Original Article

Effectiveness of Hemorrhagic Fever with Renal Syndrome Bivalent Vaccine in China: A Meta-analysis

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Objective To evaluate the effectiveness of Hemorrhagic Fever with Renal Syndrome (HFRS) bivalent vaccine in field.

Methods The articles on effectiveness of HFRS bivalent vaccine were retrieved from Vip Database, China Journal Full-text Database, Wanfang database, China Hospital Knowledge Database, Chinese Biomedical Literature Database, MEDLINE and ProQuest. Two persons extracted data and evaluated the quality of data together for meta-analysis.

Results Seven articles were included into the analysis, and two articles were random clinical trials, five were quasi-trials. Meta-analysis showed that the overall effectiveness of HFRS bivalent vaccine was 85% (95% confidence interval: 53%-95%) within one year after vaccination, and the effectiveness in two-dose recipients and three-dose recipients was 87% (95% confidence interval: 54%-96%) and 60%, respectively; it was 96% (95% confidence interval: 78%-99%) within 2-5 years after vaccination, and the effectiveness in two-dose recipients and three-dose recipients was 95% (95% confidence interval: 19%-100%) and 96% (95% confidence interval: 70%-99%), respectively; it was 100% (only one article included) within 6-9.6 years after vaccination. The effectiveness in two-dose recipients was 88% (95% confidence interval: 62%-96%) during 1-2.5 years after vaccination, and that in three-dose recipients was 94% (95% confidence interval: 70%-99%) during 1-5 years after vaccination.

Conclusions HFRS bivalent vaccine is effective in field, and there is no difference between two-dose recipients and three-dose recipients. We should do some further studies on the long-term effectiveness of HFRS bivalent vaccine and on the age of vaccine reception.

Key words: HFRS; HFRS Bivalent Vaccine; Effectiveness; Meta-analysis

METHODS

Hemorrhagic Fever with Renal Syndrome (HFRS), a rodent-borne viral disease caused by different species of Hantaviruses, is one of the class B communicable diseases in Mainland China, which accounts for 90% of total HFRS cases worldwide.¹ The annual incidence rates (per 100 000 population) varied from 0.003 to 11.08, and the number of cases was over 110 000 in 1986.² At present, HFRS viruses in epidemic area are mainly mixture of Seoul virus and Hantaan virus. According to viruses, China uses HFRS bivalent vaccines to control and prevent this disease which may have played an important role in controlling HFRS. But the effectiveness of HFRS bivalent vaccines reported by some Chinese studies varied from 58.61% to 100%. To enhance customer confidence in HFRS vaccine, a meta-analysis on effectiveness of HFRS bivalent vaccine was conducted.

A review of articles was carried out by searching Vip Database, China Journal Full-text Database, Wanfang database, China Hospital Knowledge Database, Chinese Biomedical Literature Database, MEDLINE, ProQuest and their references of included papers from 1990 to 2010. HFRS bivalent vaccine or Epidemic Hemorrhagic Fever (EHF) bivalent vaccine (in Chinese and English) were the key words to search. First, we skimmed the titles and abstracts of the articles we found; then the inclusion of the studies was based on reading through the full-text. Only the studies used HFRS bivalent vaccine in human and gave raw information about effectiveness of HFRS bivalent vaccine were included into the analysis. Only articles of randomized clinical trials or quasi-trials were included in this analysis. Articles with scare information or incomplete data or review articles were excluded. The effectiveness of HFRS bivalent vaccine was calculated with the following formula: $(1 - \text{relative risk}) \times 100\%$.

HFRS cases were diagnosed with HFRS diagnostic

criteria (GB/15996-1995). Both laboratory-confirmed cases and clinical cases were included in our study.

For quality control, two persons independently read the articles and extracted data. If there was a controversy, the articles included or not should be discussed by these two persons or consult experts. The articles that met the inclusion criteria were included and Excel and Review Manager 4.2 software were used to extract and analyze data for this meta-analysis.

RESULTS

Search results

Figure 1. Flowchart on selecting studies.

Table 1. Characteristics of eligible articles on HFRS bivalent vaccine effectiveness

No.	The year published	Leading author	Age (year)	Study site	Immunization schedule	Time of booster
1	2002	Zhang ZB ³	16-60	Junan of Shandong	0, 14 d	6 m
2	2002	Xing FK ⁴	15-60	Changping of Beijing	0, 7, 28 d	1 y
3	2006	Cai ZH ⁵	16-60	Xian of Shaanxi	0, 14 d	6 m
4	2006	Chen Yang ⁶	16-60	Fujian	0, 14 d	6 m
5	2007	Sun MY ⁷	16-60	Tangshan of Hebei	0, 14 d	/
6	2008	Han ZY ⁸	16-60	Tangshan and Qinghuangdao of Hebei	0, 14 d	/
7	2008	Xu JP ⁹	15-60	Jiande of Zhejiang	0, 7, 28 d	1 y

	Study design	Length of follow-up (year)	Incidence of vaccinated group (after vaccination)	Incidence of control group (before vaccination)	Effectiveness% (vaccine coverage)
1	random clinical trials (RCT)	1	0/10,787 (0/100,000)	9/11,625 (77.42/100,000)	100 (100)
2	quasi-trials	2	0/150,000 (0/100,000)	10/97,847 (10.22/100,000)	100
3	quasi-trials (self control)	1	107/496,042 (21.57/100,000)	258/495,152 (52.11/100,000)	58.61
4	quasi-trials (self control)	2.5	0/4279 (0/100,000)	10/4279 (233.70/100,000)	100
5	quasi-trials (self control)	1	0/18980 (0/100,000)	26/16,724 (155.47/100,000)	100 (85.04)
6	quasi-trials (self control)	1	9/47905 (18.79/100,000)	80/48,031 (166.56/100,000)	88.72
7	RCT	1 - 9.6	0/10,694 (0/100,000)	0-15/12,726 (0-117.87/100,000)	100

Notes: a: boosting was conducted in six months after routine immunization; b: boosting in one year after routine immunization.

According to the selection strategy, 129 articles were found in the first search with title and abstract screened. But only seven articles met our inclusion criteria (Figure 1).

Characteristics of articles included

Of seven articles, two were random clinical trials and five were quasi-trials and there was not allocation concealment reported. The articles were published between 2002 and 2008, and the study sites located in 6 provinces: Shandong, Shaanxi, Hebei, Zhejiang, Fujian and Beijing. From the seven included articles, the follow-up after vaccinating with HFRS bivalent

Review: analysis of HFRS bivalent vaccine effectiveness

Comparison: 01 intervention (vaccination with HFRS bivalent vaccine) group versus control group

Outcome: 02 analysis of HFRS bivalent vaccine effectiveness (within one year after vaccination)

Figure 2. Analysis on HFRS bivalent vaccine effectiveness within one year after vaccination.

Review: analysis of HFRS bivalent vaccine effectiveness

Comparison: 01 intervention (vaccination with HFRS bivalent vaccine) group versus control group

Outcome: 05 analysis of HFRS bivalent vaccine effectiveness (within 2-5 years after vaccination)

Figure 3. Analysis on HFRS bivalent vaccine effectiveness within 2-5 years after vaccination.

vaccine were between 1 and 9.6 years. The follow-up was 1 year in five articles, 2-3 years in two articles and from 1 year to 9.6 years only found in one article. The summary of the included studies can be found in Table 1.

These seven articles on HFRS vaccine effectiveness in the population aged 15-60 years or 16-60 years. Vaccines studied in this article were all HFRS bivalent vaccines produced by Hang zhou tian yuan. The routine immunization strategy was mainly two-dose immunization (0, 14 d) or three-dose immunization (0, 7, 28 d).

Effectiveness of HFRS bivalent vaccine within different follow-up time

Effectiveness of HFRS bivalent vaccine within one year after vaccination

Effectiveness data extracted from five articles^{3,5,7-9} (four articles on two-dose group, one article on three-dose group) within one year after vaccination was analyzed with meta-analysis software (Figure 2). Results showed that these five studies were heterogeneous ($\chi^2 = 20.07$, $P = 0.0005$), so a random effect model was applied. All

of the studies showed an effectiveness of the vaccine against HFRS (ranged between 58.61% and 100%). The overall effectiveness of the vaccine as calculated after pooling the raw data was 85% [95% confidence interval (CI):53%-95%], of which two-dose group and three-dose group were 87% (95% CI:54%-96%) and 60% (only one article included), respectively.

Effectiveness of HFRS bivalent vaccine at least two years after vaccination

Effectiveness data extracted from three articles^{4,6,9} (one article on two-dose group, two articles on three-dose group) within 2-5 years after vaccination was analyzed by meta-analysis software (Figure 3). Results showed that the three studies were homogenous ($\chi^2 = 0.07$, $P = 0.96$), so a fixed effect model was applied. The overall effectiveness of the vaccine as calculated after pooling the raw data was 96% (95% CI:78%-99%), of which two-dose group and three-dose group were 95% (95% CI: 19%-100%) and 96% (95% CI: 70%-99%), respectively.

Only one study reported the effectiveness of HFRS bivalent vaccine from 1 year to 9 years after vaccination. And no other studies with over five years

Review: analysis of HFRS bivalent vaccine effectiveness

Comparison: 01 intervention (vaccination with HFRS bivalent vaccine) group versus control group

Outcome: 06 effectiveness of two-dose routine immunization regimen

Figure 4. Analysis on HFRS bivalent vaccine effectiveness of two-dose routine immunization.

Review: analysis of HFRS bivalent vaccine effectiveness

Comparison: 01 intervention (vaccination with HFRS bivalent vaccine) group versus control group

Outcome: 07 effectiveness of three-dose routine immunization regimen

Figure 5. Analysis on HFRS bivalent vaccine effectiveness of three-dose routine immunization.

follow-up after vaccination were found out.

Effectiveness of HFRS bivalent vaccine with different routine immunization strategies

Effectiveness of HFRS bivalent vaccine with two-dose regimen

Effectiveness data extracted from five articles was analyzed with meta-analysis software (Figure 4). Results showed that the five studies were heterogeneous ($\chi^2 = 22.28$, $P = 0.0002$), so a random effect model was applied. All of the studies showed an effectiveness of the vaccine against HFRS (ranged between 58.61% and 100%). The overall effectiveness of the vaccine as calculated after pooling the raw data was 88% (95% CI: 62%-96%) within 1-2.5 years after vaccination.

Effectiveness of HFRS bivalent vaccine with three-dose regimen

Effectiveness data extracted from two articles was analyzed with meta-analysis software (Figure 5). Results showed that the five studies had homogeneity

($\chi^2 = 1.55$, $P = 0.46$), so a fixed effect model was model was applied. The overall effectiveness of the vaccine as calculated after pooling the raw data was 94% (95% CI, 70%-99%) within 1-5 years after vaccination.

DISCUSSION

HFRS is one of the class B communicable diseases which required to be reported through the China Information System for Disease Control and Prevention. Case numbers of HFRS showed a decreasing trend in recent years.^{10,11} HFRS vaccine immunization may have played an important role in incidence decreasing.¹¹ As time going on, co-circulation of Hantaan viruses and Seoul viruses exists in most of the HFRS epidemic areas and areas only with Hantaan viruses or Seoul viruses do not exist.^{12,13} As HFRS monovalent vaccine can not meet the requirements of disease prevention and control, it was gradually replaced by HFRS bivalent vaccine. HFRS bivalent vaccine was licensed in the

1990s in China,¹³ which provides a convenient and effective way for HFRS control.

From the published articles,^{6-9,12,13} the effectiveness of HFRS bivalent vaccine was 58.61%-100%. The difference may come from vaccine coverage, geographic region, population under study and the time after vaccination. This study indicated that HFRS bivalent vaccine had good short- and mediate-term protective effect. The effectiveness of two-dose group and three-dose group were 88% (95% CI, 62%-96%) and 94% (95% CI, 70%-99%), respectively.

The vaccines coverage of the target population in the included studies were different, of which the highest was 100% and the lowest was 35.4%.⁶ For HFRS is a kind of vector-borne disease, we should consider the vaccine coverage when assessing HFRS vaccine's effectiveness.

In addition, the maximum incubation period of HFRS may last for 45 days and HFRS cases may be found around the whole year. Although vaccines are required to be administrated before peak season, patients within the incubation period may be diagnosed through clinical or laboratory tests after vaccination, which will affect the effectiveness calculation. So, we should remove HFRS cases appearing during one maximum incubation period after inoculation when vaccine protective effect assessment is carried out. Indeed, at present, we can not find the onset time of HFRS disease in the studies of vaccine effect assessment.

Furthermore, most studies only compared incidence before and after vaccination, and only two studies were random clinical trials.

In this study, we found that studies on effectiveness of HFRS bivalent vaccine were rare and study design varies. Of these studies, only two used random sampling method on choosing vaccinated group and control group. The long-term follow-up on effectiveness after vaccination was rarer and cost-effectiveness analysis in detail was rare, too.

Recently, the proportion of HFRS cases under 16 and over 60 years of age increased gradually. This may stem from the lack of protection conferred by vaccination since they are beyond the age of receiving vaccine. Thus it is urgent to investigate whether it is necessary to expand eligible age groups for vaccination.

In summary, it is important to further evaluate HFRS vaccine effectiveness in the era of free vaccine available, in order to provide information for HFRS control and potential recommendation change.

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