Original Article

Spatio-temporal Evolution on Geographic Boundaries of HFRS Endemic Areas in Shandong Province, China*

LIU Yan Xun[1], WANG Zhi Qiang[2], GUO Jing[1], TANG Fang[1,3], SUN Xiu Bin[1], XUE Fu Zhong[1], and KANG Dian Min[2,4,#]

1. Department of Epidemiology and Biostatistics, School of Public Health, Shandong University, Jinan 250012, Shandong, China; 2. Shandong Center for Disease Control and Prevention, Jinan 250014, Shandong, China; 3. Shandong Qianfoshan Hospital, Jinan 250014, Shandong, China; 4. Shandong Key Laboratory for Epidemic Disease Control and Prevention, Shandong CDC, Jinan 250014, Shandong, China

Abstract

Objective To take effective strategies and measures for the prevention and control of hemorrhagic fever with renal syndrome (HFRS) endemic areas by investigating its dynamic geographical boundaries in Shandong Province, China.

Methods The incidence of HFRS from 1982 to 2008 in Shandong Prvince, China, was detected with inverse distance weighting (IDW) interpolation based on geographical information system (GIS). Dynamic geographical boundaries of HFRS endemic areas in Shandong Province, China, were analyzed by geographical boundary analysis.

Results The HTN-type endemic areas of HFRS were located in Linyi City in phase 1 (1982-1986), the SEO-type endemic areas of HFRS were located in Jining City in phase 2 (1987-2003), and the endemic areas of HFRS in Jining City gradually disappeared and the endemic areas of HFRS with mixed-types of reservoir rodents were located in Linyi City in phase 3 (2004-2008). Meanwhile, new endemic areas emerged in the northwestern Shandong province, China.

Conclusion The SEO-type endemic areas of HFRS are located in western Shandong Province, China, and the HTN-type endemic areas of HFRS are located eastern Shandong Province, Chin, indicating that the endemic areas of HFRS should be vaccinated and rodents should be controlled.

Key words: Hemorrhagic fever with renal syndrome; Border analysis; Geographical information system (GIS)

Biomed Environ Sci, 2013; 26(12): 972-978 doi: 10.3967/bes2013.032 ISSN: 0895-3988

www.besjournal.com (full text) CN: 11-2816/Q

INTRODUCTION

China is the most severe endemic area of hemorrhagic fever with renal syndrome (HFRS) in the world with 30 000-50 000 cases reported annually, accounting for more than 90% of the total number of cases globally[1]. The reported cases in Shandong Province, China, accounted for approximate one third of the total HFRS cases in the whole country, and the incidence of HFRS in Shandong province, China, reached over 180 per 100 000 annually. HFRS is a zoonosis caused by different species of Hantavirus (HV) and its distribution generally coincides with the distribution of host species. The majority of causative HFRS strains are known as Hantaan virus (HTNV) whose

*This research was supported by the National Natural Science Foundation of China (grant number: 81072340).

#Correspondence should be addressed to KANG Dian Min. Tel: 86-531-82679612. Fax: 86-531-82679620. E-mail: dmkang@sohu.com

Biographical note of the first author: LIU Yan Xun, male, born in 1962, associate professor, majoring in epidemiology and biostatistics.

Received: December 18, 2012; Accepted: May 27, 2013

natural host is the rodent Apodemus agrarius and Seoul virus (SEOV) transmitted by the rodents rattus and R. norvegicus[2-3]. It was reported that the incidence of HFRS is significantly associated with environmental factors, including topography (elevation), precipitation, normalized difference vegetation index (NDVI), annual cumulative air temperature, soil type (semihydromorphic soils), and land use (timber forests, and orchards)[2,4-5]. According to the host species, the endemic areas of HFRS in China can be classified into HTN-type endemic areas, SEO-type endemic areas and mixed-type endemic areas. It has been shown that with the changes of altitude and geographic latitude, the distribution of HFRS endemic areas demonstrate an apparently geographical gradient and spatial heterogeneity, and the type of HFRS endemic areas changes with different periods in some specific regions[6-8]. Elucidating the spatio-temporal dynamic evolution of HFRS endemic areas can help clarify the epidemic mechanism of HFRS and predict the disease level[9], thus providing valuable information for adjusting and optimizing spatio-temporal scope of vaccination and rodent control.

Forty-four surveillance spots were set up in this study in Shandong Province in 1982 to detect the distribution of different species of rodents and the pattern of different virus species causing HFRS, and follow-up study was conducted to observe the incidence of HFRS from 1982 to 2008. Spatial database was developed following the GIS framework, spatial clines map was plotted for the incidence of HFRS using inverse distance weighting (IDW) interpolation, and spatio-temporal evolution pattern of HFRS endemic areas in Shandong Province, China, was analyzed by geographical border analysis.

MATERIALS AND METHODS

Data Collection

The monthly and annual incidence of HFRS was estimated in 141 counties of Shandong Province, China, from 1982 to 2008 in each surveillance spot. Snap traps were set up in the field and in residential areas. Traps were bated with peanuts or fried flour pancakes in the evening before 7 o'clock and the trapped rodents were collected in the next morning. The number of trapped rodents in each spot, the proportion of different species of reservoir rodents, and the intensity of rodents were calculated. Lung tissues were taken from the rodents and stored in a portable liquid-nitrogen freezer. Hantavirus antigen and antibody were detected by Laboratory of Shandong CDC and Hantavirus-specific antigens and antibodies were detected by direct and indirect immune fluorescent assay[10]. The number of rodents carrying virus in each surveillance spot and the proportion of each rodent species carrying virus were counted.

Spatial Database and GIS

A spatial matrix of the average HFRS incidence in *n* counties in the geographical areas of Shandong Province, China, is defined as

$$C_{n\times 3}=\begin{pmatrix} x_1 & y_1 & \overline{p}_1 \\ x_2 & y_2 & \overline{p}_2 \\ \vdots & \vdots & \vdots \\ x_n & y_n & \overline{p}_n \end{pmatrix}$$

where the (x_i,y_i) denotes the geographical location of the i^{th} county, and $\overline{p}_i$ is its average incidence within a specific period, i=1,2,..., n.

The spatial matrix of epidemiological surveillance data for *m* spots in the geographical landscape of Shandong Province, China, is defined as

$$C_{m\times(2+k)}=\begin{pmatrix} x_1 & y_1 & \overline{q}_{11} & \overline{q}_{12} & \cdots & \overline{q}_{1k} \\ x_2 & y_2 & \overline{q}_{21} & \overline{q}_{22} & \cdots & \overline{q}_{2k} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ x_m & y_m & \overline{q}_{m1} & \overline{q}_{m2} & \cdots & \overline{q}_{mk} \end{pmatrix}$$

where the (x_i,y_i) denotes the geographical location of the i^{th} surveillance spot, and the $\left(\overline{q}_{i1} \quad \overline{q}_{i2} \quad \cdots \quad \overline{q}_{ik}\right)$ is the vector of epidemiological surveillance data at the i^{th} surveillance spot with *k* variables, including the average monthly incidence of HFRS, density of different rodent species, and rate of rodents carrying virus, i=1,2,..., *m*.

A spatial database of the average incidence was developed and its epidemiological surveillance data were recorded by ArcGIS (Environmental Systems Research Institute Inc., USA).

Spatial Statistical Analysis

Spatial patterns of HFRS incidence were observed with IDW interpolation and geographic clines were detected as previously described[11-12]. Contour spatial variable maps were plotted with IDW method for the average annual incidence of HFRS at 141 surveillance points [counties, Figure SI (See the website of www.besjournal.com)], in which its inter-plots were estimated according to the values at nearby locations weighted by their distance from the point. The geographic clines were classified as previously described[13]. The variable search radius option provided by ArcGIS was used in IDW interpolation to overcome the possible problem caused by the IDW function with a forced maximum or minimum at the data points or on a boundary of the study region. Spatial boundaries indicating abrupt changes were observed. The boundaries were identified using the 'improved Monmomier's algorithm' model (BARRIER version 2.2)[14-15] to find the largest difference in neighboring vector pairs of epidemiological surveillance data in the spots within a specific period. Variables considered in the vector included the average monthly incidence of HFRS, the density of different rodent species, and the number of rodents carrying virus. The distance was measured according to the Euclidean distance. The relative strength of boundaries was assayed by bootstrap re-sampling.

All maps were plotted using the ArcGIS9.0 (Environmental Systems Research Institute, Inc, USA).

RESULTS

Identification of HFRS Specific Epidemic Phases in Shandong Province, China

The monthly HFRS incidence from 1982 to 2008 in Shandong Province, China, is shown in Figure 1. The epidemiological annual (EA) was defined as the period from 1982.09.01 to 1983.08.31. The fifth EA was the turning point according to the seasonal characteristics of monthly HFRS incidence. The annual incidence of HFRS at this point was up to the historical peak from 1982 to 2008 at provincial level, although it was higher at the following point than at this point in some counties. An example at Fangzi County in Weifang City of central Shandong Province is shown in Figure S2 (see the website of www.besjournal.com). Before this turning point, the seasonal distribution was represented by double peaks with spring & winter being dominated, and both HTN-type and SEO-type endemic areas of HFRS were found in the western and eastern Shandong Province, China (Figure 2). The SEO-type endemic areas of HFRS remained unchanged until EA 22 (2002.09.01 to 2003.08.31) with a relatively high incidence while the HTN-type endemic areas of HFRS almost disappeared from 1991 to 2003 (Figure 3). The incidence of HFRS decreased significantly without noticeable seasonal peak, and the mixed HTN-type and SEO-type endemic areas emerged in the high incidence regions from 2004 to 2008 (Figure 4). Therefore, the specific epidemic phase was divided into phase 1 (1982-1986), phase 2 (1987-2003), and phase 3 (2004-2008).

Spatial Structure of Geographical Clines and Boundaries in Phase 1

The map of average incidence of HFRS in phase the first (Figure 2) revealed an obvious north-south geographic cline with a high incidence zone (137/100 000-220/100 000) distributing throughout western to eastern Shandong Province, China. However, the high HFRS incidence zone was divided into western and eastern subzones by a medium incidence zone (24/100 000-44/100 000). The western subzone was located in the southwestern Shandong Province, China, where the pie charts in the map showed that

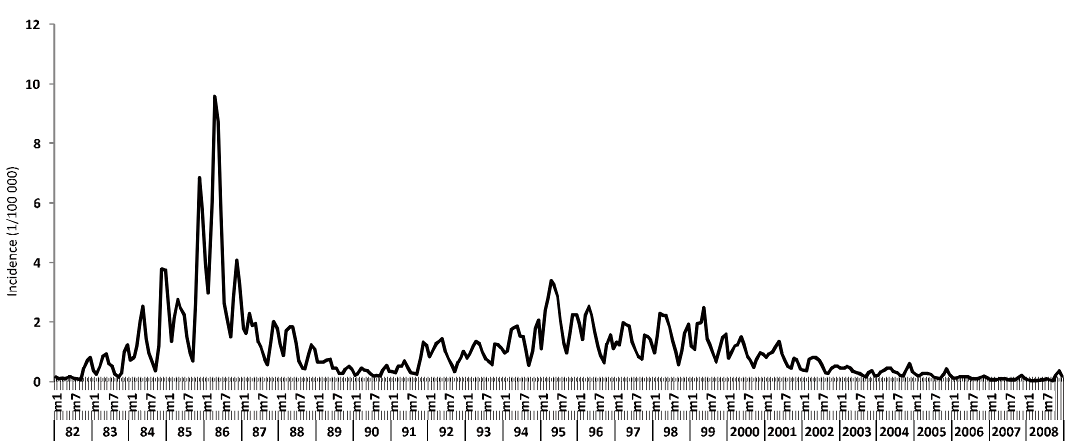

Figure 1. Epidemic curve for monthly incidence of HFRS from 1982 to 2008 in Shandong Province, China.

the SEO-type endemic area was dominant with positive rodent *R. norvegicus,* while the eastern zone was located in the southeastern Shandong Province, China, where the HTN-type endemic area was dominant with positive rodent *Apodemus agrarius*. In addition, some non-endemic areas in this phase were located in northern and northeast Shandong Province, China.

As shown in below Figure 2, Shandong Prvince was divided into four sub-regions by the boundaries in phase 1. A longitude dominant boundary set partitioned the landscape of Shandong Province into western and eastern parts. A latitude boundary located in the north of Yellow River, partitioned western part into southern sub-region (sub-region 1) and northern sub-region (sub-region 2). The high epidemic central sub-region 1 was located in Jining City, a hydrographic net and lake areas in the southwestern plain of Shandong Province. From the central sub-region 1, the descending geographical cline extended to the southwestern, southeastern, and northern areas. In particular, the geographical cline toward north crossed over Yellow River, and extended to the northwestern plains of Shandong Province. The SEO-type endemic area was dominant in sub-region 1 with positive rodent *R. norvegicus* (Figure 2). The sub-region 2 is adjacent to Hebei Province, China, and its endemic areas remained unknown due to the lack of data.

The eastern part of Shandong Province was divided into the sub-region 3 and sub-region 4. The high epidemic central sub-region 3 was located in Linyi City. The HTN-type endemic area was dominant in this sub-region with positive rodent *Apodemus agrarius* (Figure 2). The sub-region 4, a non-endemic area, was located in Jiaodong area of Shandong province.

In phase 1, therefore, SEO-type endemic area (sub-region 1) was independent of HTN-type endemic area (sub-region 3).

Spatial Structure of Geographical Clines and Boundaries in Phase 2

The incidence of HFRS was lower in phase 2 than in phase 1, but there was an obvious geographic cline with a relative high incidence zone (22.2/ 100 000-45.2/100 000) in southeastern Shandong Province, where the HTN-type endemic area changed to mixed HTN-type and SEO-type epidemic area with positive rodent *R. norvegicus* (Figure 3). The incidence of HFRS was lower (19/100 000) in phase 2 than that in phase 1. The north and northeast non-endemic areas still existed.

The longitude dominant boundary set in phase 1 still exited, but it moved to central Shandong Province, the boundary between SEO-type and HTN-type endemic areas located along Taiyi mountain areas throughout the northwest and southeast Shandong Province and divided the landscape of Shandong Province into western and eastern parts (Figure 3). In the western part, a longitudinal boundary was divided into western region (sub-region 1) and eastern region (sub-region 2). Sub-region 1 was the original SEO-type endemic area with positive rodent *R. norvegicus* in southwestern Shandong Province, and its epidemic level was lower in phase 2 than in phase 1 with the high epidemic center disappeared. In sub-region 2, the pattern of geographical boundaries was rather complicated in that there were some sub-boundaries in it, reflecting the geographical expanding, overlapping and mixing from SEO-type endemic area to HTN-type endemic area from west to east. This sub-region to the west of Taiyi mountain areas became mixed HTN-type and SEO-type dominant endemic area with positive rodents *R. norvegicus* after the expanding and overlapping of SEO-type endemic area to HTN-type endemic area (Figure 3). The northwest-southeast boundary of the eastern part was divided into west region (sub-region 3) and east region (sub-region 4) in phase 2 as in phase 1. In sub-region 3, the high epidemic center was located in the east Taiyi mountain areas and expanded to the northeastern Shandong Province positive rodent *Apodemus agrarius* when the epidemic level gradually decreased. Therefore, it belonged to mixed HTN-type and SEO-type epidemic area. The sub-region 4 was still a non-endemic area located in the Jiaodong region of Shandong Province.

Generally speaking, SEO-type and HTN-type endemic areas were overlapped and mixied in phase 2 and divided into west Taiyi mountain area and east Taiyi mountain areas.

Spatial Structure of Geographical Clines and Boundaries in Phase 3

Similar to phase 2, only one relatively high incidence zone was located in the southeastern Shandong Province in the phase 3 (Figure 4), a mixed SEO-tye and HTN-type epidemic area withpositive rodent *R. norvegicus*. However, its spatial scope was becoming smaller. The endemic areas were expanding

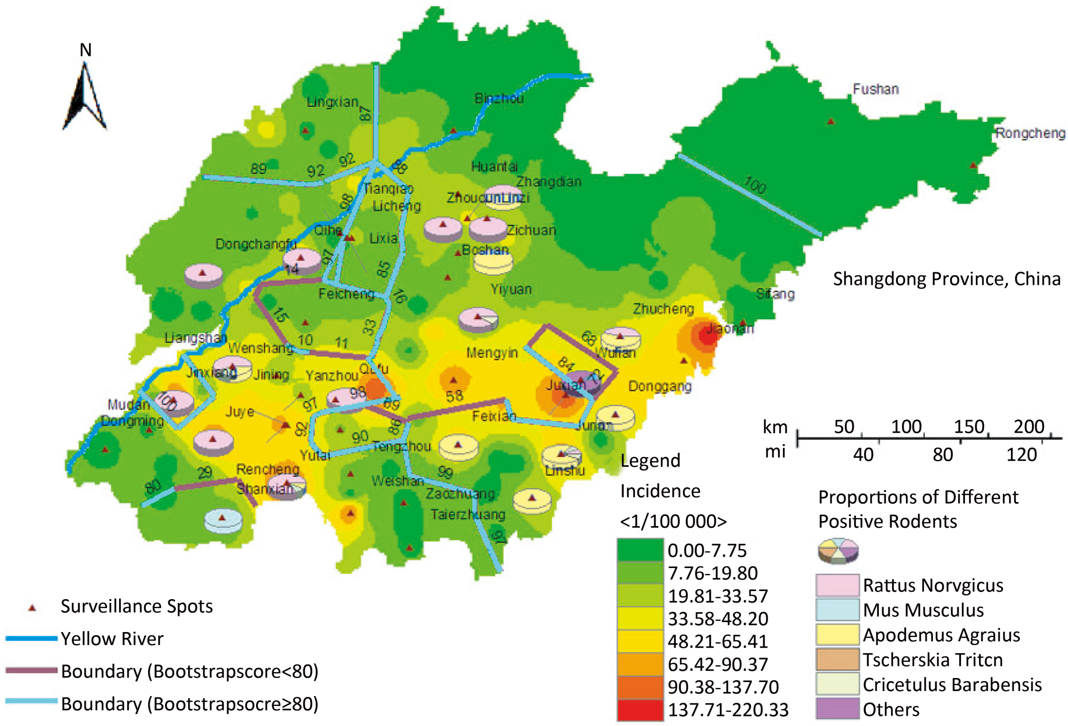

Figure 2. Spatial distribution map of average incidence and geographical boundaries pattern of HFRS endemic areas in phase 1.

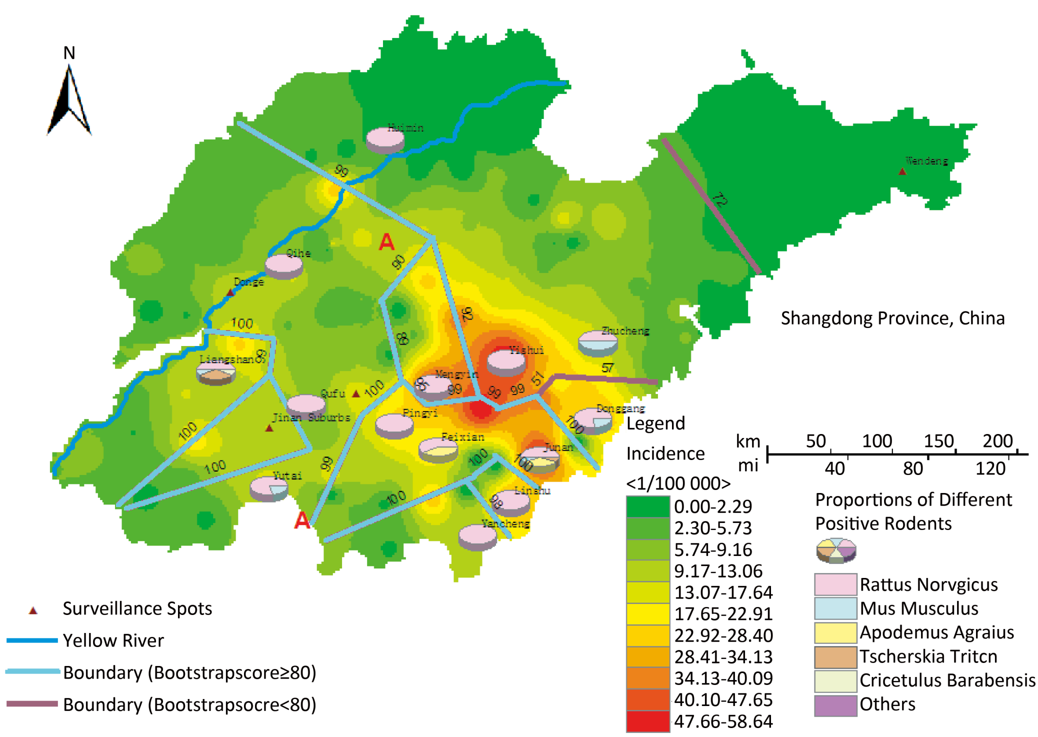

Figure 3. Map of spatial distribution for average incidence and geographical boundary pattern of HFRS endemic areas in phase 2.

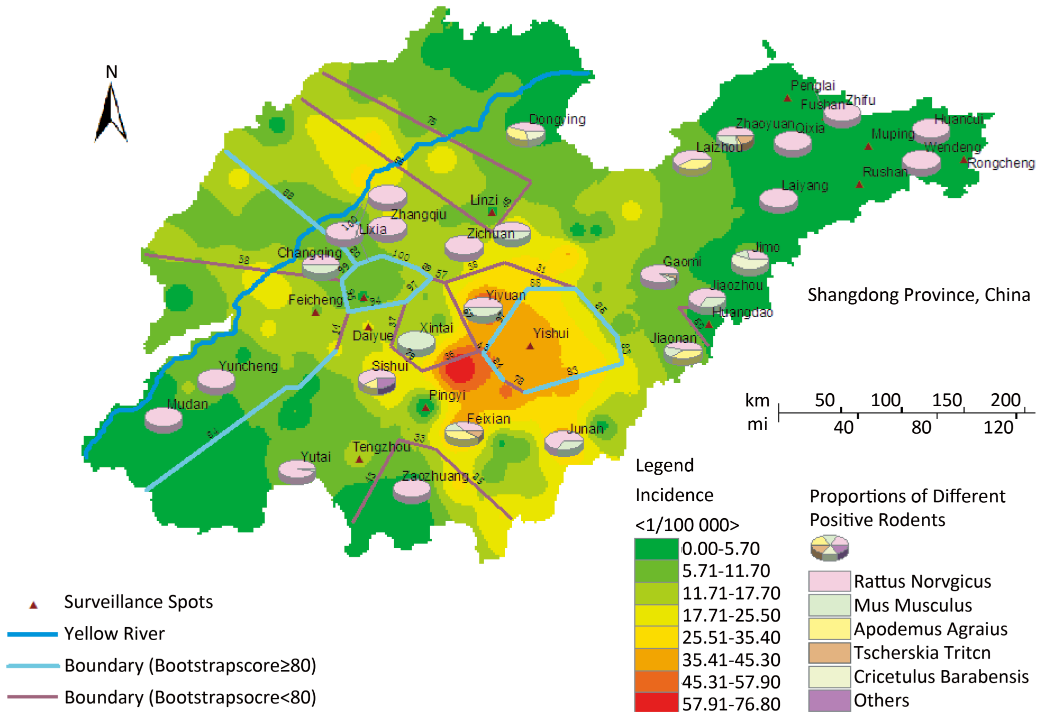

Figure 4. Map of spatial distribution for average incidence and geographical boundary endemic areas of HFRS in phase 3.

to almost the whole landscape of Shandong Province, with the north and northeast non-endemic areas almost disappeared.

Although some local sub-regions closed by sub-boundaries were revealed, the dominant geographical boundaries of endemic areas were clear in the landscape of the whole province. Therefore, the geographical expanding, overlapping and mixing were completed, and the whole landscape of Shandong Province became a uniform mixed HTN-type and SEO-type endemic area with dominant rodents *R. norvegicus* and *R. Mus*. The spatial pattern of mixed HTN-type and SEO-type endemic area was formed, and the relatively high epidemic area was located in Yimeng mountain areas in the southeastern Shandong Province and the whole landscape became a uniform ecological and epidemiological entirety.

DISCUSSION

Although various measures have been taken to control rodents and HFRS in Shandong Province for a long time, the incidence of HFRS is still high. The existed endemic areas are still expanding with new endemic areas emerged. It was reported that the high incidence of HFRS is due to the ecological features and environmental changes[2,4-5], and the dynamic evolution of endemic areas has not been fully understood[16]. It is, therefore, difficult to make effective prevention and control policies based on dynamic changes of endemic areas, such as regionalized vaccination according to the demographic features of reservoir rodents.

In this study，laboratory tests of virus carried by the reservoir rodents in the surveillance spots in Shandong Province were performed from 1982 to 2008. According to the carrier rate and proportions of different types of virus in the rodents, the spatio-temporal evolution in the geographic boundaries of HFRS endemic areas in Shandong Province was studied under the geographical information system (GIS) framework. The epidemic time of HFRS rom 1982 to 2008 could be divided into phase 1 (1982-1986), phase 2 (1987-2003), and phase 3 (2004-2008). The HTN-type endemic areas were located in Linyi City in phase 1, and the SEO-type endemic areas were located in Jining City with a high incidence in phase 2, and the endemic areas gradually disappeared in Jining City with mixed-types of reservoir rodents located in the Linyi City with a high incidence in phase 3. Furthermore, the dynamic boundaries of HFRS endemic areas and the spatial-temporal dynamic features of endemic areas could be speculated that the SEO-type western endemic areas are independent of HTN-type eastern endemic areas, the SEO-type in the western endemic areas spreads to the eastern endemic areas, the mixed HTN-type and SEO-type endemic areas are formed as the main type in western endemic areas.

The logical connection in the 3 phases can be mainly explained by the inappropriate intervention and the changes of socio-economic status in Shandong Province. No specific intervention was implemented in phase 1. However, a universal deratization to Rattus was carried out in endemic areas of Shandong Province by the end of phase 1. The incidence of HFRS decreased dramatically, which can be explained by the loss of ecological balance between Rattus and Vole due to the inappropriate intervention. As the density of Rattus decreased rapidly in households and the Vole entered into household from farm field, the contact between resident and apodemus agrarius with HTN virus became more frequent, the incidence of HTN-type increased dramatically in eastern endemic areas. The inappropriate universal intervention lasted to the end of phase 2 with frequent communications between the east and west due to the socio-economic development, the SEO-type in the western endemic areas was spread gradually to the eastern endemic areas, and the mixed SEO-type and HTN-type epidemic areas are finally formed in phase 3 as main type in westernern endemic areas. Therefore, the epidemic regions were vaccinized and the rodents were controlled in phase 3 according to the dynamic reservoir rodents.

The spatial-temporal dynamic evolution of endemic areas is complex due to multiple factors, including the above-mentioned inappropriate universal deratization, landform, hydrology, climate, soil, vegetation, and landscape ecological environment. The spatial-temporal dynamic evolution of HFRS endemic areas in Shandong Province was highlighted in this study, which is of great significance for the prevention and control of HFRS. The HFRS surveillance spots in Shandong Province should be re-assigned according to the spatial-temporal dynamic evolution characteristics, the deratization methods should be further optimized according to the spatial-temporal dynamic evolution, and the regional deratization strategy should be implemented from the ecological balance perspective, vaccine immunity strategy should be adjusted and improved based on the spatial-temporal dynamic types of endemic areas, and further evolution trends should be tracked to optimize and regulate the prevention and control measures.

ACKNOWLEDGMENTS

The authors highly appreciate Shandong Provincial Center for Disease Control and Prevention for kindly providing the disease data.

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