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ARTICLE

Effectiveness of the HFRS Bivalent Vaccine in Field Settings: A Meta-Analysis of Vaccination Studies

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Abstract

Hemorrhagic fever with renal syndrome (HFRS) is a severe disease caused by Hantavirus infection. The objective of this study was to evaluate the effectiveness of the HFRS bivalent vaccine in field settings. Relevant articles were retrieved from multiple databases, and data extraction and quality evaluation were performed for meta-analysis. Seven articles, including two randomized clinical trials and five quasi-trials, were included in the analysis.

Meta-analysis results revealed that the overall effectiveness of the HFRS bivalent vaccine was 85% (95% confidence interval: 53%-95%) within one year after vaccination. The effectiveness in recipients of two doses and three doses was 87% (95% confidence interval: 54%-96%) and 60%, respectively. Within 2-5 years after vaccination, the effectiveness was 96% (95% confidence interval: 78%-99%), with a similar efficacy in two-dose recipients (95%; 95% confidence interval: 19%-100%) and three-dose recipients (96%; 95% confidence interval: 70%-99%). For the 6-9.6 year period after vaccination, the effectiveness was 100% based on one included article.

Moreover, during 1-2.5 years after vaccination, the two-dose recipients exhibited an effectiveness of 88% (95% confidence interval: 62%-96%), while three-dose recipients showed 94% efficacy (95% confidence interval: 70%-99%) within 1-5 years after vaccination.

In conclusion, the HFRS bivalent vaccine demonstrates effectiveness in field settings, with no significant difference observed between two-dose and three-dose recipients. Further studies are warranted to assess the long-term effectiveness of the vaccine and determine the optimal age for vaccination.

Introduction

Hemorrhagic Fever with Renal Syndrome (HFRS) is a significant communicable disease in Mainland China, responsible for the majority of HFRS cases worldwide. It is caused by various species of Hantaviruses transmitted by rodents (Hang et al., 2006). The incidence rates of HFRS in China have shown considerable variation, ranging from 0.003 to 11.08 cases per 100,000 population, with over 110,000 cases reported in 1986 (Zhang et al., 2004). Currently, the predominant viruses causing HFRS in epidemic areas of China are a mixture of Seoul virus and Hantaan virus. In an effort to control and prevent this disease, China has implemented the use of the HFRS bivalent vaccine, which has played a crucial role in mitigating the

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impact of HFRS outbreaks. However, studies evaluating the effectiveness of HFRS bivalent vaccines in China have reported varying efficacy rates, ranging from 58.61% to 100%. To address this variability and provide a comprehensive assessment of the vaccine's effectiveness, a meta-analysis was conducted to evaluate the efficacy of the HFRS bivalent vaccine, aiming to enhance public confidence in its efficacy and value.

Methods

A comprehensive review of relevant articles was conducted by searching multiple databases, including Vip Database, China Journal Full-text Database, Wanfang database, China Hospital Knowledge Database, Chinese Biomedical Literature Database, MEDLINE, and ProQuest. The search encompassed articles published from 1990 to 2010. The key search terms used were "HFRS bivalent vaccine" or "Epidemic Hemorrhagic Fever bivalent vaccine" in both Chinese and English languages. Initially, titles and abstracts of the identified articles were screened, followed by a thorough examination of the full-text articles for inclusion. Only studies that utilized the HFRS bivalent vaccine in human subjects and provided raw information regarding its effectiveness were eligible for inclusion in the analysis. Specifically, only articles reporting randomized clinical trials or quasi-trials were considered for this analysis, while articles with insufficient or incomplete data, as well as review articles, were excluded. The effectiveness of the HFRS bivalent vaccine was calculated using the formula: (1 - relative risk) × 100%.

Diagnosis of HFRS cases was based on the HFRS diagnostic criteria (GB/15996-1995), encompassing both laboratory-confirmed cases and clinically diagnosed cases. To ensure the quality and accuracy of data extraction, two independent reviewers conducted the assessment and extraction process. In case of any discrepancies or disagreements, the reviewers would discuss the articles in question or seek expert consultation to reach a consensus. Only articles meeting the predetermined inclusion criteria were included in the analysis. Data extraction and analysis were performed using Excel and Review Manager 4.2 software, respectively, for conducting the meta-analysis.

Results

1. Search Results

A total of 129 articles were initially identified through the search of title and abstract using the selection strategy. However, after careful evaluation, only seven articles met the inclusion criteria for analysis (Figure 1).

2. Characteristics of Included Articles

Among the seven articles included in the analysis, two were random clinical trials, while the remaining five were quasi-trials. None of the articles reported allocation concealment. The publication dates of the articles ranged from 2002 to 2008, and the studies were conducted in six provinces across China, namely Shandong, Shaanxi, Hebei, Zhejiang, Fujian, and Beijing. The follow-up periods after vaccination with the HFRS bivalent vaccine ranged from 1 to 9.6 years, with five articles having a follow-up of 1 year, two articles having a follow-up of 2-3 years, and one article having a follow-up of 1-9.6 years.

The studies included in this analysis focused on the effectiveness of the HFRS bivalent vaccine in individuals aged 15-60 years or 16-60 years. All the vaccines studied were HFRS bivalent vaccines produced by Hangzhou Tian Yuan. The routine immunization strategy primarily involved either a two-dose immunization schedule (0, 14 days) or a three-dose immunization schedule (0, 7, 28 days).

Table 1 provides a summary of the included studies.

3. Effectiveness of HFRS Bivalent Vaccine at Different Follow-up Times

3.1 Effectiveness of HFRS Bivalent Vaccine within One Year after Vaccination

Data on the effectiveness of the HFRS bivalent vaccine within

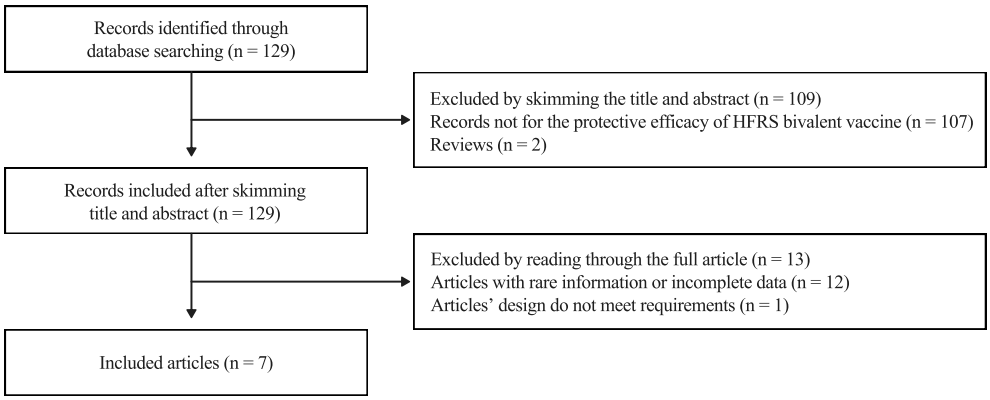

Figure 1. Flow chart on selecting studies

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

S/N	The year published	Leading author	Age	Study site	Immunization schedule	Time of booster
1	2002	Zhang Zunbao[3]	16-60	Junan of Shandong	0,14d	6m(#1)
2	2002	Xing Fukun[4]	15-60	Changping of Beijing	0,7,28d	1y
3	2006	Cai Zhenghua[5]	16-60	Xian of Shanxi	0,14d	6m
4	2006	Chen Yang[6]	16-60	Fujian	0,14d	6m
5	2007	Sun Mingyou[7]	16-60	Tangshan of Hebei	0,14d	/
6	2008	Han Zhanying[8]	16-60	Tangshan and Qinghuangdao of Hebei	0,14d	/
7	2008	Xu Jiaoping[9]	15-60	Jiande of Zhejiang	0,7,28d	1y(#2)

S/N	Study design	Length of follow-up	Incidence of vaccinated group (after vaccination)	Incidence of control group (before vaccination)	Time of booster
1	random clinical trials(RCT)	1 year	0/10787(0/100000)	9/11625(77.42/100000)	100(100)
2	quasi-trials	2 years	0/150000(0/100000)	10/97847(10.22/100000)	100
3	quasi-trials (self control)	1 year	107/496042(21.57/100000)	258/495152(52.11/100000)	58.61
4	quasi-trials(self control)	2.5 years	0/4279(0/100000)	10/4279(233.70/100000)	100
5	quasi-trials(self control)	1 year	0/18980(0/100000)	26/16724(155.47/100000)	100(85.04)
6	quasi-trials(self control)	1 year	9/47905(18.79/100000)	80/48031(166.56/100000)	88.72
7	RCT	1-9.6 years	0/10694(0/100000)	0-15/12726(0-117.87/100000)	100

Notes: #1 boostering was conducted in six months after routine immunization; #2 boostering in one year after routine immunization.

one year after vaccination were extracted from five articles (Zhang et al., 2002; Cai et al., 2006; Sun et al., 2007; Han et al., 2008; Xu et al., 2008), with four articles focusing on the two-dose group and one article on the three-dose group. Meta-analysis of these studies using appropriate software (Figure. 2) revealed heterogeneity among the studies (χ^2 = 20.07, P = 0.0005), thus a random effect model was applied. All studies reported vaccine effectiveness against HFRS, ranging from 58.61% to 100%. The overall effectiveness of the vaccine, as calculated by pooling the raw data, was 85% (95% confidence interval [CI]: 53%-95%). The effectiveness for the two-dose group was 87% (95% CI: 54%-96%), while the effectiveness for the three-dose group (based on one article) was 60%.

3.2 Effectiveness of HFRS Bivalent Vaccine at Least Two Years after Vaccination

Data on the effectiveness of the HFRS bivalent vaccine within 2-5 years after vaccination were extracted from three articles (Xing et al., 2002; Chen et al., 2006; Xu et al., 2008), with one article focusing on the two-dose group and two articles on the three-dose group. Meta-analysis of these studies using appropriate software (Figure. 3) revealed homogeneity among the studies (χ^2 = 0.07, P = 0.96), thus a fixed effect model was applied. The overall effectiveness of the vaccine, as calculated by pooling the raw data, was 96% (95% CI: 78%-99%). The effectiveness for the two-dose group was 95% (95% CI: 19%-100%), while the effectiveness for the three-dose group was 96% (95% CI: 70%-99%).

Notably, only one study reported the effectiveness of the HFRS bivalent vaccine from 1 year to 9 years after vaccination, and no other studies with follow-up periods exceeding five years after vaccination were found.

3.3 Effectiveness of HFRS Bivalent Vaccine with Different Routine Immunization Strategies

1)Effectiveness of HFRS Bivalent Vaccine with Two-Dose Regimen

Data on the effectiveness of the HFRS bivalent vaccine with a two-dose regimen were extracted from five articles and analyzed using appropriate software (Figure. 4). The studies demonstrated heterogeneity (χ^2 = 22.28, P = 0.0002), thus a random effect model was applied. All studies reported vaccine effectiveness against HFRS, ranging from 58.61% to 100%. The overall effectiveness of the vaccine, as calculated by pooling the raw data, was 88% (95% CI: 62%-96%) within 1-2.5 years after vaccination.

2)Effectiveness of HFRS Bivalent Vaccine with Three-Dose Regimen

Data on the effectiveness of the HFRS bivalent vaccine with a three-dose regimen were extracted from two articles and analyzed using appropriate software (Figure. 5). The studies exhibited homogeneity (χ^2 = 1.55, P = 0.46), thus a fixed effect model was applied. The overall effectiveness of the vaccine, as calculated by pooling the raw data, was 94% (95% CI: 70%-99%) within 1-5 years after vaccination.

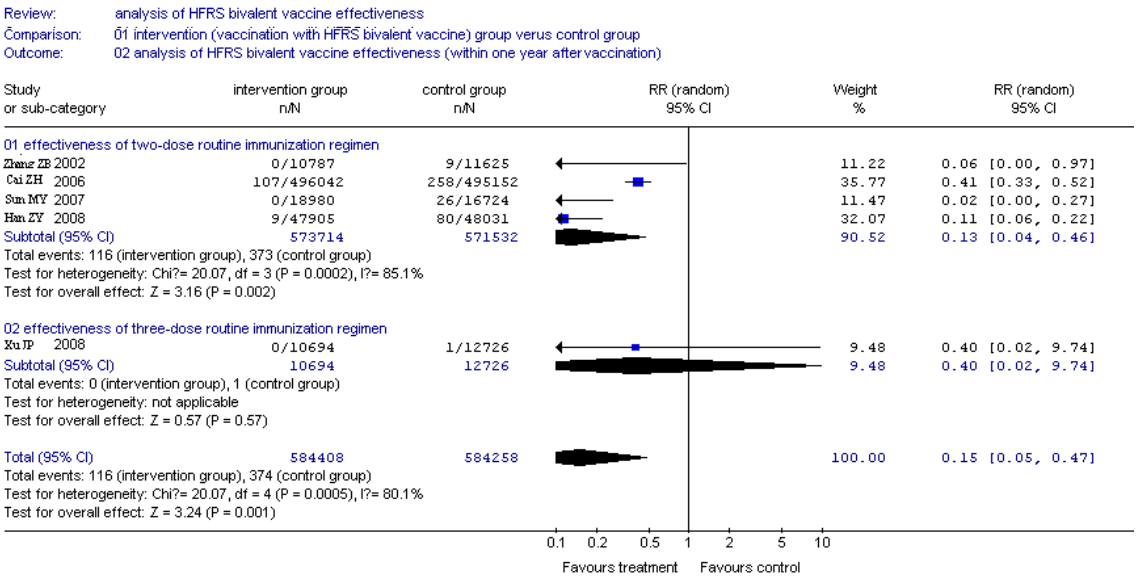

Figure 2. Analysis on HFRS bivalent vaccine effectiveness within one year after accination

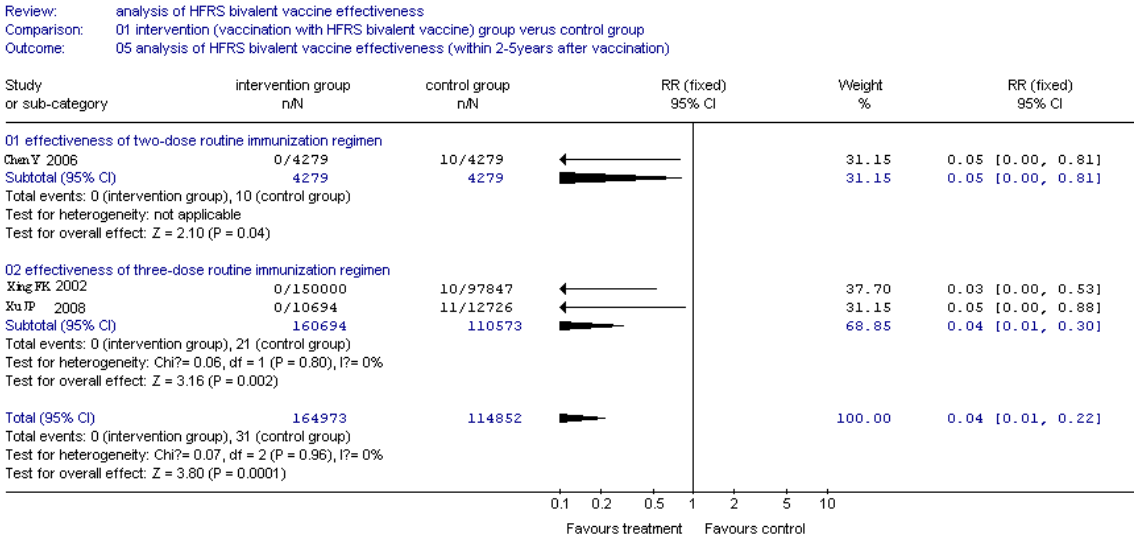

Figure 3. Analysis on HFRS bivalent vaccine effectiveness within 2-5 years after vaccination

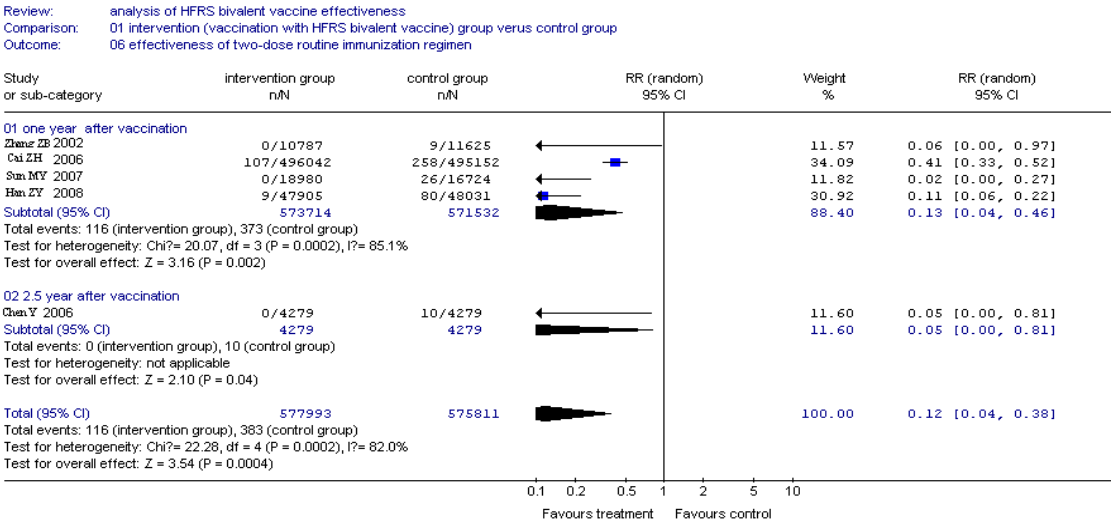

Figure 4. Analysis on HFRS bivalent vaccine effectiveness of two-dose routine immunization

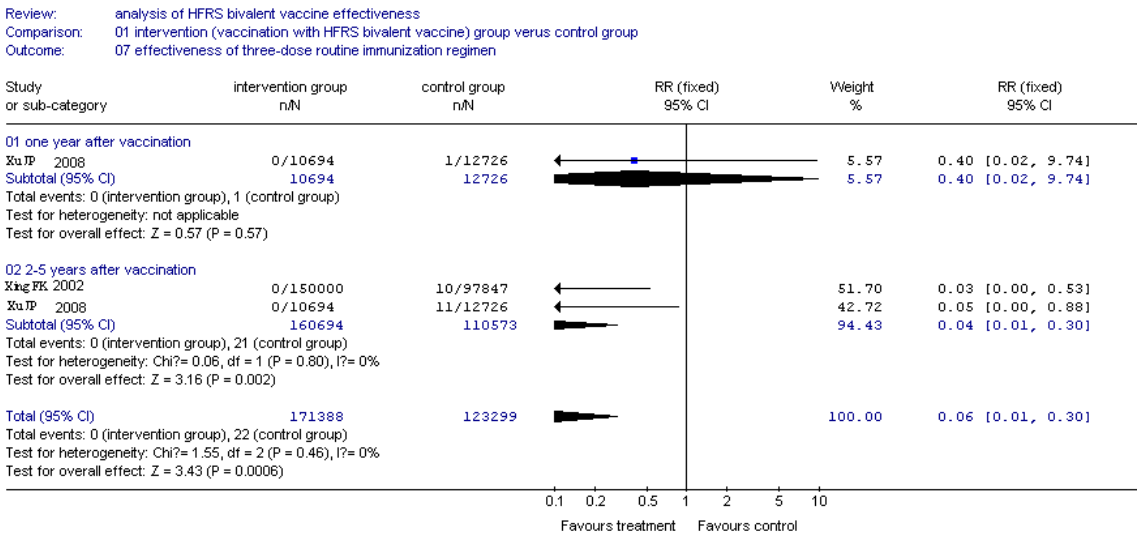

Figure 5. Analysis on HFRS bivalent vaccine effectiveness of three-dose routine immunization

Discussion

Hemorrhagic Fever with Renal Syndrome (HFRS) is classified as a class B communicable disease that requires reporting through the China Information System for Disease Control and Prevention. Recent studies have shown a decreasing trend in HFRS cases, and it is suggested that HFRS vaccine immunization has played a crucial role in this decline. Co-circulation of Hantaan viruses and Seoul viruses has been observed in most HFRS epidemic areas, while areas with only one of these viruses are rare. As the HFRS monovalent vaccine is unable to meet the requirements for disease prevention and control, it has been gradually replaced by the HFRS bivalent vaccine, which was licensed in the 1990s in China, providing a convenient and effective way to control HFRS (Wang et al., 2014; Fang et al., 2004; Cao et al., 2003).

The effectiveness of the HFRS bivalent vaccine reported in published articles has ranged from 58.61% to 100%, which can be attributed to factors such as vaccine coverage, geographic region, population under study, and the duration after vaccination (Chen et al., 2006; Sun et al., 2007; Han et al., 2008; Xu et al., 2008; Fang et al., 2004; Cao et al., 2003). The present study reveals that the HFRS bivalent vaccine demonstrates a favorable short- and medium-term protective effect. The effectiveness of the two-dose group and three-dose group were found to be 88% (95% CI: 62%-96%) and 94% (95% CI: 70%-99%), respectively.

Vaccine coverage among the target population varied across the included studies, ranging from 100% to as low as 35.4% (Chen et al., 2006). Since HFRS is a vector-borne disease, assessing the effectiveness of the vaccine necessitates considering the vaccine coverage. Additionally, HFRS has a maximum incubation period of up to 45 days, and cases can be identified throughout the year. While vaccines are administered before the peak season, individuals within the incubation period may still be diagnosed with the disease through clinical or laboratory tests after vaccination, thus affecting the calculation of effectiveness. Therefore, it is crucial to exclude HFRS cases that occur within one maximum incubation period after vaccination when assessing the vaccine's protective effect. Unfortunately, the onset time of HFRS disease is often not recorded in studies evaluating vaccine effectiveness.

Furthermore, most studies only compared the incidence before and after vaccination, with only two studies employing a randomized clinical trial design. In this study, we found a scarcity of research on the effectiveness of the HFRS bivalent vaccine, with variations in study designs. Only two studies utilized random sampling methods to select vaccinated and control groups. Long-term follow-up assessments of vaccine effectiveness were infrequent, as were detailed cost-effectiveness analyses.

Recently, there has been a gradual increase in the proportion of HFRS cases among individuals under 16 and over 60 years of age. This could be attributed to the lack of protection conferred by vaccination in these age groups, as they are beyond the eligible age for vaccination. Thus, it is essential to investigate the necessity of expanding the eligible age groups for vaccination.

In conclusion, in the era of freely available HFRS vaccines, it is crucial to further evaluate the effectiveness of the HFRS bivalent vaccine. This evaluation will provide valuable information for HFRS control strategies and potential recommendations for vaccination adjustments.

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