Age Distribution Changes of Hemorrhagic Fever with Renal Syndrome: an Implication of China’s Expanded Programme of Immunization

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Abstract

**Background:** The vaccine of hemorrhagic fever with renal syndrome (HFRS) has been applied successfully more than 20 years in China. Moreover, the government has implemented the Expanded Programme of Immunization (EPI) in regions with high incidence since 2008. In this study, we analyzed the EPI-related age distribution changes in reported cases and proposed new ideas for the prevention and control of HFRS.

**Methods:** Data of the HFRS region and age distribution were collected throughout the China Information System for Disease Control and Prevention (CISDCP) from 2005 to 2010. The Excel, SPSS 18.0 software, $\chi^2$ test and descriptive methodology were used for analysis.

**Results:** A total 75,434 HFRS cases were reported in 28 provinces in China between 2005 and 2010. The majority of HFRS cases occurred in adults aged 30 to 55 and account for 68.3% of the total. With the implementation of the immunization programme, HFRS age distribution has clearly changed in recent years. The proportion of HFRS cases among individuals targeted by EPI (16–60 years of age) decreased from 86.9% (2005) to 81.9% (2010). However, the proportion of non-vaccinated aged (<16 and >60) individuals have increased from 13.1% (2005) to 18.1% (2010). Notably, in the >60 age group the proportion rose from 8.8% in 2005 to 14.7% in 2010. The differences were statistically significant.

**Conclusion:** HFRS vaccination has played an important role in HFRS control and
prevention in China. However, since the proportion of HFRS cases over 60 years old increased significantly during EPI, it is recommended that the age limit for vaccination be reconsidered. This finding may have practical applications for more effective HFRS vaccination.

**Keywords:** Hemorrhagic Fever with Renal Syndrome, Expanded Program of Immunization, Age distribution
Background

Hemorrhagic fever with renal syndrome (HFRS) manifests in humans after infection with Hantavirus that is principally transmitted through contact with infected rodent excretions such as saliva, feces, and urine[1]. There are two main species of Hantavirus in China: Hantaan virus (HTNV) and Seoul virus (SEOV)[2]. China has reported over 1.5 million cases of HFRS since 1950[3]. Till the end of 2010, all provinces of China reported cases except Hainan province[4-6]. The annual number of cases was the highest in the world during the last two decades, accounting for approximately 90% of the total cases reported worldwide. But the number of HFRS cases in China has experienced a continued decline in recent years[5, 7]. By 2009, the nationwide number of reported cases (8842 cases) reached the lowest level in nearly two decades.

Aiming at two species of Hantavirus (HTNV and SEOV), an effective and safety bivalent HFRS vaccine was developed in the 1990s[8] and has been successfully applied[9-12]. In 2008, the HFRS-targeted Expanded Programme on Immunization (EPI) was implemented by China Central Government in order to reduce the HFRS incidence further. Free vaccine was provided to seven provinces with the highest incidence: Heilongjiang, Jilin, Liaoning, Shandong, Hebei, Shaanxi and Zhejiang. One year later, in 2009, HFRS rates were found to have significantly decreased in EPI regions, and the vaccination-based programme was further expanded to 10 other provinces: Hunan, Jiangxi, Inner Mongolia, Hubei, Henan, Jiangsu, Fujian, Anhui, Sichuan and Guangdong. As the number of cases aged between 16 and 60 account
for more than 80 percent of the total in China[13, 14], and because the Pharmacopoeia of People’s Republic of China (2005)[15] specified that the vaccines could only be used in persons between 16 and 60 years old, the programme was focusing on late adolescent to adult aged individuals (16–60 years old)[16]. However, the bivalent HFRS vaccine was also considered safety for other age group individuals[10].

In this study, we analyzed the reported HFRS case data from all 17 EPI regions and determined the age distribution changes between the targeted groups by EPI (16–60 years of age) and those non-targeted groups (<16 and >60 years of age).

Methods

Data collection and Statistical Analysis

HFRS, a rodent-borne viral disease caused by Hantaviruses, is characterized by fever, hemorrhagic manifestations and renal dysfunction[1, 2]. HFRS was classified as a Class B notifiable communicable disease of China in 1989; since then, the number of annual cases throughout the country has been recorded in the national health database and is available for epidemiologic study. In our study, the data were obtained from the China Information System for Disease Control and Prevention (CISDCP) and provincial monitoring reports of previous years. This system, established in 2004, is a web-based reporting system of nationally notifiable infectious diseases and public health emergencies throughout the country[17, 18]. The HFRS cases were diagnosed in the hospital or the local CDC according to the
Diagnostic Criteria for Epidemic Hemorrhagic Fever. Two types of cases were analyzed in our study: clinically diagnosed patients and laboratory confirmed cases. Clinical diagnosis criteria include: exposure history (i.e. direct or indirect exposure to rodents and their excreta and saliva within two months before onset of illness); acute onset with at least two clinical symptoms (i.e. symptoms of hemorrhagic fever, and one of hypotension, oliguresis or renal damage). Laboratory confirmed case diagnosis criteria were clinical diagnosis with one of the positive laboratory tests (HFRS IgM antibody positive, 4 fold rise of IgG antibody between acute and convalescent phage, Hantavirus RNA positive or Hantavirus was isolated in patients)[19]. Then the individual information of HFRS patients was reported via CISDCP according to the Nationwide Surveillance Programme for HFRS (try out)[20].

We obtained the following variables for HFRS cases from 2005 to 2010: gender, date of onset, date of birth and resident address. Analysis was carried out in Microsoft Excel. We calculated the age of onset by the patients’ dates of onset and dates of birth. Then we classed the data into <16 years, 16–60 years and >60 years age groups by different provinces. HFRS annual incidence per 100 000 population for the nation and each province were collected from the Annual Epidemic Report which is provided by CISDCP as the Summary Analysis of the Epidemic. Demographic data was collected from the Basic Information System which is one subsystem of CISDCP. The number of cases was evaluated by the χ2 test in SPSS software to determine the statistical significance of the differences in proportion observed before and after the introduction of the vaccine. Since the coverage of CISDCP was not fully extended to
the township level in some western parts of China, only 82.2% of township hospitals were covered in 2008[21]; now more than 85% are covered (not published). Some cases may not be reported, but the evaluations on the quality of the reporting system have shown that the rate of missing reports has been reduced as much as possible[22, 23].

Results

HFRS age distribution in China from 2005 to 2010

The total number of HFRS cases from 2005 to 2010 in China included in our analyses was 75,434. The cases were reported in 28 provinces, autonomous regions and municipalities; no cases were reported in Xizang autonomous regions, Qinghai or Hainan provinces in these six years. The ratio of male to female cases was approximately 3.15:1 (57,272/18,162); there was no change in recent years. The majority of HFRS cases occurred in adults aged 30 to 55 (68.3%; 51,527/75,434). This pattern was similar in all six years evaluated (Figure 1).

The proportion of HFRS cases among individuals targeted by EPI (16–60 years of age) was decreased with each year that the immunization programme was conducted (Table 1). The proportion of HFRS cases in the non-EPI-targeted (non-immunized) age group increased significantly during the EPI years.

The $\chi^2$ test results for HFRS annual number of cases of all provinces for the EPI-targeted and non-targeted age groups indicated that there was no significant difference for the years between 2005 and 2007 ($\chi^2 = 1.449, P = 0.485$), when the EPI
had yet to be implemented. In contrast, a significant difference was found when cases from any EPI year (2008–2010) were compared with those from any non-EPI year (2005–2007) ($\chi^2 = 51.095$, $P < 0.05$).

The data evaluated from 2005–2010 included two non-vaccination age groups: children and early- to mid-adolescents (<16 years), and older adults (>60 years). When the <16 age group HFRS cases were compared between non-EPI years (2005–2007) and EPI years (2008–2010), it was found that the numbers did not change significantly ($P = 0.142$). In contrast, the number of HFRS cases in the >60 age group was significantly different ($P<0.05$) between non-EPI and EPI years. HFRS cases in the older non-vaccinated population (>60 years) rose from 8.8% in 2005 to 14.7% in 2010.

When the nationwide HFRS cases were split among the high-incidence, EPI-targeted provinces and the low-incidence, non-EPI provinces and analyzed, it was found that the low-incidence provinces were characterized by a different age distribution pattern for the same period. The proportion of HFRS reported cases for the 16–60 age groups actually rose (from 82.9% in 2009 to 87.1% in 2010) in the non-EPI regions (Table 2).

**Analysis of high-incidence, EPI-targeted provinces**

Despite the implementation of EPI, HFRS cases have remained mainly concentrated in Northeast and East China, where the seven high-incidence provinces are located. In 2010, these seven provinces accounted for 74.3% (6978/9407) of the total cases
reported in China, changing very little from the other five years: 81.7% (2005, 17383/21281), 78.6% (2006, 12129/15429), 74.5% (2007, 8380/11248), 75.4% (2008, 6958/9227) and 72.2% (2009, 6380/8842).

Over the last three years the number of HFRS cases in Shaanxi province has steadily trended upward. In 2010, the total annual reported cases (2356) increased 65% over 2009 (1428), representing the highest number of HFRS cases in any year since 2005[5]. This might be induced partly by a periodic change of Zoonoses and some social or environmental factors. Like other high-incidence provinces, the proportion of cases in the 16–60 age groups has declined since 2008 when EPI was first implemented in Shaanxi. However, the proportion of HFRS cases among the >60 age group has been substantially higher than other high-incidence provinces. From 2009 to 2010 the HFRS cases in >60 year old Shaanxi residents increased by 67.2% (413 to 247) (Figure 2).

Heilongjiang, Jilin, Liaoning, Shandong, Hebei and Zhejiang provinces showed a steady decline in total HFRS cases since 2005, but the slope of this downward trend has decreased in recent years. Moreover, the incidence per 100 000 population in Liaoning, Shandong and Zhejiang provinces rebounded slightly in 2010. In each of these six provinces, the proportion of cases in 2010 among the respective 16–60 age groups decreased (ranging from 0.7% in Heilongjiang to a high of 8.1% in Shandong) and the proportion of cases in the >60 age groups increased (ranging from 26.7% in Zhejiang to 45.9% in Liaoning). The proportion of HFRS cases among the respective <16 age groups did not experience any obvious changes in the years examined.
Discussion

As a zoonose, HFRS shows periodic variation, which may be one of the reasons that the number of cases decreased in the years 2005-2007. HFRS also has been shown to be associated with geographical locale, employment type, living (hygienic) conditions and the rodent-vector[3, 24, 25]. The national implementation of a comprehensive prevention and control strategy, involving rodent control, environment management and vaccination, has corresponded to a remarkable decline in Chinese incidence of HFRS.

In order to reduce the incidence further, the EPI was applied since 2008. When the proportions of cases among the different HFRS age groups were analyzed, it was found that the age distribution changed in recent years in EPI regions. The group that was targeted by EPI (16–60 years of age) experienced a significant decrease in the proportion of HFRS cases for each year that EPI was implemented, suggesting that vaccination might have played a considerable role in China’s HFRS prevention and control. Further analysis revealed that the proportion of cases in children less than 16 years old was relatively unaffected during this period. Moreover, this stable profile remained when only the <16 years old, non-EPI-targeted HFRS cases were analyzed (<10 years old vs. 10–16 years old, for all years examined; data not shown).

We were intrigued to discover that the proportion of HFRS cases in the population over 60 years old in EPI-targeted provinces increased annually from 2008 to 2010. In
fact, Shandong province peaked with 20.2% of its HFRS cases in the >60 age group in 2010. In stark contrast, proportion over 60 years of age and residing in non-EPI-targeted provinces declined in 2010.

The observation that the proportion of HFRS cases over 60 years of age has risen in EPI-targeted regions may be explained by the following reasons. In recent years, more rural young people have travelled to the cities for work, increasing the field work time for the elderly who have stayed behind. The elderly then represent the population most in contact with rodents and potential transmission of Hantavirus. Likewise, the gradual extension of average life expectancy may have merely increased the proportion of individuals in the >60 age group who are still alive and working (and potentially coming into contact with Hantavirus). Another potential explanation may that China Pharmacopoeia defined the HFRS bivalent vaccine-target group as 16–60 years old, and over the dozen years since HFRS vaccination the current >60 years age group might not have been afforded sufficient opportunity for immunization.

Conclusions

The recent trend in the increasing proportion of HFRS cases in individuals over 60 years of age has occurred in regions undergoing rodent-based prevention strategies and environmental remediation and in which comprehensive public health education is widely available; unfortunately, these non-vaccine based eradication strategies are not sufficient to protect this population from HFRS. Therefore, we recommend that
the age limit for EPI vaccination be extended beyond 60 years old. It would be beneficial to HFRS control and prevention in China.

Competing interests

The authors declare that they have no competing interests.

Author’s contributions

HX and WS contributed equally to this work.

Acknowledgements

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References


**Table 1.** HFRS cases among EPI-targeted age group and non-targeted age group in 2005–2010 for all provinces in China

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases</th>
<th>16–60†</th>
<th>&lt;16</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>21,281</td>
<td>18,501 (86.9)</td>
<td>911 (4.3)</td>
<td>1,869 (8.8)</td>
</tr>
<tr>
<td>2006</td>
<td>15,429</td>
<td>13,479 (87.4)</td>
<td>566 (3.7)</td>
<td>1,386 (9.0)</td>
</tr>
<tr>
<td>2007</td>
<td>11,248</td>
<td>9,790 (87.0)</td>
<td>302 (2.7)</td>
<td>1,156 (10.3)</td>
</tr>
<tr>
<td>2008*</td>
<td>9,227</td>
<td>7,890 (85.5)</td>
<td>254 (2.8)</td>
<td>1,083 (11.7)</td>
</tr>
<tr>
<td>2009*</td>
<td>8,842</td>
<td>7,497 (84.8)</td>
<td>226 (2.6)</td>
<td>1,119 (12.7)</td>
</tr>
<tr>
<td>2010*</td>
<td>9,407</td>
<td>7,703 (81.9)</td>
<td>322 (3.4)</td>
<td>1,382 (14.7)</td>
</tr>
</tbody>
</table>

*Note.* *EPI conducted; †EPI-targeted. Data presented as% of total HFRS cases/yr.

**Table 2.** HFRS cases among EPI-targeted age group and non-targeted age group in 2005–2010 for Non-EPI and targeted for EPI provinces

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of cases</th>
<th>Incidence per 100,000</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>16-60 years of age</td>
<td>&lt;16 years of age</td>
</tr>
<tr>
<td></td>
<td>Population</td>
<td>2005</td>
<td>2006</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>Non-EPI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>provinces</td>
<td></td>
<td>669</td>
<td>432</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.22</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>614(91.8)</td>
<td>392(90.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21(3.1)</td>
<td>16(3.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34(5.1)</td>
<td>24(5.6)</td>
</tr>
<tr>
<td><strong>Provinces</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>targeted for</td>
<td></td>
<td>17 402</td>
<td>12 137</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.93</td>
<td>3.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 177(87.2)</td>
<td>10 680(88.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>742(4.3)</td>
<td>436(3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1483(8.5)</td>
<td>1021(8.4)</td>
</tr>
<tr>
<td><strong>EPI since 2008</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td>8374</td>
<td>6959</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.34</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7394(88.3)</td>
<td>5975(85.9)</td>
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<tr>
<td></td>
<td></td>
<td>208(2.5)</td>
<td>184(2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>772(9.2)</td>
<td>800(11.5)</td>
</tr>
<tr>
<td><strong>Provinces</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>targeted for</td>
<td></td>
<td>2644</td>
<td>2049</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.42</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2195(83.0)</td>
<td>1723(84.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84(3.2)</td>
<td>62(3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>365(13.8)</td>
<td>264(12.9)</td>
</tr>
</tbody>
</table>

*Note.* *Statistically significant decrease (p<0.05) in the number of cases from pre-vaccine years (2005-2007).* **Statistically significant decrease in the number of cases (p<0.05) from pre-vaccine years (2005-2008).
Figure 1. Age distribution of HFRS in China from 2005 to 2010.
Figure 2. Proportion of HFRS among different age groups and the incidence per 100,000 population of each province in seven EPI-target provinces from 2005 to 2010.