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The impact of the vaccination program for hemorrhagic fever with renal syndrome in Hu County, China☆

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ABSTRACT

The incidence of hemorrhagic fever with renal syndrome (HFRS) in Hu County ranked third of all counties in China in 2010. Although this county has provided a HFRS vaccination program freely since 1994, the impact of HFRS remains quite substantial. In order to continue the vaccination program effectively and control HFRS, a detailed understanding of the effect of the vaccination program should be undertaken. The Cochran–Armitage trend test was employed to examine the temporal trends of HFRS incidences, mortality rate and vaccination compliance. Temporal cluster analysis was performed to detect time periods of high HFRS risk. Cross correlation analysis was conducted to detect the correlation between HFRS incidence and vaccination compliance. Wavelet analysis was employed to detect the shift of the periodicity of HFRS. Between 1971 and 2011, the HFRS incidence and mortality rate ranged from 9.53/100,000 to 300.57/100,000 and 0 to 24.91/100,000, respectively, with a fluctuating but distinctly declining trend (incidence: $Z = -34.38$, $P < 0.01$; mortality rate: $Z = -23.44$, $P < 0.01$). The vaccination compliance ranged from 4.55% to 83.67%, with a distinctly increasing trend ($Z = 1621.70$, $P < 0.01$). The most likely temporal cluster of the HFRS epidemic was between 1983 and 1988 (RR = 3.44, $P < 0.01$) or 1979–1988 (RR = 3.18, $P < 0.01$) with different maximum temporal cluster size. There was a negative correlation between HFRS incidence and vaccination compliance when the lagged year was 1 and 2 (cross correlation coefficient = −0.51 and −0.55). The periodicity of HFRS epidemic was prolonged from about 5 years during 1976–1988 to 15 years after 1988, especially after the start of HFRS vaccination in 1994. In conclusion, the increase in vaccination compliance may play an important role in HFRS control and prevention in Hu County, China.

1. Introduction

Hemorrhagic fever with renal syndrome (HFRS) is a zoonosis caused by Hantaviruses. It is widely distributed in eastern Asia, particularly in China. The number of HFRS cases and deaths in China is the highest in the world and therefore HFRS is an important public health problem in China [1]. Hu County is one of the main HFRS epidemic areas in China, with the third highest HFRS incidence among all counties of China in 2010 [2]. Both Hantaan virus (carried by *Apodemus agrarius* mice that thrive in the wild) and Seoul virus (carried by *Rattus norvegicus* rats that thrive in residential areas) were detected in this county, with the Hantaan virus as the primary cause. Since 1994, Hu County has offered a free HFRS vaccination program to people between 16 and 60 years of age. The HFRS vaccines were supplied free of charge by the government in October to December of each year to people who had never received this vaccination. An HTNV-inactive vaccine was provided during 1994 to 2003 in Hu County and an inactive bivalent vaccine, consisting of HTNV and SEOV, was provided from 1994 to 2011. People younger than 16 and older than 60 years were suggested to avoid contact with rats and its excreta. However, this county is still severely threatened by HFRS, with an incidence of 48.5 per 100,000, which was 68.3 times higher than that in the rest of China in 2011 [3]. Some important considerations remained, including the effectiveness of the vaccination program and the necessity to continue to provide the HFRS vaccination freely in Hu. There have been no reports published about the vaccination program offered in Hu in

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the last 20 years. Therefore, the effect of HFRS vaccination remains unclear. In order to carry on the vaccination program effectively and control HFRS in Hu, a detailed understanding of the effect of vaccination on HFRS epidemic must be obtained.

There are two ways to evaluate the effect of a vaccine in epidemiological terms. The first method is a calculation of indices, including the protective rate and seroconversion rate. The method is performed at the individual level, in which results are obtained through an epidemiological survey of each person [4–6]. This method has been used to evaluate the effect of the HFRS vaccine in some areas of China, including Shannxi Province and Zhejiang Province [7–9]. The second method is a correlation analysis that analyzes the relationship between the fluctuation of the disease epidemic and the vaccination rate. The analysis is performed at the population level, in which results are obtained through surveillance data. The wavelet analysis is another important method for assessing the effect of a vaccine in population level. It can detect the shifts of the periodic mode of a time series by quantifying the periodicities of the time series and show when they are dominant [10]. Wavelet analysis has been used to evaluate the effect of vaccines, such as the measles and *Bordetella pertussis* vaccines [11–13]. Wavelet analysis has also been used to detect the influencing factors of infectious diseases, such as climate factors, normalized difference vegetation index and El niño-southern oscillation [14–16]. In this study, wavelet analysis will be used to evaluate the effectiveness of the HFRS vaccination program in Hu.

Cluster analysis is commonly used to quantitatively detect the area or time period with a high risk of disease. The dynamic scanning window makes the clusters flexible enough by using a likelihood ratio test [17]. This method has been used to identify the spatial or space-time disease clusters of many infectious diseases, such as malaria, HFRS, and dengue [17–19]. In this study, temporal cluster analysis will be used to detect the time period with the highest risk of HFRS in Hu in order to show whether the HFRS epidemic was more prevalent before or after the initiation of the vaccination program.

The principal aim of this study was to explore the effect of the HFRS vaccine program by analyzing the influence of vaccination on the secular trend, temporal clusters, and cyclical fluctuation of the HFRS epidemic in Hu. The study will provide a scientific basis for the evaluation and improvement of the HFRS vaccination planning strategy.

2. Material and methods

2.1. Study area

The study area is located southwest of Xi'an City, at 30°45′–34°20′ N, 108°20′–108°50′ E in central China. The region has an area of 1250 km^2 and a population of 0.60 million [20]. Qinling Mountain is present in south Hu County, with an altitude of 3015 m. A plain is present in north Hu County with an altitude of 400 m, which has a temperate continental monsoon climate. The climate and terrain in Hu is suitable for the survival and reproduction of the rat and mouse, which are important host and transmission media of HFRS. Most farmlands and rural dwellings of Hu County are located in this plain, as is the *A. agrarius* mice and *R. norvegicus* rats. Therefore, farm-working and other outdoor activities may increase people's exposure to infected rodents and their excrements and increase the risk for HFRS infection in this area.

2.2. Vaccination program

During 1994 to 2003, an HTNV-inactive vaccine was given to people between 16 and 60 years of age in Hu County as a series of four doses at 0 days, 7 days, 28 days and 12 months. After 1994, an inactive bivalent vaccine that consisted of HTNV and SEOV was provided as a series of three doses at 0 days, 14 days and 6 months. Both regimens were carried out according to the instructions of the commercial vaccine. The vaccine was provided to people aged 16–60 because the number of these people accounted for more than 80% of the total cases in China [21,22], and because the Pharmacopeia of People's Republic of China (2005) [23] specified that the vaccines could only be used in persons between 16 and 60 years of age. This vaccination program may decrease the proportion of HFRS cases among the targeted population and increase that in the non-vaccinated population.

2.3. Data collection and management

HFRS is a class B notifiable communicable disease in China and Hu County is one of the monitor sentinels for HFRS in China [24]. The annual records of HFRS cases and deaths in Hu during 1971–2011 and vaccination compliance during 1994–2011 were obtained from the Hu Center for Disease Control and Prevention (CDC). The HFRS cases were diagnosed using the national standard clinical criteria before 1982 [1]. After 1982, the HFRS cases were first diagnosed in the medical and health units of the county and then were laboratory-confirmed at the Hu CDC. Only a few sudden death cases were not laboratory confirmed. Both the annual population of all ages and those 16–60 years of age in Hu during 1971–2011 were collected from the Hu Bureau of Statistics in Hu. Population data was estimated using the annual records of household registration maintained by the local police departments. The vaccination compliance (VC) was calculated as follows:

$$VC = \frac{n}{N}$$

where n is the number of people that received the HFRS vaccination and N is the number of people between 16 and 60 years of age.

2.4. Secular trend analysis

The annual mortality and HFRS incidence rates between 1971 and 2011 as well as the annual HFRS vaccination compliance between 1994 and 2011 in Hu were calculated and plotted to show their annual fluctuations. The Cochran–Armitage trend test was employed to examine the temporal trends in the annual HFRS incidence, mortality rate and annual vaccination compliance. The index $Z > 0$ denoted an increasing trend, while $Z < 0$ denoted a declining trend. The trend was considered significant when P was <0.05. The Cochran–Armitage trend test was performed using SAS 9.2 (SAS Institute Inc., USA).

2.5. Temporal cluster analysis

A temporal cluster analysis of the HFRS epidemic between 1971 and 2011 was performed using the annual incidence data to detect the time periods of high HFRS risk. The procedure involves gradual scanning of a data window across time and noting the number of observed and expected observations inside each of the windows. For each scanning window of varying time, position and size, the risk of HFRS within and outside the window was tested by the likelihood ratio (LLR) test, with the null hypothesis being equal risk. The expression of LLR was calculated as follows:

$$LLR = \left(\frac{c}{E(c)}\right)^{c} \times \left(\frac{C-c}{C-E(c)}\right)^{C-c} \times I(\,)$$

where C is the total number of cases, c is the observed number of cases within the window, and $E(c)$ is the covariate adjusted