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The protective efficacy of inactivated vaccine against hemorrhagic fever with renal syndrome
A meta-analysis

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Abstract

Background: Hemorrhagic fever with renal syndrome (HFRS) is a kind of natural epidemic diseases with rodents as the main source of infection. The main clinical manifestations of HFRS are fever, hemorrhage, congestion, hypotensive shock and kidney damage. Some studies showed that vaccination populations in infected areas with inactivated vaccines can reduce the incidence of the disease, but there are variations in protection rates among these studies. The aim of this study is to systematically evaluate the protective effect of inactivated vaccines against HFRS.

Methods: Web of Science, PubMed, SinoMed, Proquest, China National Knowledge Infrastructure Database, Wanfang Database, VIP Database were searched from their inception to December 2024. Newcastle-Ottawa Scale (NOS) was used to assess the quality of evidence, and a random-effects meta-analysis was done to calculate pooled risk ratios for vaccination uptake. All the relevant data were analyzed by using STATA 15.0.

Results: A total of 15 articles were included, all of which explicitly reported the total number of vaccinated and unvaccinated people in the vaccination group, and the number of cases that developed during the observation period. Six of these articles reported positive antibody transfer rates. The protection rate of the inactivated HFRS vaccine reached 86%, and a subgroup analysis showed that there was a significant difference in the protection rate of the inactivated vaccine between Korea and China. The positive IgG antibody transfer rate was 97%, and neutralizing antibody transfer rate was 37%.

Conclusion: The results indicated that inactivated vaccine has a good protective effect against HFRS and should be universally administered to populations in high prevalence areas to control the harm caused by HFRS epidemics.

Abbreviations: ANDV = Andes virus, DOBV = Dobrava virus, HCPS = Hantavirus pulmonary syndrome, HFRS = hemorrhagic fever with renal syndrome, HTNV = Hantaan virus, PUUV = Puumala virus, SNV = Sin Nombre virus.

Keywords: inactivated vaccination, meta-analysis, protection rate, vaccine effectiveness

1. Introduction

Hemorrhagic fever with renal syndrome (HFRS), also known as epidemic hemorrhagic fever, is caused by hantaviruses (family Bunyaviridae), with rodents serving as the primary transmission source.[1] Hantavirus infection can cause hantavirus cardiopulmonary syndrome (HCPS) and hemorrhagic fever renal syndrome (HFRS), driven by complex biogeographic and anthropogenic environmental pressures, HFRS is mainly caused by Old World viruses like Hantaan virus (HTNV), Puumala virus (PUUV), and Dobrava virus (DOBV), but HCPS is usually the result of infection by New World viruses such as Andes virus (ANDV) and Sin Nombre virus.[2,3] Hantaviruses are responsible for an estimated 200,000 human infections annually worldwide. The case fatality rate ranges from 5% to 15% for HFRS and can reach up to 40% for HCPS.[4] China has the highest morbidity rate of hantavirus infection, accounting for more than 90% of the total number of HFRS cases worldwide.[2] Currently, there is no specific therapy for HFRS,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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and clinical treatment is mainly based on the replication process of the virus or in response to the progression of the disease at each stage.[5,6] Therefore, the development of safe and effective vaccines to inoculate populations in infected areas is currently the most effective strategy to control hemorrhagic fever epidemic.[7] Now types of vaccines include inactivated vaccines, DNA vaccines, subunit vaccines, and viral particle-like vaccines, but only inactivated vaccines have been applied to human beings, while the other vaccines are currently in the clinical trial stage.[8]

Inactivated hantavirus vaccine (IHV) is manufactured by means of inactivating the virus with either aluminum adjuvant or formalin, this makes the virus lose its ability to infect people and keeps only its ability to trigger an immune response.[9,10] But it is currently widely used only in China, South Korea, and North Korea, where it plays an important role in the prevention of hemorrhagic fever.[11] Current studies on HFRS vaccines primarily evaluate protective effects through immunogenicity indicators (e.g., seroconversion rate, antibody titers) and safety (e.g., adverse reactions). However, this study focuses on the vaccine effectiveness (VE) of IHV, which compares HFRS incidence between vaccinated and unvaccinated populations. IHV has several advantages. Firstly, since the pathogens in inactivated vaccines have been completely inactivated, eliminating the possibility of regaining virulence through mutation or replication errors, as can occur with live-attenuated vaccines, thus making these vaccines safer for immunocompromised individuals; Secondly, immunization with inactivated vaccines can mitigate disease severity in patients with HFRS; Furthermore, studies have shown that patients vaccinated with IHV are significantly less likely to develop acute kidney injury.[5,11] A retrospective study implemented in 1 Korean army found that the VE value of 3-stage inactivated vaccine reached 58.1%;[5] QING W et al reported the VE was 74.88% in vaccinated population aged 60 to 70 years in Shaanxi Province,[12] Conversely, a study conducted in Longquan City reported a significantly higher rate of 94.28%.[13] In other countries, inactivated vaccines are currently undergoing clinical trials. For instance, Dzagurova et al developed a multivalent inactivated vaccine based on 3 viral strains: PUU-TKD/VERO, HTN-P88/VERO, and DOB-SOCHI/VERO. This multivalent formulation demonstrated comparable immunogenicity against all 3 target viruses. It was found that the use of low-toxicity lipopolysaccharides in the vaccine may increase the long-term immunization effect.[4]

Overall, there is currently insufficient systematic evaluation of the protective effect of inactivated vaccines to clarify the degree of their importance in the prevention and control of HFRS, and more attention has been paid abroad to how to modify DNA vaccines to improve the effect on human humoral and cellular immunity.[14] This large difference in VE may be caused by the region of the vaccinated population or the sample size.[15] In order to understand the effect of HFRS vaccines on population protection rate impact, we conducted a meta-analysis based on published studies with the aim of providing a comprehensive analysis of existing studies to support the promotion of immunization.

Although inactivated vaccines are now continuing to be developed in various countries, only whole-virus inactivated vaccines against HTNV or SEOV have been approved for use in Korea and China, but protective effects of these vaccines are remaining uncertain.[1] This is a discrepancy caused by different geographical areas of research, and the purpose of this study is to conduct a meta-analysis of existing studies. Meanwhile, we comprehensively evaluate protective effects of inactivated vaccines in patients with hemorrhagic fever renal syndrome and to provide a reference for the improvement of vaccination program for HFRS.

2. Materials and methods

2.1. Search strategy

As of December 17, 2024, systematic searches were conducted in Web of Science, PubMed, SinoMed, Proquest, China National Knowledge Infrastructure Database, Wanfang Database, VIP Database. Search terms are combined in "HFRS," "Hemorrhagic Fever with Renal Syndrome," "Epidemic Hemorrhagic Fever," "effect," "protect," "vaccine," "VE", "control." There was no language restriction in the literature search. Relevant reviews and the reference list of the included articles were also checked to search for additional studies.

2.2. Selection criteria

In this study, inclusion of studies must be based on 1 or more of the followings items were adopted for the diagnosis of HFRS: serum-specific IgM positivity or recovery serum IgG antibody titers that are more than 4 times higher than in the acute phase; detection of viral RNA in patient specimens or isolation of hantaviruses from patient specimens; study type was prospective or retrospective study, either case-control or cohort study; studies that involve a history of vaccination, as well as a total number of people in the vaccination group and the number of people in the control group and cases in each group during the observation period. Studies were excluded if they met any of the following criteria: duplicates or non-duplicates but using the same database; conferences, reviews, or case reports; data not mentioned or could not be calculated.

2.3. Data extraction or quality assessment

All included articles were carefully reviewed and screened by 2 independent reviewers. The assessment was completed by 2 reviewers independently, and the discrepancy was resolved by consulting a third reviewer. Data information extracted included first author, time of publication, study area, basic information about the population, type of study, total number of people in the inoculation group and number of people in the control group, and the number of morbidities in each of the 2 groups during the observation period.

All of included studies were evaluated using the Newcastle-Ottawa Scale (NOS). Case-control studies were evaluated based on following domains: selection of study subjects, comparability between groups, and exposure, and cohort studies evaluated in terms of selection of study subjects, comparability between groups, and outcome, with a total of 9 stars on the scale, with 0 to 3 stars being low quality, 4 to 6 stars for medium quality, and 7 to 9 stars for high quality.[16]

2.4. Statistical analyses

The extracted data were tested for heterogeneity using Stata 15.0, and a fixed-effects model ($P > .05$ and $I^2 < 50\%$) or a random-effects model ($P < .05$ or $I^2 \geq 50\%$) was selected based on the test results, a forest plot was drawn to calculate the combined OR value and VE value, and 95% confidence interval, with VE = (1-OR) × 100%. Funnel plots were plotted to initially assess publication bias, and then the symmetry of the funnel plots was tested using the Egger test to further determine the presence of publication bias. Sensitivity analysis was plotted to determine the stability of the results.

2.5. Ethical statement

This study was a meta-analysis of previously published data and did not involve the collection of personal information and humans, and institutional review board review (IRB) was waived for this study.

3. Results

3.1. Selection of study

After using the search, a total of 1807 studies were retrieved, of which 635 were duplicates, of which 1172 remained after deletion. 1073 irrelevant articles were excluded after reading article titles and abstracts, and the remaining 99 were excluded after reading through the full text and quality assessment of 84 articles, resulting in 15 studies included in the analysis (Fig. 1).

Of these 15[12,17–30] articles included, only 2 were foreign and both were from Korea, while the remaining 10 were from China. Both of the 2 Korean articles were published in English and both were implemented as matched case-control studies in the Korean military. Twelve of the thirteen articles published in Chinese included people aged 16 to 60 years old, and only 1 article from Hu Yi District, Shaanxi Province, did the study in people aged 60 to 70 years old.[12] The methodological quality of these included studies in this study was strong, as evidenced by the fact that 4 of the included articles received 7 stars and 11 received 6 stars after the NOS scale rating (Table 1).

3.2. Overall protection rate of inactivated vaccines

Of the 15 studies included, there were cases 591HFRS patients, 47 of whom were vaccinated, with 12 studies reporting vaccine protection rates of more than 90% and 2 Korean studies reporting VE values of around 50%. According to the results obtained from Stata analysis, a random-effects model with an OR = 0.14, 95% CI of (0.07–0.30), and an overall protection rate of 86%, with a 95% CI of (70%, 93%), was selected for meta-analysis based on the Stata analysis results, which showed significant heterogeneity of studies ($P = .001$, $I^2 = 60.3\%$) (Fig. 2).

3.3. Publication bias

Egger test was performed to assess publication bias and the funnel plot symmetry was examined. Funnel plot indicated little publication bias on average (Fig. 3). Egger test showed that $P < .001$, indicating the likelihood of publication bias. Given that the presence of publication bias may affect the credibility of the results of this study and make them unstable, the trim and filling approach was employed to observe the bias (Fig. 4).

After 2-step iterative operation, the funnel plot demonstrated the absence of both the spurious supplementation of potentially missing literature and the trimming of the extant results, and finally combined results were the same as the previous. Eventually, the combined outcomes remained consistent with the previous ones. In conjunction with the sensitivity analysis plot, this implies that publication bias exerted no substantial influence on the study's findings, thereby rendering the results robust.

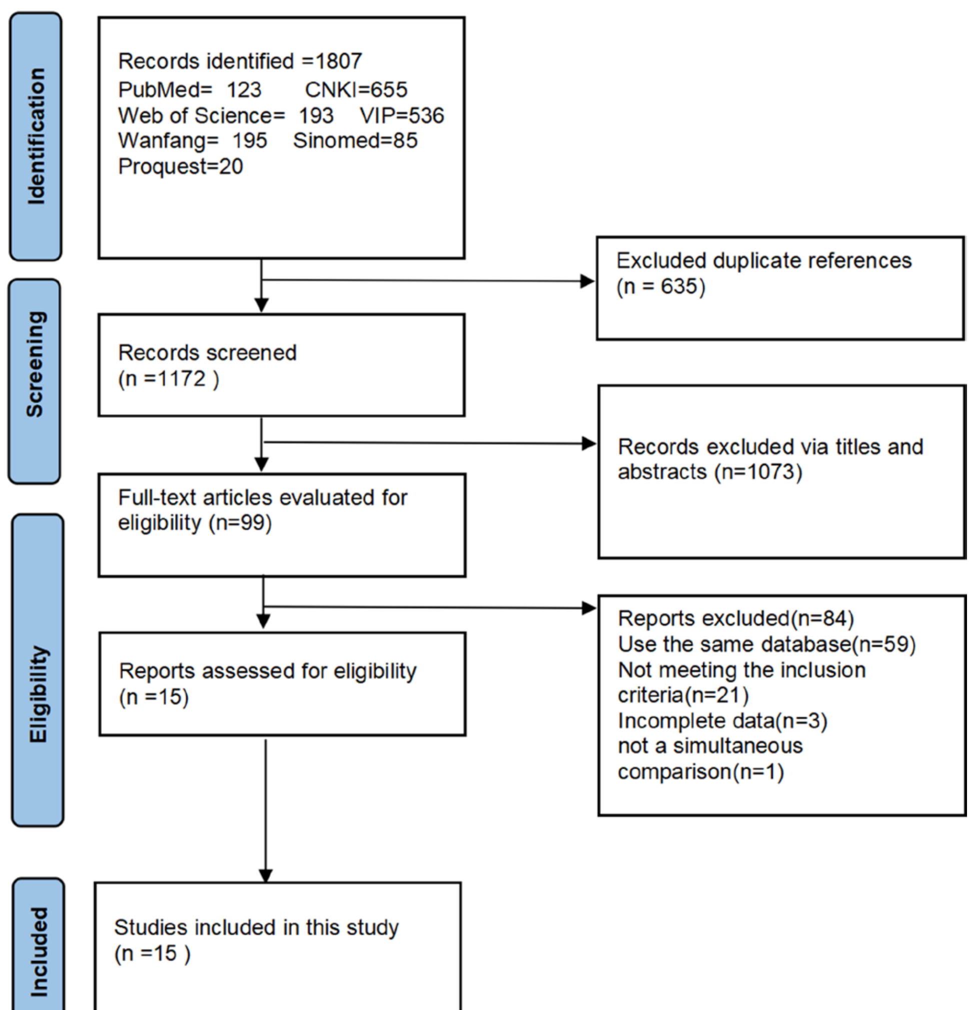

Figure 1. Screening literature process.

Table 1

General characteristics of studies included in the meta-analysis.

					Case group		Control group		
ID	**First author**	**Publication year**	**Country**	**Research design type**	**Events**	**Total**	**Events**	**Total**	**Score**
1	Jung	2018	South Korea	Case control	27	100	40	100	6
2	Park	2004	South Korea	Case control	12	41	15	41	6
3	Wang	1999	China	Cohort study	1	19	10,972	21,449	7
4	Liu	1999	China	Cohort study	0	3	7499	14,757	6
5	Hao	2003	China	Cohort study	2	38	9998	19,962	6
6	Long	1999	China	Cohort study	0	8	4081	8325	6
7	Ruan	1999	China	Cohort study	0	15	7866	15,717	7
8	Xu	2008	China	Cohort study	0	15	100,694	113,405	6
9	Hu	1999	China	Cohort study	0	10	6140	14,671	6
10	Zhang	1996	China	Cohort study	0	25	11,510	23,335	6
11	Zhao	1999	China	Cohort study	1	151	8273	90,972	6
12	Zhang	1998	China	Cohort study	0	27	1873	4319	6
13	Wei	2021	China	Cohort study	1	5	192	381	6
14	Jiang	1996	China	Cohort study	2	92	28,829	62,397	7
15	Gong	2012	China	Cohort study	1	42	10,177	26,295	7

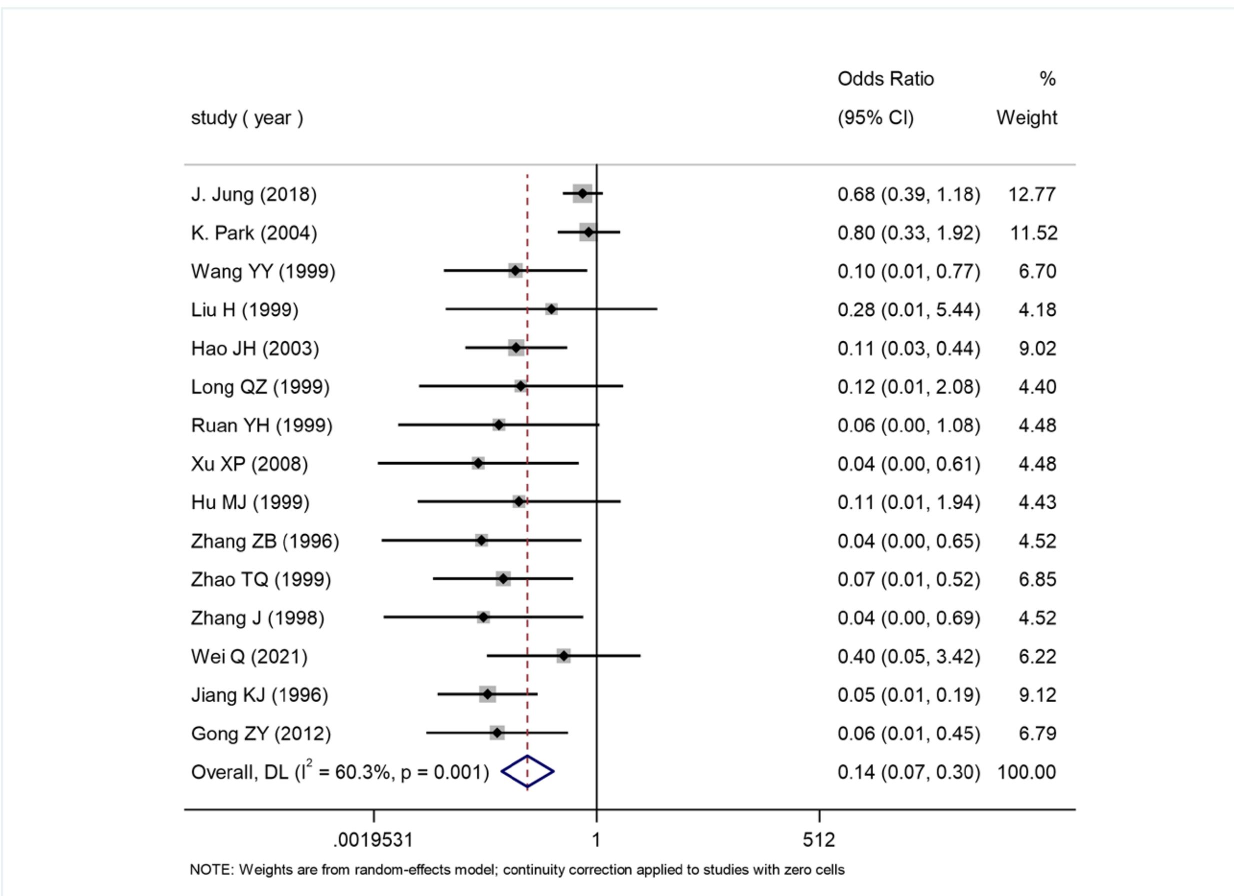

Figure 2. Forest plot for meta-analysis of the protective effect of HFRS inactivated vaccine. HFRS = hemorrhagic fever with renal syndrome. 95% CI = 95% confidence interval.

3.4. Subgroup analyses

Subgroup analysis of these included studies according to area, NOS score, and vaccination type (Table 2) revealed that the OR value of Korean group was 71% (95% CI: 0.44–1.14), which meant that the protection rate of Korea was 29%, indicating that the inactivated vaccine did not have a significant effect on HFRS. The protection rate of HFRS inactivated vaccine in China was 86% (95% CI: 70%–93%). Subgroup analyses of country and NOS scores revealed publication bias with a *P*-value of <.05 for the Egger test for the Korean group and NOS scores for subgroup 6. The VE for the Chinese region reached 95% with its 95% CI (0.90–0.97), and there were 4 articles with 7-star study quality and a VE of 94% with a 95% CI (0.84–0.98). Ten of the included studies described the type of vaccine used, of which 4 were gopher vaccines, 4 were gerbil vaccines, and 2 were suckling-mouse vaccines. The protective

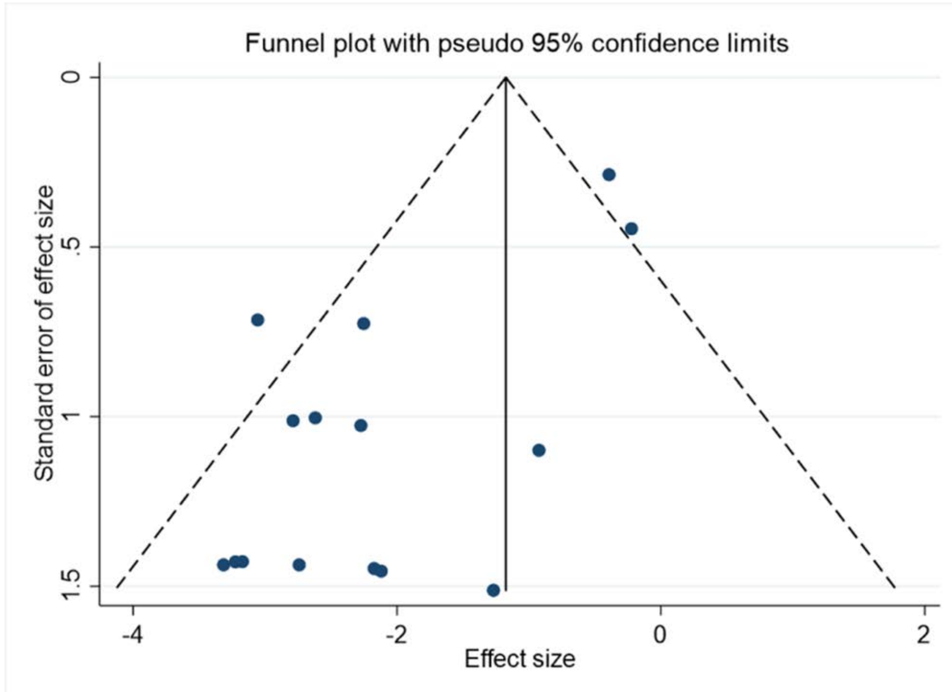

Figure 3. Funnel plot for meta-analysis of the protective effect of HFRS inactivated vaccine. HFRS = hemorrhagic fever with renal syndrome.

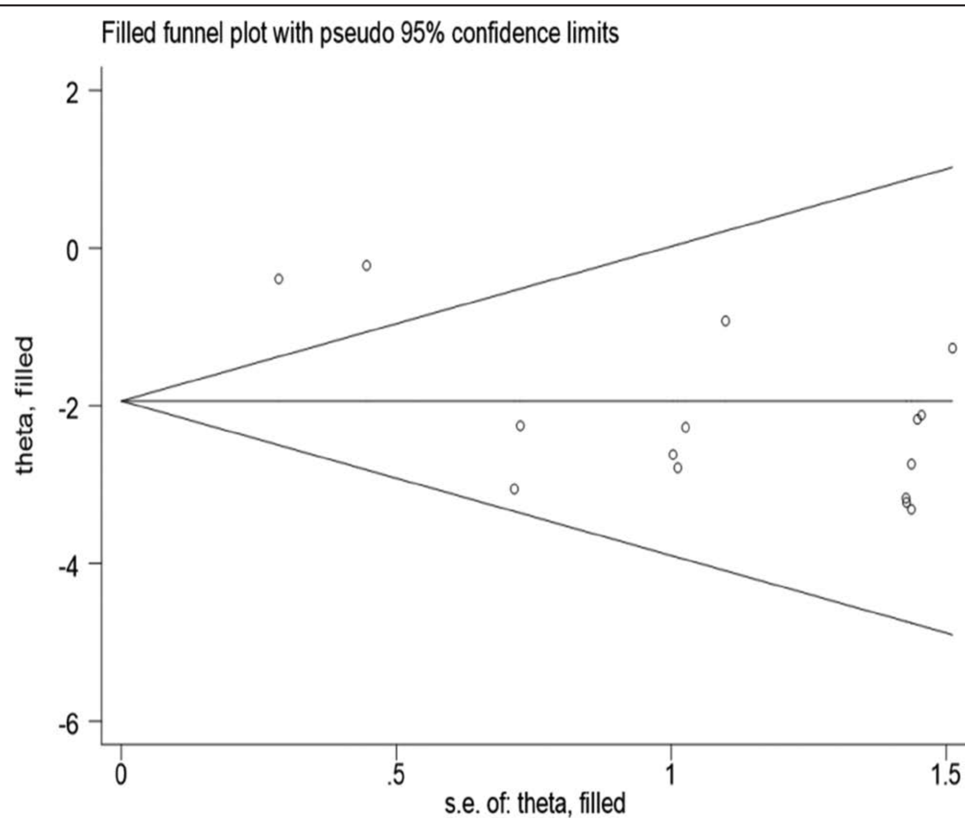

Figure 4. Publication bias was corrected through trim and filling method.

efficacy of the 3 types of vaccine was approximately the same in patients with HFRS, with a VE of 96% (95% CI: 0.87–0.99) for the gerbil vaccine, 96% (95% CI: 0.75–0.99) for the hamster vaccine and VE was 95% (95% CI: 0.64–0.99) for suckling-mouse vaccines.

3.5. Sensitivity analysis

Sensitivity analysis is a method used by researchers to evaluate for the presence of bias in this study by retrieving evidence from a variety of small sample studies. By excluding the included studies 1 by 1, OR and VE values were calculated, both of which, like the sensitivity analysis plot, showed that the results were robust (Fig. 5).

3.6. The seroconversion rate of antibodies

Among the 15 incorporated articles, 7 detailed the positivity of IgG antibodies, while 8 elaborated on the positivity of neutralizing antibodies, with all of them being published in the Chinese language. Four of the studies describing positive IgG antibody conversion rates were 14 days after primary immunization, 2 were 42 and 56 days after primary immunization, and 1 was not explicitly mentioned. Of the studies describing neutralizing antibodies, 5 were 14 days after basal immunization, 2 more were 42 and 56 days after basal immunization, and 1 was not explicitly mentioned. Upon systematic analysis of the antagonist positivity rates separately by forest plot, the I^2 for IgG antibody positivity was 98.6%, $P < .001$ (Fig. 6), with a total effect value of 97% (95% CI: 95%–98%), and for neutralizing antibody positivity the I^2 was 94.8%, $P < .001$, with a total effect value of 37% (95% CI: 33%–41%) (Fig. 7).

4. Discussion

HFRS is a zoonotic disease contracted by rodents and predominantly endemic in Asia and Europe, which has not been eliminated and has even become endemic to new areas more than 100 years since it was first reported historically.[8,31] Since the implementation of expanded immunization in China, some regions have reported significant reductions in the incidence of HFRS and morbidity and mortality,[32,33] South Korea also has reported a reduction in the prevalence of HFRS since the introduction of inactivated vaccines[29] Based on the search strategy, we included 15 studies for a systematic meta-analysis of the VE values of inactivated vaccines.

The results of the current study showed that the total VE value of inactivated vaccine reached 86% (95% CI: 70%, 93%), which indicated that the overall protection rate of the vaccine was good, but the VE value in Korea was only 29% (95% CI: −0.14 to 0.56), which indicated that the inactivated vaccine did not have a significant rate of protection in the population in Korea. Some studies conducted by Korean scholars have asserted that all the current research on the IHV in Korea

Table 2

The pooled incidence of hemorrhagic fever with renal syndrome in each subgroup analysis.

Subgroup	Number of studies	OR	95% CI	Heterogeneity I^2 (%)	Heterogeneity P	Egger test t	Egger test P
Country							
South Korea	2	0.71	(0.44,1.14)	0	.749	.	.
China	13	0.05	(0.03,0.10)	0	.851	0.34	.738
Study score							
6 star	11	0.21	(0.10,0.45)	53.2%	.019	−4.57	.01
7 star	4	0.06	(0.02,0.16)	0	.942	0.98	.431
IHV type							
Gerbil vaccine	4	0.04	(0.01,0.13)	0	.838	0.18	.873
Hamster-derived Vaccine	4	0.04	(0.01,0.25)	0	.415	0.63	.593
Suckling-mouse vaccine	2	0.05	(0.01,0.36)	0	.528	.	.

CI = confidence interval, IHV = inactivated hantavirus vaccine, OR = odds ratio.

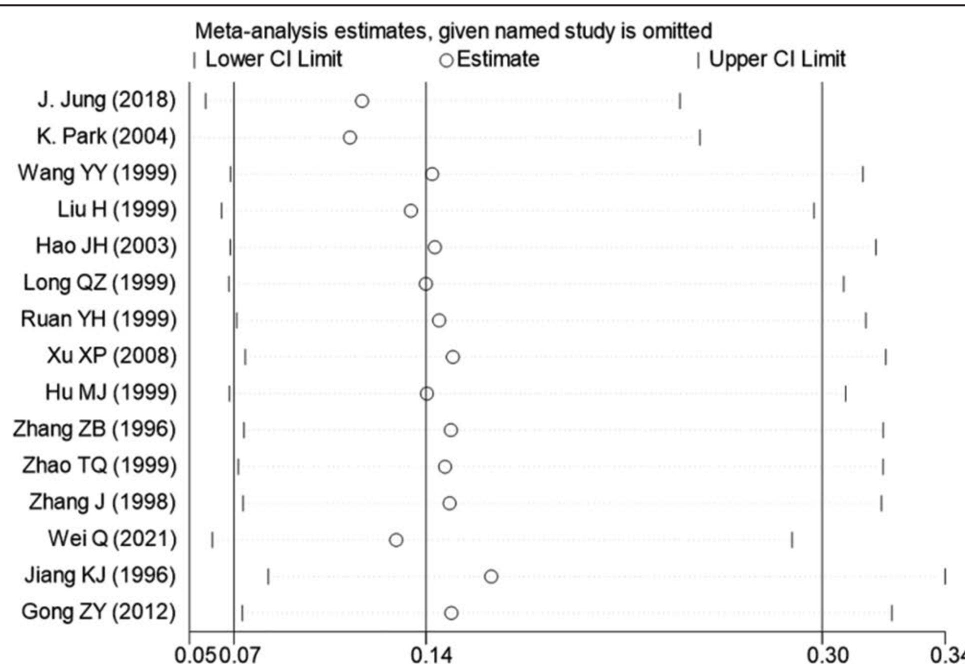

Figure 5. Sensitivity analysis plot of protective efficiency of HFRS inactivated vaccine. HFRS = hemorrhagic fever with renal syndrome.

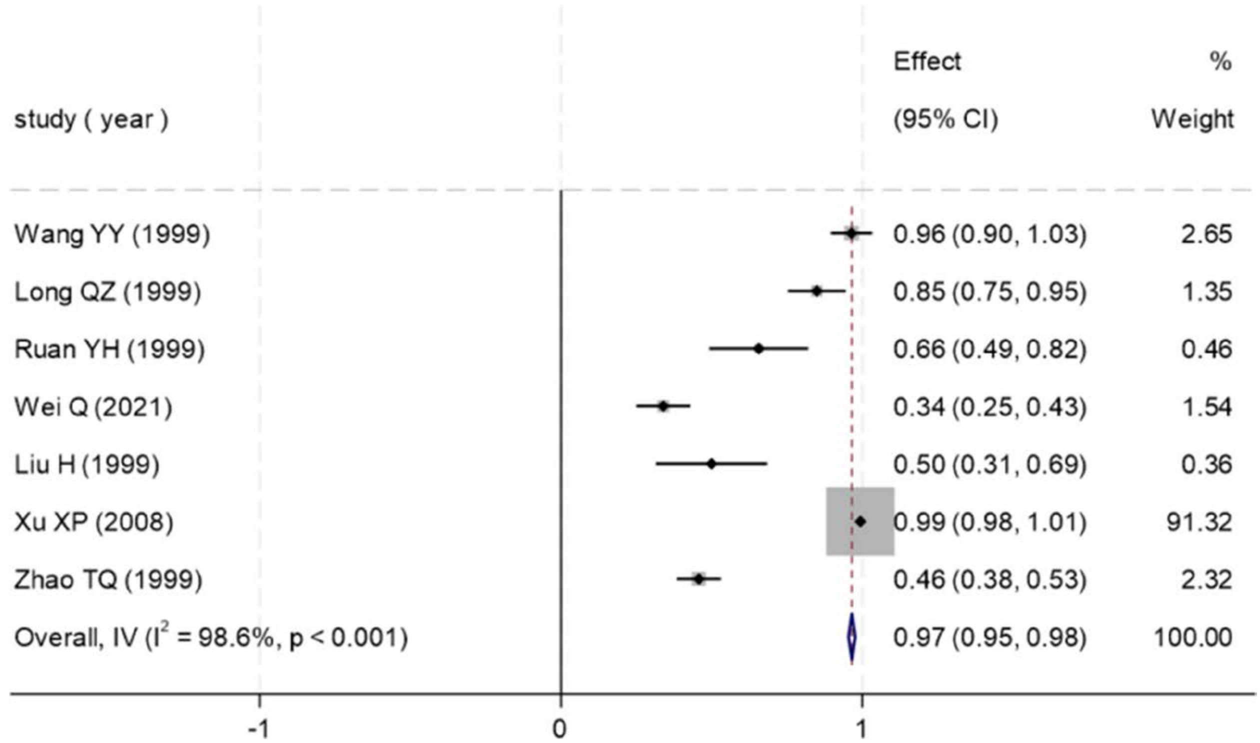

Figure 6. Forest plot of positive transfer rate of IgG antibodies. 95% CI = 95% confidence interval.

pertains to small sample sizes and retrospective design, so the effectiveness of this vaccine has not been confirmed, and inactivated vaccine has not been included in the immunization program in Korea.[34] After subgroup analysis of countries, it was found that the *P*-value of Egger test was <.05 in the Korean group and that in the Chinese group was .738. There was no publication bias in the study of the Chinese group, and for the group with a NOS score of 6 stars also included all the Korean studies, there was a publication bias in the results obtained, so we hold the opinion that the results of the present study may be related to small number of relevant foreign literatures that could be retrieved, and the small sample size included in the studies. In addition, the vaccine protection rates in the included Chinese studies were mostly recent protection effects, which may also be related to the fact that their VE values were as high as 95% after the combined effect, and some studies have shown that the efficacy values of vaccines are greatly reduced after a long period of time.[35]

The meta-results showed a positive conversion rate of 97% for IgG antibodies and 37% for neutralizing antibodies. This finding is consistent with the results reported in 2 studies on the medium- to long-term effectiveness of inactivated HFRS vaccines.[35,36] IgG antibodies serve as a marker of immunity, and multiple studies have demonstrated significantly higher IgG levels in vaccinated individuals compared to unvaccinated controls, further supporting the enhanced protective efficacy of inactivated HFRS vaccination.[37] In contrast, neutralizing antibodies appear to exhibit no significant association with disease severity. A study by Iheozor-Ejiofor et al investigating the relationship between neutralizing antibody titers and Puumala virus infection found no significant correlation between antibody levels and clinical disease severity, which was different from previous studies.[38]

The inactivated HFRS vaccine has not been included in the national immunization program in China, and it is recommended that the vaccine be expanded to reduce the incidence of HFRS and the morbidity and mortality of HFRS. The current vaccination population mainly ranges from 16 to 60 years old, and some studies have shown that the vaccine is also effective between 6 to 15 years old and 60 to 70 years old,[12,39] which suggested that the scope of the immunization population should be expand to further prevent the prevalence of HFRS.

5. Strengthens

To our knowledge, this is the first meta-analysis of vaccine VE as well as a meta-analysis of antibody positivity rates expressed in the included studies to comprehensively demonstrate the protective effect of inactivated vaccines in patients with HFRS. This study included high-quality articles assessed by the NOS scale, and the methodological quality of the included studies was reliable. More importantly, we have included quite a number of large-sample studies. The test for and presence of publication bias was also elaborated.

6. Limitations

The study has some limitations. First, studies were only from China and South Korea, with China being the majority, and no relevant articles published in other countries were retrieved. Second, due to the limited studies that could be retrieved, some of the sample sizes were small, which may have affected the results. Third, 1 of the literatures studied people aged 60 to 70 years and reported different vaccine protection rates than other Chinese studies, and this study may not be able to accurately assess the impact of the vaccine in all age groups. It was also not possible to assess other reasons that may affect the VE of HFRS inactivated vaccine, such as the number of doses and the duration of immunization. Fourth, there was publication bias in this study, which was not considered to be caused by the quality of the study; several no-full-text abstracts with relevant data were retrieved but not included, and it is not clear whether these studies would have reduced the bias. Therefore, the results of this paper need to be treated with caution.

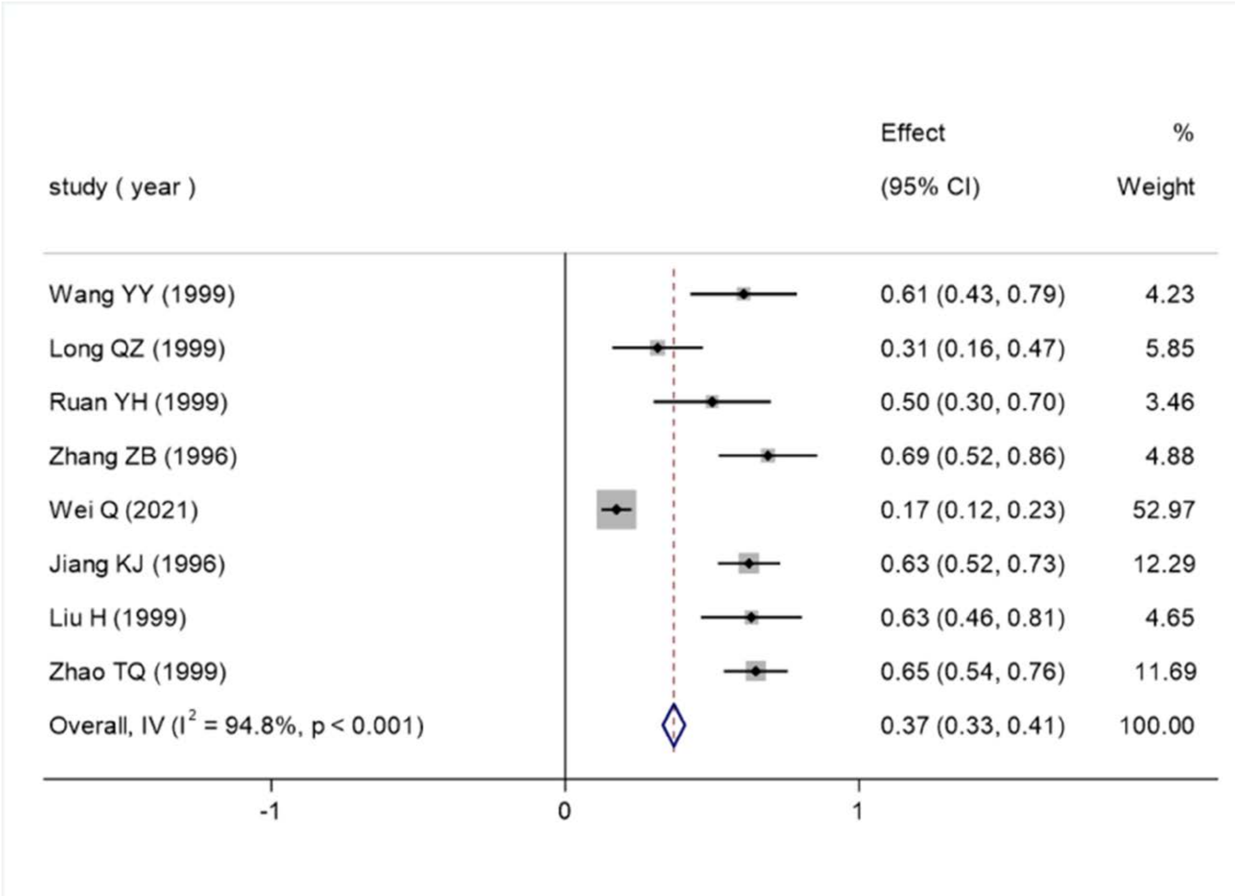

Figure 7. Forest plot of neutralizing antibody positivity. 95% CI = 95% confidence interval.

7. Conclusion

The findings of this study demonstrate that inactivated vaccines exhibit significant effectiveness in China, and vaccination population in infected areas and those at risk of developing the disease are needed to prevent the expansion of HFRS epidemics. In addition, larger observational studies are needed to more accurately assess the potential relationship between the inactivated vaccine and the incidence of HFRS, and the future vaccination strategy are expected to be administered to high-risk individuals (i.e., People aged 60 and above) as well.

Author contributions

Conceptualization: Weiting Wu, Jie Liu, Shicheng Guo, Han Zhao.
Data curation: Weiting Wu, Jie Liu, Han Zhao.
Methodology: Weiting Wu, Jie Liu, Xuli Yang.
Software: Weiting Wu, Han Zhao.
Writing – original draft: Weiting Wu, Han Zhao.
Writing – review & editing: Jie Liu, Xuli Yang.

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