Hemorrhagic fever with renal syndrome caused by destruction of residential area of rodent in a construction site: epidemiological investigation

Xiao Wei1†, Biao Meng1,2†, Hong Peng1, Yan Li1, Min Liu3, Hairui Si3, Rui Wu4, Hailong Chen4, Ying Bai3, Yan Li3, Qunling Feng3*, Changjun Wang1,2* and Xiangna Zhao1,2*

Abstract
Background: An outbreak of hemorrhagic fever with renal syndrome (HFRS), caused by a Hantavirus, affected nine adult males in the southwest area of Xi’an in November 2020 was analyzed in this study.

Methods: Clinical and epidemiological data of HFRS patients in this outbreak were retrospectively analyzed. The whole genome of a hantavirus named 201120HV03xa (hv03xa for short) isolated from Apodemus agrarius captured in the construction site was sequenced and analyzed. In addition, nine HFRS patients were monitored for the IgG antibody against the HV N protein at 6 and 12 months, respectively.

Results: In this study, inhalation of aerosolized excreta and contaminated food may be the main source of infection. Genome analysis and phylogenetic analysis showed that hv03xa is a reassortment strain of HTNV, having an S segment related to A16 of HTN 4, an M segment related to Q37 and Q10 of HTN 4, and an L segment related to prototype strain 76–118 of HTN 7. Potential recombination was detected in the S segment of hv03xa strain. The anti-HV-IgG level of all the patients persist for at least one year after infection.

Conclusions: This report documented an HFRS outbreak in Xi’an, China, which provided the basic data for epidemiological surveillance of endemic HTNV infection and facilitated to predict disease risk and implement prevention measures.

Keywords: Hemorrhagic fever with renal syndrome, Hantavirus, Hantaan virus

Introduction
Hemorrhagic fever with renal syndrome (HFRS) is a group of clinically similar illnesses caused by hantviruses (such as Hantaan virus, Dobrava virus, Seoul virus, and Puumala virus), each of which causes diseases with different severity [1]. Hantaviruses are emerging public health threat and widely distributed in eastern Asia and Europe [2, 3]. In China, 30,000–50,000 cases of HFRS are documented annually, accounting for > 90% of total numbers worldwide [4, 5], and Hantaan virus and Seoul virus are the two main pathogens [6]. Shaanxi province is one of the provinces with the most serious incidence of HFRS in China [7, 8]. In 2010, the number of HFRS cases in Shaanxi province ranked the top among all provinces in
China, and the incidence of HFRS in Xi’an city accounts for more than 90% of Shaanxi province [6, 9].

Generally, symptoms of HFRS appear within 1–2 weeks of exposure to source of infection [10]. Early symptoms such as headache, back and abdominal pain, fever, chills, nausea and blurred vision develop suddenly, and later progress to acute kidney injury and severe fluid overload [10, 11]. Complete recovery will take weeks or months. The severity of the disease varies depending upon the virus causing the infection. Hantaan and Dobrava viruses show the highest mortality ranging from 5 to 10% [12].

Hantaviruses (Family Hantaviridae, Order Bunyavirales) are negative sense RNA viruses and consists of four proteins, RNA-dependent RNA polymerase (RdRp), two membrane glycoproteins (G$_N$ and G$_C$), and a nucleocapsid (N) protein. N protein is encoded by S fragment, and the main function is to wrap three fragments of viral RNA, and the protein has strong immunogenicity. Both G$_N$ and G$_C$ are membrane glycoproteins encoded by M fragment with neutralizing antigen sites and hemagglutination sites. G$_C$, with membrane-distal localization and G$_N$, with selective pressure of the humoral immune response, these two antigenic sites exist independently but may overlap partially. L segment encodes RNA-dependent-RNA polymerase, which plays an important role in viral replication [13, 14].

Rodents are the natural reservoir for hantaviruses [15]. Contact with rodent feces or aerosol particles formed after bites from infected rodents are the main routes of hantavirus transmission to humans [7]. 30 Apodemus agrarius were captured in the construction site after the outbreak and 4 of them were detected positive for HTNV. A HTNV strain named 201120HV03xa (hv03xa for short) was isolated in the A. agrarius and the sequence was analyzed.

Reassortment, recombination, and genetic drift confer the genetic diversity in RNA viruses in nature. Segmented RNA viruses preferentially give rise to genetic reassortment rather than recombination [16]. The hv03xa strain isolated in this study is likely a reassortment strain, having an S segment related to A16 of HTN 4, an M segment related to Q37 and Q10 of HTN 4, and an L segment related to prototype strain 76–118 of HTN 7 [17].

**Materials and methods**

**Outbreak detection**

On November 15th, 2020, No. 986 hospital received a positive case of Hantavirus and reported that there was a possible outbreak of HFRS. In the following 3 days, 3 more HFRS patients were confirmed. As of December 2, a total of nine patients had been diagnosed with HFRS (Fig. 1). The site of the outbreak is in a new construction site, the construction action destructed the rodent’s residence. Between the two rows of dormitories where the patients lived there was a garbage station. In the north of the dormitory there was a tent, piled with Chinese cabbages and other vegetables for daily consumption. Rat tracks were observed inside the tent and near the garbage station (Fig. 2). The patients were classified into mild, moderate, and severe based on clinical classification of HFRS [10].

![Fig. 1 Timeline of relevant exposures and clinical symptoms of the 9 patients with HFRS](image-url)
Case definition in outbreak
HFRS was diagnosed in all cases according to Enzyme-linked immunosorbent assay (ELISA)-based detection of anti-HV IgM in serum samples obtained from patients during acute phase of the disease [18]. The so-called acute phase of the disease is defined as the period of febrile, hypotensive, and oliguric phases [10, 18, 19]. In this study, ELISA was also used to detect the titers of serum IgG/M antibody over time in patients.

Epidemiological investigation
An epidemiological investigation was carried out after confirmation of the HFRS outbreak. HFRS-like syndrome (fever, hypotensive, proteinuria, and acute renal failure), activity tracks, clinical symptoms, and medical records of febrile patients residing at the construction site were retrospectively collected. The Hantavirus IgG antibody levels of all patients were monitored.

Measures taken to control HFRS expansion
Epidemic prevention measures were carried out immediately after the outbreak. Rodent capture equipment, including 200 sticky rat boards, 800 traps and 30 cages, was set up immediately after the occurrence of the index case. The delivery of outdoor anticoagulant rodenticide was finished on November 16th. The garbage station was cleaned on November 12th-13th, the vegetables were removed from the tents and final disinfection was
performed on the sites. A customized mouse baffle is installed in the canteen, and closed storage of materials is adopted. The local CDC strengthened the canteen daily cleaning, tableware/kitchenware strict disinfection, the management of water sanitation, the quarantine of personnel and vehicles. By the end of December, 1268 people had been vaccinated with inactivated bivalent (HTN+SEO type) HFRS vaccine made from hamster kidney cell culture (Changchun Institute of Biological Products, China). Experts were invited to carry out disease knowledge education, provide guidance on prevention and control work, educate personnel to maintain hygiene habits, and avoid panic. The temperatures of all staff were measured daily to check for fever or other uncomfortable conditions, and medical treatment was arranged in time when abnormal conditions occurred. The epidemic was basically brought under control about December 6 and eliminated about December 15th.

Isolation of Hantaan virus and genome sequencing

*A. agrarius* collected was sterilized with 75% alcohol, and the chest was dissected and a small lung tissue was taken out with a sterile scissors and tweezers. Appropriate amount of Trizol was added followed by tissue polishing. Magnetic bead method was used for nucleic acid extracting. HTNV-specific reverse transcription-polymerase chain reaction (RT-PCR) was conducted for viral RNA [20]. T25 VERO-E6 cells were cultured to a single layer, and the above-mentioned positive lung specimens were added to the cells for tiled adsorption [21]. Supernatant was removed and cell-sustaining fluid was added after 1.5 h. Viral CT values were detected after continuous cultivation of 21 days [22].

Viral RNA was extracted using RNeasy Plus Mini Kit (50) (QIAGEN 74134) [23]. Reverse transcription and amplification were performed using Ovation RNA-Seq System V2 (Tecan 7102-08). Amplification products were subjected to sequencing using Oxford Nanopore Gridion X5 instrument [24]. Library was constructed using ligation sequencing kit (SQK-LSK109) and the sequencing chip used in this study was FLO-MIN106D [25]. The consistency sequences were generated by mapping, with the known Hantaan virus whole genome as a reference sequence.

Phylogenetic and recombination analysis

The nucleotide sequences of S, M, and L segments of hv03xa strain were determined from virus-infected lungs of *A. agrarius*. Sequences were aligned and compared with HTNV sequences available in GenBank using Mega (version 7.0) with default parameters [26]. For the phylogenetic analysis, the Maximum likelihood phylogenetic trees were generated, and topologies were evaluated by 1000 bootstrap replicates [26].

Alignments of Sequence sets to HTNV S, M, and L segments were analyzed using the Recombination Detection Program 4 (RDP4) software package [27]. RDP [28], GENECONV [29], BOOTSCAN [30], MaxChi [31], Chimera [30], SISCAN [32] and 3SEQ [33] were used only on events with P values less than 0.05. The recombination event was confirmed if it satisfied by four or more methods when the P-value < 0.05 and the RDP recombination consensus score (RDPRCS) was > 0.6 [34]. The P-value < 0.05 with the RDPRCS between 0.4 and 0.6 indicated the possibility of the recombination event [34]. RDPRCS < 0.4 and P-value < 0.05 suggested the rejection of the recombination [34]. All parameters were left at the default settings of RDP4.

Antibody response to HTNV in patients

With a goal of determining the dynamics and duration of immunity produced after HTNV infection, sera collection was made 6 months and 12 months post-symptom onset. The anti-HV-IgG was tested by ELISA (ZC-M6404, Shanghai zcbio technology Co., Ltd) according to the manufacturer’s instructions. Briefly, the test was carried out by adding diluted serum onto a HV nucleocapsid protein antigen coated plate. After incubation for 30 min at 37 °C, wells were washed and incubated with 100 μl mouse anti-human IgG antibody labelled with horse-radish peroxidase for 30 min at 37 °C. The IgG antibody captured by the antigen was detected by measuring the optical density (OD 450 nm) after adding the stop solution (0.2 M sulfuric acid). Each sample was repeated three times.

Ethics statement

All participants signed an informed consent form prior to entering the study. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All human and animal experimental protocols in this study were approved by the Ethics Committee of the PLA 63750 Hospital. All human and animal experimental procedures were carried out in accordance with relevant guidelines and regulations.

Results

Descriptive epidemiology

Nine HFRS patients developed symptoms consecutively from November 10th to 29th at Chang’an district, located in the southwest of Xi’an. All the patients were from the same construction site. The rodent residence in the surrounding place was destroyed because of the construction action. It is said that the rodent population density was significantly increased comparing with the same
period in the past. Some Chinese cabbage was stored in a tent of their residence for their daily consumption (Fig. 2). On November 2nd, the index patient (a 22-year-old male) transported the cabbage from the tent to the kitchen with two other patients (P 2 and P6). They saw rats in the tent and in the garbage station near the tent (less than 50 m). The index patient developed a headache (November 10th) eight days after transporting the cabbage and vomited on the evening of November 13th. On the morning of November 14th, he developed a fever (39 °C) and was admitted to the hospital. Nucleic acid tests confirmed that he was not infected with COVID-19. On November 15th, he was diagnosed with hemorrhagic fever with renal syndrome (HFRS) and classified as moderate patient. P2 and P6 became ill on November 15th and November 25th, respectively. P3, P4, P7, and P8 lived in a dormitory near the garbage station (Fig. 2), and they frequently took out garbage to the garbage station before the onset of illness. P5 and P9 frequently visited the tent before they had symptoms. The timeline of disease prevalence was presented in Fig. 1.

The clinical characteristics of the patients were summarized in Additional file 1: Table S1. Based upon clinical classification of HFRS [10], of the 9 patients, 2 had no bilateral renal abnormalities, no hemorrhagic spots, and no bulbar conjunctival congestion, they were classified as mild. Four patients experienced moderate illness, they presented with symptoms such as oliguria, bulbar conjunctival congestion, and subcapsular effusion of both kidneys. Three patients presented with oliguria, bilateral bulbar conjunctival hyperemia and edema, visible hemorrhagic spots, hypotension, bilateral kidney pain, bilateral subcapsular effusion and other symptoms, they were defined as severe patients.

**The possible source of the outbreak**

The index case transported Chinese cabbage that may have been contaminated by the rodents lived inside or outside the tent. One week later, the index case presented with symptoms like HFRS. We cannot directly prove that the rodents visited the tent led to this outbreak; however, there was a probable association. First, the patients (P2 and P6) who transported Chinese cabbage with the index patient presented with symptoms afterwards. Second, the construction action caused the destruction of rodent residence and their migration to the workers’ residence (the food storage tent, garbage station, etc.). Traces of rodents were also observed in areas where the patients had been visited. The contact between humans with contaminated vegetables in the tent and aerosolized excrement (saliva, urine, and feces) in the garbage station greatly increased the risk of infection. Third, a Hantavirus strain was isolated from the lung tissue in *A. agrarius* captured in the construction site.

**Control measures**

After confirmation of the outbreak on November 15th, demic prevention guarantee initiated a rodent eliminate program. Rodent capture was performed in the surrounding place. Meantime, publicity education efforts was also taken to control HFRS expansion. After that, the rodent density dropped obviously after rodent control efforts. Correspondingly, patient counts dramatically declined after December 1, approximately 10 days after the implementation of rodent control.

**Phylogenetic analysis of HTNV**

The full-length of S, M, L segments from a hantavirus strain (named 201120HV03xa, hv03xa for short) isolated from *A. agrarius* was sequenced and analyzed. The GenBank accession number for the S, M, L segment of 201120HV03xa reported in this paper is ON661335, OP094683, ON661337, respectively. The full-length S segment of hv03xa strain is 1696 nucleotides, with a predicted nucleocapsid protein of 429 amino acids. The entire M segment of hv03xa strain is 3615 nucleotides, encoding a predicted Gn/Gc envelope glycoproteins with functional roles in the viral escape from immunological responses. The glycoprotein precursor contains 1,135 amino acids with the highly conserved pentapeptide WAASA motif being found at amino acid positions 644–648. The full-length L segment from hv03xa strain is 6,533 nucleotides, with a predicted RdRp (RNA-dependent RNA polymerase) of 2,151 amino acids, starting at nucleotide position 38 and including 43 nucleotides of the 3’ noncoding region.

Strains information for sequence analysis in this study were shown in Table 1. The branches of the phylogenetic tree of Hantaan virus formed nine HTN clades (designated subtypes HTN 1–9) [17]. Phylogenetic analysis indicated that the hv03xa strain is likely a reassortment strain of HTNV. S segment nucleotide sequence of hv03xa strain was closely related to isolates of subtype HTN 4, including Xi’an isolates XAHu09066, CA09082007, CA10081206 and Shanxi isolate A16 [7], with identity of 98.94%, 98.88%, 98.53% and 98.70%, respectively. M segment of hv03xa strain was closely related to Guizhou strains Q37, Q10, CGHu3614, CGHu3612, CGRni1, CGAa31P9 and CGHu2 of subtype HTN 4 [17], with identity of 99.33%, 98.67%, 98.20%, 98.09%, 98.06%, 92.93% and 92.79%, respectively. L segment of hv03xa strain was closely related with strains originated from South Korea, including 76–118/PRO (84.27% identity), Aa04–722 (84.64% identity), Aa19–57.
| Group       | Strains | Accession no          | Host        | Country | Province |
|-------------|---------|-----------------------|-------------|---------|----------|
|             |         |                       |             |         |          |
| **HTN Viruses** |         |                       |             |         |          |
| HTNV 1      | AH09    | AF285264              | Niviventer niviventer | China  | Anhui    |
|             | NC167   | AB027523              | Niviventer niviventer | China  | Anhui    |
| HTNV 2      | B78     | AB027093              | Homo sapiens | China  | Shandong |
|             | H5      | AB127996              | Homo sapiens | China  | Heilongjiang |
|             | Liu     | AF288649              | Homo sapiens | China  | Shandong |
| HTNV 3      | Q7      | AB027095              | Apodemus agrarius | China  | Guizhou |
|             | Q20     | AB027096              | Apodemus agrarius | China  | Guizhou |
|             | Q36     | AB027094              | Apodemus agrarius | China  | Guizhou |
| HTNV 4      | A16     | AB027099              | Apodemus agrarius | China  | Shantui |
|             | XAHu09066 | JF421284            | Homo sapiens | China  | Xi’an    |
|             | CA09082007 | HQ834499         | –            | –       | –        |
|             | CA10081206 | HQ834503        | –            | –       | –        |
|             | CGAas19P9 | –                  | –            | –       | –        |
|             | CGHu2   | –                    | Homo sapiens | China  | Guizhou |
|             | CGHu3612 | –                   | Homo sapiens | China  | Guizhou |
|             | CGHu3614 | –                   | Homo sapiens | China  | Guizhou |
|             | CGRn1   | –                    | Rattus nuditidis | China  | Guizhou |
|             | Q10     | –                    | Apodemus agrarius | China  | Guizhou |
|             | Q22     | DQ371906              | Apodemus agrarius | China  | Guizhou |
|             | Q32     | –                    | Apodemus agrarius | China  | Guizhou |
| HTNV 5      | 84FLi   | AF366568              | Homo sapiens | China  | Shanxi   |
|             | Chen4   | AB027101              | Homo sapiens | China  | Anhui    |
| HTNV 6      | Bao14   | AB127998              | Apodemus agrarius | China  | Heilongjiang |
| HTN261      | AF252259 | –                  | –            | –       | –        |
|             | Q33     | AB027065              | Apodemus agrarius | China  | Guizhou |
| HTNV 7      | 76-118/PRO | KT885049            | Apodemus agrarius | South Korea | –        |
|             | CUMC-B11 | U37768              | –            | –       | South Korea |
|             | S85-46  | AF288659              | Crocidura russula | China  | Sichuan |
|             | LR1     | AF288294              | Apodemus agrarius | China  | –        |
|             | Aa04-722 | –                  | Apodemus agrarius | South Korea | –        |
|             | Aa19-57 | –                    | Apodemus agrarius | South Korea | –        |
|             | Aa16-176 | –                  | Apodemus agrarius | South Korea | –        |
| HTNV 8      | Z10     | NC_006433             | Homo sapiens | China  | Zhejiang |
| HTNV 9      | A9      | AF329390              | Apodemus agrarius | China  | Jiangsu |
|             | Hu      | AB027111              | Homo sapiens | China  | Hubei    |
| Other HTN virus strains of undetermined subtype |         |                       |             |         |          |
|             | TJ16    | AY839871              | Rattus confucianus | China  | Tianjin |
|             | CGAA75  | EU092220              | Apodemus agrarius | China  | Guizhou |
|             | CGRn53  | EF900907              | Rattus norvegicus | China  | Guizhou |
|             | CGRn93MP8 | EF900905          | Rattus norvegicus | China  | Guizhou |
|             | YU61    | AY748308              | –            | –       | –        |
|             | YU62    | AY748309              | –            | –       | –        |
|             | KY      | GU140008              | White rat    | China  | Yunnan   |
|             | Z37     | AF187082              | –            | –       | –        |
| Reference strains |         |                       |             |         |          |
| ANDV        | AH-1    | AF324902              | –            | Argentina | –        |
| PUUV        | P360    | L11347                | –            | Russia  | –        |
(84.63% identity) and Aa16-176 (84.62% identity), which were in the subtype HTN 7 clade (Fig. 3).

Recombination analysis of HTNV
Different methods were employed to provide evidence that recombination could occur in HTNV. Potential recombination event was detected (Table 2). The hsv03xa strain may have a recombinant S segment, in which nt 1–1664 originate from the Jiangsu strain A9 of HTNV 9, and nt 1665–1695 originates from Seoul virus strain ZT10 isolated from Zhejiang (Fig. 4). P-value of the analyses was from 3.74E-04 to 1.32E-10 and the RDP recombination consensus score was higher than 0.6 (0.679). The result indicated that hsv03xa may have a partial S-segment exchange recombination. No recombination events were detected in the M or L segments of hsv03xa strain.

IgM and IgG antibody response in patients
The titer above 40 is considered a positive for HTNV-NP-specific IgM and IgG antibodies [9]. Overall, HFRS patients’ serum IgG antibody titers remain detectable and relatively stable one-year PSO (post–symptom onset) (Fig. 5). At 6 months PSO, the geometric mean

| Group | Strains | Accession no | Host | Country | Province |
|-------|---------|--------------|------|---------|----------|
| SEOV  | L99     | AF288299     | Rattus losea | China | Jiangxi  |
|       | ZT10    | AY766368     |                  | China | Zhejiang |
| DOBV  | Dobrava-Belgrade | JQ026204  | Apodemus flavicollis | Germany | – |
| SNV   | NMR-11  | L37904       | Peromyscus maniculatus | The United States | – |

Table 2
Potential recombination event of hsv03xa strain

| Recombinant sequence | hsv03xa S segment |
|----------------------|-------------------|
| Estimated breakpoint positions | 1744–1774 nt |
| Parental sequences | Major A9 |
| Minor ZT10 |
| P-Values of different methods | RDP 1.59E-09 |
| GENECONV 1.32E-10 |
| BOOTSCAN 3.00E-10 |
| MaxChi 3.74E-04 |
| Chimaera 1.45E-05 |
| SiScan 2.16E-08 |
| 3Seq 3.42E-08 |
titer (GMT) was 1248.09 (95% confidence interval [CI] 1067.39–1428.78). At one year after infection, IgG antibody titers were detected in all of 9 patients with a GMT of 1210.48 (95%CI 1085.20–1335.76), which has no significant difference with that of 6 months PSO (p < 0.05, Kruskal–Wallis test). The serum IgG antibody titers of patients with HTNV infection was not significantly decreased compared in 1 year later. The HTNV-NP-specific IgM antibody were negative at 6 months and 12 months in all serum samples.

### Discussion

Hantaviruses can survive at room temperature for more than 10 days [35]. Exposure to rodent excrement containing Hantaviruses is the main pathway of human infection with Hantaviruses [35, 36]. The diagnosis of human hantavirus infection can be determined by combining epidemiological and clinical information with laboratory tests. Typical clinical symptoms of HFRS include fever, conjunctival bleeding, abdominal pain, nausea and vomiting, and severe oliguria and acute kidney injury occur in some patients. HFRS patients often have abnormal laboratory markers, such as leukocytosis, thrombocytopenia and elevated serum creatinine and lactate dehydrogenase [11, 12, 37]. In this study, ELISA was used to detect IgM/IgG antibodies of three structural proteins of Hantavirus [18, 19], which suggested that the anti-HV-IgG level of all the patients persist for at least one year after infection.

Among the total nine patients, three took part in carrying cabbages, and four often takes out the rubbish, and two usually went to the tent warehouse. Rats and traces of mouse activity were found in the cabbage tent and the dump, which was considered the most likely risk factors for exposure.

The exchange of genetic components conceals important information, including virus pathogenicity [38]. In this study, nine patients diagnosed with HFRS were most likely acquired HTNV infections from *A. agrarius* positive of HTNV. The genome sequence of the HTNV strain isolated from *A. agrarius* was completely obtained, and phylogenetic analysis indicated that the virus causing this
process, more attention should be paid to the destruction of urbanization, especially the construction cut off the transmission of hantavirus infection. In the elimination rodents are still important measures to Avoiding contact with rodents contaminated food and were detected positive for HTNV (data not shown).

is ON661335, OP094683, ON661337, respectively. The data and materials in this study are freely available. The GenBank accession number for the S, M, L segment of 201120HV03xa reported in this paper is ON661335, OP094683, ON661337, respectively.

4 of 30. A. agrarius captured in the construction site were detected positive for HTNV (data not shown). Avoiding contact with rodents contaminated food and elimination rodents are still important measures to cut off the transmission of hantavirus infection. In the process of urbanization, especially the construction process, more attention should be paid to the destruction of the rodent’s residence and the abnormal density increase of rodents.

These data provided the basic data for epidemiological surveillance of annual endemic HTNV infection and facilitated to predict disease risk and implement prevention measures.

**Abbreviations**

HFRS: Hemorrhagic fever with renal syndrome; hv03xa: 201120HV03xa; A. agrarius: Apodemus agrarius.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07744-1.

**Acknowledgements**

We thank all patients for their participation in this study.

**Author contributions**

XZ and CW conceived the study. QF, YL, ML, HS, RW and HC collected clinical samples; XW and BM performed serological testing; XW, BM, HP and YL analyzed the data; XZ and CW drafted the manuscript. All authors reviewed and approved the final manuscript. All authors read and approved the final manuscript.

**Funding**

This work was supported by Beijing Municipal Natural Science Foundation Project (No. 5202027), National Science and Technology Major Project (No. 2018ZX10712001-12-2).

**Availability of data and materials**

The data and materials in this study are freely available. The GenBank accession number for the S, M, L segment of 201120HV03xa reported in this paper is ON661335, OP094683, ON661337, respectively.

**Declarations**

**Ethics approval and consent to participate**

All participants signed an informed consent form prior to entering the study. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All human experimental protocols in this study were approved by the Ethics Committee of the PLA 63750 Hospital. All human experimental procedures were carried out in accordance with relevant guidelines and regulations. All animal experimental protocols in this study were approved by the Ethics Committee of the PLA 63750 Hospital. All animal experimental procedures were carried out in accordance with relevant guidelines and regulations.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

1. Centers for Disease Control and Prevention of PLA, Beijing, China.
2. Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China.
3. PLA 63750 Hospital, Xi’an, Shaanxi, China.
4. Xi’an Center for Disease Control and Prevention, Xi’an, Shaanxi, China.

Received: 19 May 2022. Accepted: 20 September 2022
Published: 29 September 2022

**References**

1. Puca E, Hanni A, Pipero P, Oppa E, Zoneti G, Mucchi E, Hysenaj Z, Rista E, Toski G, Bino S. Pancreatitis in patients with hemorrhagic fever with renal syndrome: a five-year experience. J Infect Dev Ctries. 2017;11(1):900–3.
2. Yu H, Jiang W, Du H, Xing Y, Bai G, Zhang Y, Li Y, Jiang H, Zhang Y, Wang J, et al. Involvement of the Akt/NF-kappaB pathways in the HTNV-mediated increase of IL-6, CCL5, ICAM-1, and VCAM-1 in HUVECs. PLoS ONE. 2014;9(4): e93810.
3. Klempp B. Hantiviruses and climate change. Clin Microbiol Infect. 2009;15(6):518–23.
4. Tian HY, Yu PB, Luis AD, Bi P, Cazelles B, Laine M, Huang SQ, Ma CF, Zhou S, Wei J, et al. Changes in rodent abundance and weather conditions potentially drive hemorrhagic fever with renal syndrome outbreaks in Xi’an, China, 2005–2012. PLoS Negl Trop Dis. 2015;9(3): e0003530.
5. Yang X, Wang C, Wu L, Jiang X, Zhang S, Jing F. Hemorrhagic fever with renal syndrome related to secondary hemorrhagic lymphohistiocytosis in West China: a case report. BMC Infect Dis. 2019;19(1):492.
6. Zhang S, Wang S, Yin W, Liang M, Li J, Zhang Q, Feng Z, Li D. Epidemiologic characteristics of hemorrhagic fever with renal syndrome in China, 2006–2012. BMC Infect Dis. 2014;14:384.
7. Ma C, Yu P, Navaz M, Zuo S, Jin T, Li Y, Li J, Li H, Xu J, Hantavirus infections in rodents and humans, Xi’an, PR China. J Gen Virol. 2012;93Pt 10:2227–36.
8. Yu PB, Tian HY, Ma CF, Ma CA, Wei J, Lu XL, Wang Z, Zhou S, Li S, Dong JH, et al. Hantavirus infection in rodents and haemorrhagic fever with renal syndrome in Shaanxi province, China, 1984–2012. Epidemiol Infect. 2015;143(2):405–11.
9. Li Z, Zeng H, Wang Y, Zhang Y, Cheng L, Zhang F, Lei Y, Jin B, Ma Y, Chen L. The assessment of Hantaan virus-specific antibody responses after the immunization program for hemorrhagic fever with renal syndrome in northwest China. Hum Vaccin Immunother. 2017;13(4):802–7.
10. Du H, Wang PZ, Li J, Bai L, Li H, Yu HT, Jiang W, Zhang Y, Wang JN, Bai XF. Clinical characteristics and outcomes in critical patients with hemorrhagic fever with renal syndrome. BMC Infect Dis. 2014;14:191.
11. Qiu FQ, Li CC, Zhou YX. Hemorrhagic fever with renal syndrome complicated with aortic dissection: a case report. World J Clin Cases. 2020;8(22):5795–801.
12. Jonsson CB, Figueiredo LT, Vapaahalti O. A global perspective on hantavirus ecology, epidemiology, and disease. Clin Microbiol Rev. 2010;23(2):412–41.
