



Three parts from north to south: Shanbei, GuanZhong, Shannan. XA: Xi'an BJ Baoji; XY: Xianyang; TC: Tongchuan; WN: Weinan; YL: Yangling; YuL: Yulin; YA: Yan'an; HZ: Hanzhong; AK: Ankang; SL: Shangluo.

Methodology

Patient selection and data collection

The epidemiological data on HFRS cases reported in Shaanxi Province from January 2004 to December 2023 was obtained from the China Information System for Disease Control and Prevention (CISDCP). The CISDCP system, established in 2004, is a web-based reporting system for nationally notifiable infectious diseases and public health emergencies across China [19]. HFRS cases diagnosed based on clinical symptoms and laboratory test results were confirmed according to the diagnostic guidelines issued by the Ministry of Health of the People's Republic of China.

Basic demographic and diagnostic information of HFRS cases were collected via the CISDCP. Case information included gender, age, occupation, and time of onset of the disease. The data were collected and sorted using Microsoft Excel software. Descriptive epidemiological methods were used to analyze the spatial, temporal, and population distribution of HFRS, and changes in age distribution in Shaanxi Province from January 2004 to December 2023. Based on the EPI guidelines, the age range of the human target population was from 16 to 60 years. However, due to the 5-year age group classification used in the CISDCP system, the reported cases were categorized into < 15, 15–60 and > 60 years age groups.

The present study was reviewed and approved by the ethics committee of the Shaanxi Provincial Centre for Disease Control and Prevention. The committee determined that individual patient consent was waived because only aggregated surveillance data from a retrospective design were analyzed, with no personal identifiers included.

Figure 2. Monthly distribution of hemorrhagic fever with renal syndrome (HFRS) in Shaanxi Province, from 2004 to 2023.

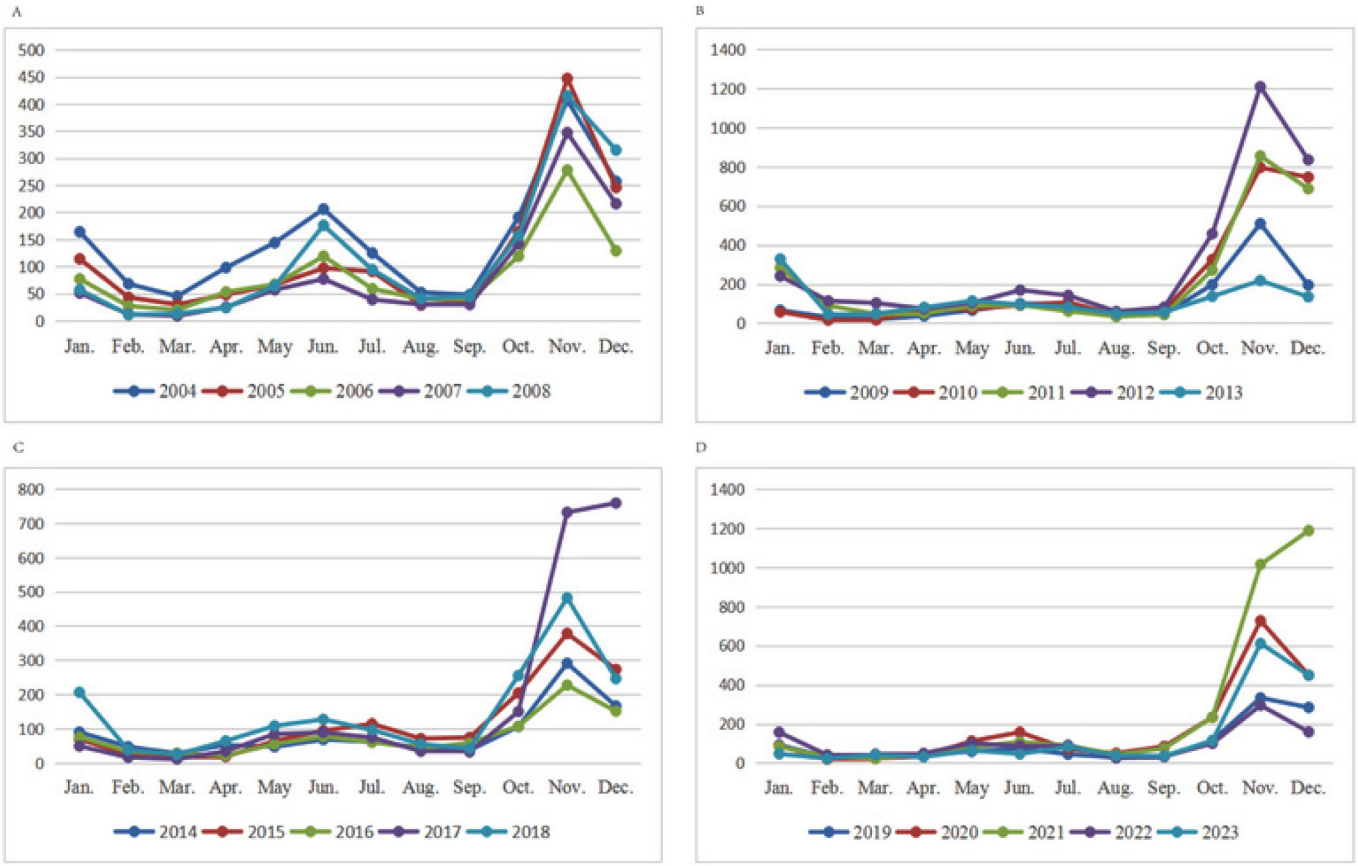


Table 1. Epidemiological characteristics of hemorrhagic fever with renal syndrome (HFRS) in Shaanxi Province from 2004 to 2023.

Year	Cases (N)	Incidence per 100,000 population	Deaths (N)	Fatality rate	Male	Female	Gender ratio (F/M)	Farmer	Students	Workers	Others	Guanzhong Plain (%)
2004	1805	4.93	24	1.33	1360	445	3.06	70.08	10.08	7.76	12.08	95.46
2005	1410	3.81	20	1.42	1075	335	3.21	70.43	9.22	6.10	14.26	95.39
2006	1027	2.76	17	1.66	790	237	3.33	68.45	9.54	6.82	15.19	94.16
2007	1035	2.77	10	0.97	774	261	2.97	69.37	8.99	6.28	15.36	94.88
2008	1412	3.77	8	0.57	1100	312	3.53	66.36	10.27	7.51	15.86	95.40
2009	1404	3.73	7	0.50	1071	333	3.22	70.94	8.76	6.05	14.25	94.59
2010	2408	6.38	29	1.20	1828	580	3.15	69.39	11.30	5.27	14.04	95.31
2011	2605	6.98	17	0.65	1939	666	2.91	74.36	9.56	3.84	12.25	95.51
2012	3591	9.59	22	0.61	2704	887	3.05	76.58	9.72	3.09	10.61	94.29
2013	1392	3.71	7	0.50	1014	378	2.68	75.43	7.90	4.02	12.64	93.39
2014	1039	2.76	4	0.38	777	262	2.97	79.79	6.16	3.56	10.49	92.59
2015	1399	3.71	2	0.14	1086	313	3.47	77.84	6.36	2.86	12.94	94.14
2016	933	2.46	1	0.11	711	222	3.20	73.31	5.79	3.11	17.79	92.82
2017	2064	5.41	14	0.68	1549	515	3.01	76.55	6.83	3.83	12.79	95.25
2018	1743	4.54	10	0.57	1317	426	3.09	71.60	7.80	4.19	16.41	93.86
2019	1164	3.01	2	0.17	865	299	2.89	71.65	7.47	3.18	17.70	90.55
2020	2051	5.29	3	0.15	1526	525	2.91	70.45	8.73	3.46	17.36	92.83
2021	3016	7.63	17	0.56	2213	803	2.76	62.77	10.68	4.48	22.08	95.13
2022	1184	2.99	4	0.34	874	310	2.82	65.79	7.09	5.57	21.54	93.07
2023	1583	4.00	2	0.13	1164	419	2.78	66.20	9.79	4.61	19.39	92.04

Statistical analysis

Statistical analyses were carried out using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel version 2020 (Microsoft Corporation, Redmond, WA, USA). The mapping was conducted using ArcGIS 10.8 software (ESRI Inc., Redlands, CA, USA). The Chi square test was performed on the patients' demographic categories. A p value < 0.05 was considered to indicate a statistically significant difference.

Results

Epidemiological characteristics of HFRS

A total of 34,265 HFRS cases were reported in Shaanxi Province from 1 January 2004 to 31 December 2023. The annual average HFRS was 4.51 cases per 100,000 individuals (range: 2.46–9.59 per 100,000 individuals), with 220 HFRS-associated deaths corresponding to an annual average fatality rate of 0.64% (range: 0.11–1.66 per 100,000 individuals). The patients included 25,737 males (75.1%) and 8,528 females (24.9%), with a mean male-to-female ratio of 3.01:1 (range: 3.53:1 to 2.68:1).

Similar trends between gender groups were observed every year in Shaanxi Province from 2004 to 2023. The annual average incidence was 6.50 per 100,000 individuals among males, and 2.28 per 100,000 individuals among females, which was a statistically significant difference ($\chi^2 = 202.82$, $p < 0.01$). A total of 24,449 HFRS cases were farmers, accounting for 71.35% of the total cases (Table 1). Additionally, 3,062 (8.94%) cases were students and 1,586 (4.63%) cases were industrial workers. The remaining 5,168 (15.08%) cases were classified as other occupational categories. The HFRS cases were geographically concentrated in the Guanzhong Plain (includes 4 cities: Xian, Weinan, Xianyang, and Baoji), accounting for 94.25% in Shaanxi Provinces (Figure 1).

HFRS incidence rates in Shaanxi fluctuated significantly over the past two decades, without a stable or consistent trend (Table 1). The incidence rates were higher during 2010–2012, 2017, and 2020–2021, which were more than 5 HFRS cases per 100,000 individuals (Table 1). A bimodal seasonal distribution was observed: the primary peak number of HFRS cases was from October to January, and the second peak was from May to July. Most cases were reported in November (10,572, 30.85%), December (7,885 cases, 23.01%), and October (3,778 cases, 11.03%), as shown in Figure 2.

Change in age distribution of HFRS

The proportion of HFRS cases in the 15–60 years age group showed a decreasing trend from 86.10% in 2004 to 67.18% in 2023. The proportion of HFRS cases among the > 60 years age group increased by 150.94% (from 11.68% to 29.31%), and a greater increase was observed among males (from 11.47% to 26.12%) than females (from 13.03% to 38.19%) during the same period. The proportion of the < 15 years age group showed an increasing trend, from 2.44% to 8.40% per year. From 2004 to 2013, the proportions of HFRS cases in < 15, 15–60, and > 60 years age groups were 3.66%, 79.27%, and 17.07% respectively. From 2014 to 2023, the proportions of HFRS cases in < 15, 15–60, > 60 years age groups were 5.27%, 67.73% and 27.00% respectively. The average proportion of HFRS cases in individuals aged > 60 years exhibited an increase from 13.31% (2004–2008) to 19.27% (2009–2013), 26.26% (2014–2018), and ultimately reaching 27.58% (2019–2023) (Figure 3, Table 2).

Discussion

This study analyzed data from a 20-year surveillance of HFRS cases to provide a comprehensive epidemiological analysis of HFRS in Shaanxi Province, China. HFRS showed periodic variations, probably because HFRS is related to the geographical location, living (hygiene) conditions, employment type, and the epidemiology of the rodent hosts [4,20]. This study revealed a higher prevalence of infections in males (75.1%) than in females (24.9%), with a male-to-female ratio of 3.01:1. One explanation for more infections among males may be related to the fact that more males engage in agricultural work, leading to greater exposure to virus-contaminated excreta (urine, feces, and saliva)

Figure 3. Proportion of hemorrhagic fever with renal syndrome (HFRS) cases among <15 years, 15–60 years, and > 60 years age groups in Shaanxi Province from 2004 to 2023.

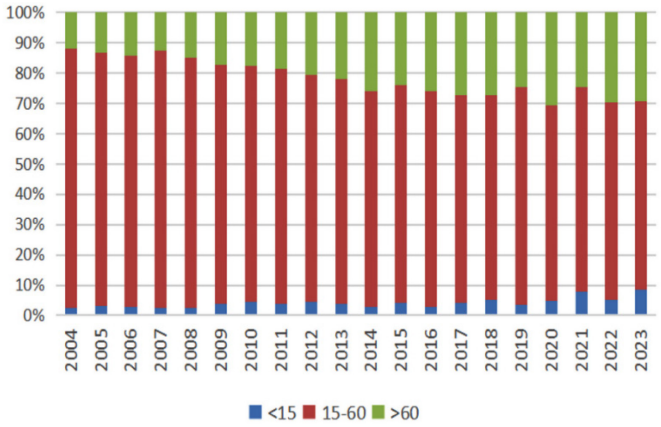


Table 2. Proportions of hemorrhagic fever with renal syndrome (HFRS) cases in the 3 age subgroups among males and females in Shannxi province from 2004 to 2023.

Year	Male						Female					
	<15 years		15–60 years		>60 years		<15 years		15–60 years		>60 years	
	N	P	N	P	N	P	N	P	N	P	N	P
2004	33	2.43	1171	86.10	156	11.47	11	2.47	376	84.49	58	13.03
2005	27	2.51	911	84.74	137	12.74	16	4.78	269	80.30	50	14.93
2006	23	2.91	672	85.06	95	12.03	6	2.53	178	75.11	53	22.36
2007	16	2.07	670	86.56	88	11.37	11	4.21	207	79.31	43	16.48
2008	25	2.27	931	84.64	144	13.09	10	3.21	236	75.64	66	21.15
2009	35	3.27	876	81.79	160	14.94	18	5.41	233	69.97	82	24.62
2010	82	4.49	1478	80.85	268	14.66	29	5.00	398	68.62	153	26.38
2011	72	3.71	1563	80.61	304	15.68	28	4.20	459	68.92	179	26.88
2012	116	4.29	2083	77.03	505	18.68	49	5.52	598	67.42	240	27.06
2013	38	3.75	764	75.35	212	20.91	17	4.50	267	70.63	94	24.87
2014	18	2.32	586	75.42	173	22.27	10	3.82	156	59.54	96	36.64
2015	37	3.41	821	75.60	228	20.99	19	6.07	188	60.06	106	33.87
2016	14	1.97	537	75.53	160	22.50	11	4.95	127	57.21	84	37.84
2017	53	3.42	1132	73.08	364	23.50	31	6.02	286	55.53	198	38.45
2018	58	4.40	937	71.15	322	24.45	30	7.04	242	56.81	154	36.15
2019	24	2.77	644	74.45	197	22.77	16	5.35	191	63.88	92	30.77
2020	62	4.06	1056	69.20	408	26.74	38	7.24	264	50.29	223	42.48
2021	154	6.96	1581	71.44	478	21.60	83	10.34	451	56.16	269	33.50
2022	46	5.26	600	68.65	228	26.09	16	5.16	171	55.16	123	39.68
2023	78	6.70	782	67.18	304	26.12	55	13.13	204	48.69	160	38.19

N: number of cases; P: proportion in groups (%).

from infected wild rodents, which increases their risk of infection compared to females. Additionally, the difference between the rate of infection in males and females may be due to the differential susceptibility of males and females at the level of host immune status [21]. In China, during the period 1998–2007 the number of male patients was 3 times higher than female patients, and 70% of them were farmers [22].

The results of this study suggest that occupational exposure is an important influencing factor in HFRS transmission. Farmers and workers have more outdoor work and greater exposure to rodents or their contaminants. In recent years, several universities in Shaanxi Province were constructed near urban areas, thereby elevating the potential risk of exposure among student populations. The data analyzed in this study revealed that gender and occupation influenced the incidence of HFRS cases in Shaanxi during the period 2004–2023, and this observation is similar to a previous study [17].

Shaanxi Province can be divided into 3 parts based on the terrain: the Shanbei (northern Shaanxi) plateau with a general elevation range of 800–1300 m, the Guanzhong (central part) plain region, and the Shannan (southern Shaanxi) mountainous region. The incidence of HFRS in GuanZhong areas of Shaanxi, such as Xi'an and Xianyang, was higher than that in Shannan and Shanbei areas of Shaanxi, which is consistent with the explanation that geographical location plays important roles in the occurrence of HFRS. Previous studies have suggested that HFRS incidence may be influenced by multiple factors: land use patterns, host population dynamics (e.g., pig density), socioeconomic conditions (e.g., GDP), and climate-related variables (humidity and precipitation), which imply potential impact on regional disparities [23].

In this study, it was noted that HFRS can occur throughout the year, with an overall bimodal distribution and seasonal characteristics, which is similar to some previous studies conducted in mainland China [22,24]. HFRS incidence began to increase in April, with a secondary peak from May to July, and declined in August and September, followed by a primary epidemic peak from October to January of the following year. This observation indicates that prevention efforts and epidemiological surveillance should strengthen during the periods from May to July and from October to January. The bimodal seasonal distribution may be related to climatic factors, such as temperature, precipitation, insolation, and pressure; which are considered important for wild rodents.

The proportions of the different age groups were analyzed, and it was revealed that the age distribution changed in the past two decades in Shaanxi. The 15–60 years age group has experienced a significant decline in the proportion of HFRS, suggesting that vaccination may play an important role in China's HFRS prevention and control.

The trend showing that the proportion of HFRS cases in the > 60 years age group has increased may be explained by the following reason. With life expectancy increasing, the characteristics of the agricultural labor have changed. Young and middle-aged people from rural areas have left home to seek jobs or education. So,

it is necessary for the elderly to increase their participation in agriculture and potentially come in contact with Hantaviruses. Previous epidemiological surveys revealed that the number of HFRS cases among the 15 to 60 years age group accounted for 87.2% of the total during the period 1998–2007 [22]. In this study, a significant change was noted in the age composition of HFRS in the past decades [22].

Notably, the individuals in the > 60 years age group do not have opportunity for HFRS vaccination. The population that is > 60 years old has not received sufficient protection from HFRS due to the current vaccination strategies. Moreover, previous studies have suggested that the HFRS vaccine is considered safe for individuals > 60 years old [25]. Therefore, the HFRS vaccine should be considered for application to this older population.

Some limitations of this study should be addressed. First, the age group categorization (< 15, 15–60, > 60 years) differs from the vaccine target population (16–60 years), which may introduce bias in the results. Second, multivariable analysis for climatic and socio-economic factors, and co-infection assessment was not conducted due to data limitations. Third, this study is characterized by a geographically restricted design (single-region focus) and the absence of direct annual confirmation of viral species. To address these limitations, a multicenter cohort study is proposed for future research.

Conclusions

This study analyzed the epidemiological characteristics of HFRS in Shaanxi Province between January 2004 and December 2023. The study enhances understanding of HFRS by revealing key epidemiological insights, with important implications for prevention, control, and vaccine development. The results can be used to adjust the prevention and control strategies for HFRS, and to consider the potential expansion of vaccination to older populations.

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Conflict of interest

No conflict of interest is declared.

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