

ASSESSING THE EFFICACY AND SAFETY OF HEPATITIS B VACCINES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Hepatitis B virus (HBV) continues to be a primary source of acute and chronic liver disease, cirrhosis, and hepatocellular carcinoma. Vaccination is the major prevention tool, and vaccine platforms and target populations, immunogenicity and adverse-event profiles vary. Search strategy: A systematic review of original studies on HBV vaccination was performed on ScienceDirect, PubMed, Google Scholar and ClinicalTrials.gov, with a focus on the studies published between 2020 and 2024, but including relevant landmark studies. Forty studies were included in the qualitative synthesis, 10 were initially selected for quantitative analysis and nine provided usable data for post-vaccination fever. Odds ratios (ORs) were combined using random-effects model. Conclusions: Immunogenicity and clinical utility of recombinant, mono-antigenic, tri-antigenic and therapeutic HBV vaccines in healthy adults and in some clinical populations were confirmed by qualitative evidence. The pooled OR was 0.716 (95% CI, 0.296-1.733; Z=-0.741; p=0.458) which did not show a statistically significant difference between the vaccine group and comparator group in the fever outcome of the meta-analysis. Heterogeneity was moderate (Q=17.034, df=8, p=0.030; I²=53%; tau²=0.843), and the 95% prediction interval was 0.064-8.040. Results: HBV vaccines overall were effective and well tolerated although the pooled fever estimate was somewhat imprecise and differed between studies. Heterogeneity may be due to differences in vaccine platform, population, schedule and definition of outcomes. Comparative trials of the same size and more frequent reporting are needed to enhance safety estimates and determine vaccine selection in special populations.

1. INTRODUCTION

Hepatitis B virus (HBV) is a partially double-stranded DNA virus of the Hepadnaviridae family, which mainly infects the hepatocytes. Transmission is by contact with infected blood and body fluids, unsafe injections, sexual contact

and via the perinatal period. Viral genome enters hepatocyte and becomes covalently closed circular DNA allowing continued transcription and replication via RNA intermediate. This peculiar mode of replication is responsible for chronic

infection and viral persistence for the long term [1-3].

HBV infection can occur in either an asymptomatic or an acute, self-limited form, or as chronic hepatitis, cirrhosis, and hepatocellular cancer. Many acute infections are not associated with symptoms, allowing for the possibility of transmission prior to diagnosis. Prevention is an important public health priority and a major contributor to the global burden of disease and the devastating effects of chronic infection [3,4].

Vaccination against hepatitis B is one of the most significant success stories in the prevention of viral diseases. Early plasma-derived vaccines proved to be very effective but were complex to manufacture, had limited plasma supplies, were expensive and were a concern about contamination in the blood stream. The purification of hepatitis B surface antigen (HBsAg) via yeast recombinant DNA technology followed. The safety, scalability and ability of recombinant vaccines to provide long-lasting levels of anti-HBs immunity [5-9] led to their introduction into routine immunization programmes.

The vaccine available are conventional single antigen recombinant vaccines, multi-antigen vaccines containing pre-S1, pre-S2 and S antigen, adjuvanted vaccines, paediatric vaccines and combination vaccines. Therapeutic vaccine approaches are also under investigation for chronic HBV infection, such as antigen-based and viral-vector platforms that aim to induce HBV-specific cellular immunity. The clinical reactions can vary based on age, immune status, comorbidities, vaccine type, immunisation schedule, and concomitant medication [10-18].

While the protective effects of HBV vaccination have been well established, comparative safety and effectiveness data is still heterogeneous. Fever is very common as a systemic adverse event, and can be measured consistently between randomized comparison groups. The present manuscript thus combines the information in the source thesis and quantitatively assesses post-vaccination fever, and qualitatively assesses efficacy, immunogenicity, and safety of HBV vaccine platforms.

2. Materials and Methods

2.1 Literature search strategy

For each study, students should decide what is the purpose of the study and what sources of information are needed. The research procedures and numerical outputs were used to create a systematic review and random-effects meta-analysis. Searches in ScienceDirect, PubMed, Google Scholar and ClinicalTrials.gov were done electronically. Search terms included combinations and spelling variants of terms that included "hepatitis B vaccine," "clinical trial," and "randomized controlled trial." The clinical trials, randomized studies and publications were filtered between 2020 and 2024. The final evidence base also included relevant landmark trials in the past that were relevant for vaccine efficacy and safety.

2.2 Eligibility criteria

For the qualitative synthesis, original studies which assessed efficacy, immunogenicity, or safety of HBV vaccines, optimization of doses, adjuvants, or special populations were included. Eligible designs were preclinical investigations or Phase 1-3 clinical studies. Articles, systematic reviews, duplicate reports and articles with no original outcome data were excluded from the qualitative synthesis. For quantitative synthesis more stringent criteria were used. Comparative fever data for an HBV vaccine intervention group and control or placebo group was required. Adopting randomized and well-controlled designs was of greater priority. The studies excluded from the pooled analysis were those that did not have usable event counts, inappropriate randomization, inadequate comparator information, or duplicated populations.

2.3 Study selection and data extraction

A total of 100 records were found from the source search. Thirty copies were taken out and 70 copies were screened. There were 20 full-text exclusions and 50 reports eligible. Forty studies were selected for qualitative synthesis and 10 studies were initially selected for quantitative analysis. The event data for the reported meta-analysis of fevers came from nine studies. The following variables were extracted: study or vaccine name, number of

fevers reported, total number of participants in the intervention (study) group, number of fevers reported in the comparator (control) group, total number of participants in the comparator (control) group, odds ratio, log odds ratio, and the standard error.

2.4 Outcome and statistical analysis

The quantitative outcome was post-vaccination fever. The odds ratio (OR) was used as the effect-size measure. A random-effects model was applied because the studies represented different vaccine platforms, populations, and clinical settings. Statistical significance was assessed using the Z test at $\alpha=0.05$. Between-study heterogeneity was evaluated using Cochran's Q, I², tau², and tau. A 95% prediction interval was reported to describe the expected distribution of effects in comparable populations. Because fewer than 10 studies contributed to the pooled fever outcome, formal small-study or publication-bias testing was not emphasized.

3. Results

3.1 Qualitative synthesis

The qualitative evidence was all in favour of the clinical value of HBV vaccination. Historical plasma-derived vaccines achieved high levels of protection in high-risk groups, and recombinant vaccines allowed a more efficient and safer vaccine production process, and were the basis of routine vaccines prevention programmes [6-9,19-22]. Recent research further showed that new vaccine platforms can provide good seroprotection and antibody responses.

For the most part, tri-antigenic formulations were found to be non-inferior or superior to mono-antigenic vaccines with respect to seroprotection, especially in elderly people, but with a higher

incidence of local and systemic reactogenicity [13,14]. Studies of therapeutic vaccines were the first to give evidence of immune activation in HBV. In chronic HBV, potential reductions in HBV DNA and normalization of alanine aminotransferase (ALT) levels were associated with NASVAC, and a T-cell response against HBV-specific interferon gamma (IFN-gamma) was induced by TG1050 with minimal safety issues [10,11]. A small number of participants also had functional responses to Bepirovirsen, although injection-site reactions and the necessity for larger confirmatory trials were reported [12].

There was a variation in responses in special populations. Patients treated with biological therapy typically needed repeat doses and had lower seroconversion rates than controls [15]. Vaccination resulted in higher anti-HBs and lymphocyte responses in HBV occult infection [17] while HBV reactivation after hematopoietic stem-cell transplantation was still observed in spite of vaccination highlighting the importance of continued serological surveillance [18]. However, co-administration with BCG produced sex dependent effects on heterologous cytokine responses, reflecting the importance of context and host factors in determining vaccine-associated immune effects [16].

3.2 Quantitative analysis of fever

Nine comparative studies contributed to the random-effects analysis of fever. Event counts and study-level effect estimates are shown in Table 1. The pooled OR was 0.716 (95% CI, 0.296-1.733). The Z value was -0.741 ($p=0.458$), so the pooled effect did not differ significantly from the null value of OR=1.0.

Table 1. Study-level fever events and odds ratios included in the pooled analysis.

Study/Vaccine	Fever, intervention n/N	Fever, comparator n/N	Odds ratio	95% CI
TG1050	1/36	1/12	0.314	0.018-5.452
3-antigen (3A) HBV vaccine	0/2126	13/712	0.012	0.001-0.202
Heptavax B	6/546	5/534	1.176	0.357-3.875

Study/Vaccine	Fever, intervention n/N	Fever, comparator n/N	Odds ratio	95% CI
Inactivated hepatitis B	8/6646	0/4670	11.960	0.690-207.277
HBAI20	3/101	2/32	0.459	0.073-2.878
TAV	8/811	3/796	2.633	0.696-9.963
3-antigen (Pre-S1/Pre-S2/S)	1/53	3/47	0.282	0.028-2.809
spHb	28/101	10/32	0.844	0.355-2.005
Heptavax-B	2/946	0/78	0.416	0.020-8.732

The Q statistic was 17.034 with 8 degrees of freedom ($p=0.030$), indicating that the true effects were unlikely to be identical across studies. I^2 was 53%, suggesting moderate heterogeneity. τ^2 was 0.843 and tau was 0.918 in log-odds units. The

95% prediction interval ranged from 0.064 to 8.040, demonstrating considerable uncertainty regarding the effect expected in a new comparable population.

Table 2. Random-effects meta-analysis summary for post-vaccination fever.

Statistic	Result
Number of studies	9
Pooled odds ratio	0.716
95% confidence interval	0.296-1.733
Z value	-0.741
p value	0.458
Cochran Q (df)	17.034 (8)
Q-test p value	0.030
I^2	53%
τ^2	0.843
Tau	0.918
95% prediction interval	0.064-8.040

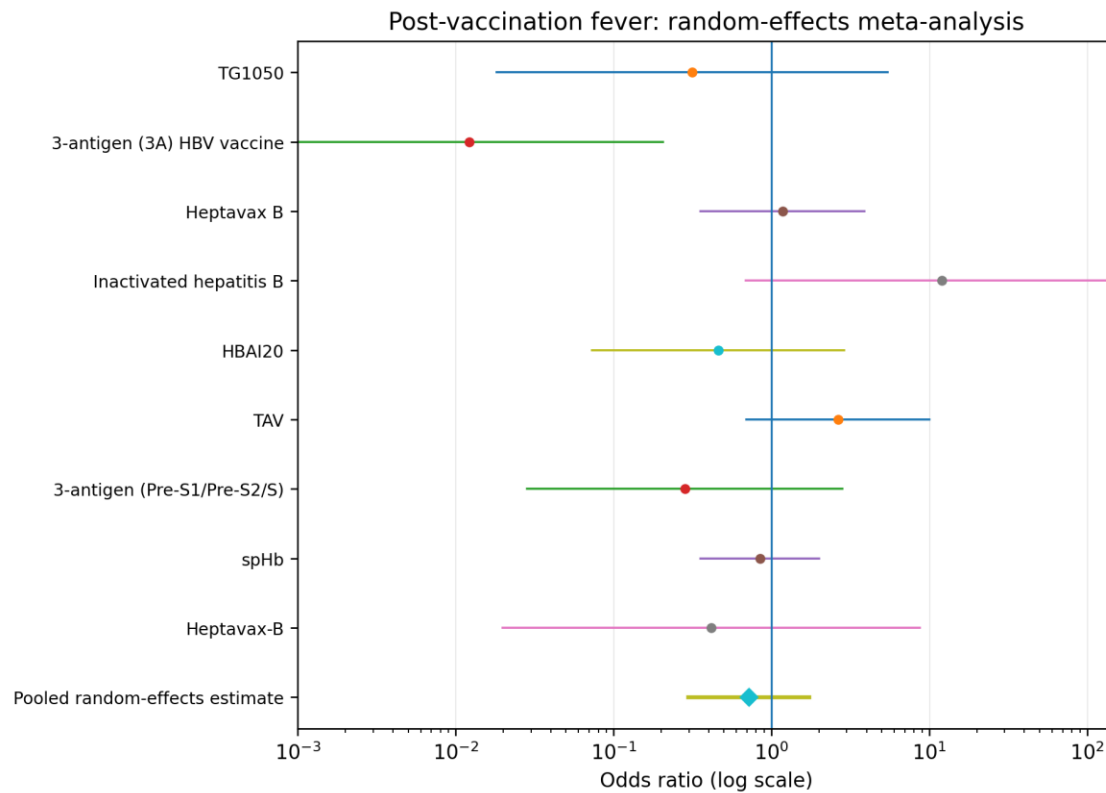


Figure 1. Forest plot of post-vaccination fever. The diamond represents the pooled random-effects estimate.

4. Discussion

This systematic review provided wide qualitative evidence of the effectiveness, immunogenicity, and tolerable safety of hepatitis B vaccination. The quantitative part of the analyses concentrated only on the fever and yielded a pooled OR of 0.716. The point estimate was in favor of the vaccine groups, but the 95% CI was not statistically significant and the p value was not significant. So, the current evidence does not show that there is a difference between the fever of the vaccine group and the comparator group. The combined result needs to be viewed with caution. The range for the confidence interval was broad and the prediction interval ranged from a significant decrease to a significant increase in the odds. This imprecision is due to variations in study size, vaccine formulation, population characteristics, control conditions and event frequency. A few studies observed only a small number of events or no events in one study arm, and this raises the level of uncertainty and makes single ORs sensitive to

continuity corrections. The I² value of 53% also shows that there was a moderate amount of variation not due to sampling error alone.

Biological plausibility for variation in vaccine platform. The conventional recombinant vaccines are produced using the antigen of HBV while the tri-antigenic vaccines contain pre-S1/pre-S2/S antigens, adjuvanted vaccines contain the antigen in an adjuvant, therapeutic vaccines are produced using the antigen, and the historical vaccines are produced using inactivated or plasma-derived antigens. The vaccines with three different antigen have demonstrated high seroprotection and antibody levels, even in populations with low responses to conventional vaccines, but have generated more local or systemic reactions [13,14]. A pooled estimate of fever should thus be considered a general measure of safety and not as an indication that all formulations have the same reactogenicity profile. The qualitative results have corroborated the known protective effect of HBV vaccination. Plasma-derived vaccines have been

shown to be effective in reducing the incidence of hepatitis B and had excellent antibody response to the vaccine in controlled trials [6,7]. Said vaccines were then manufactured as recombinant vaccines, and safe production and long-lasting seroprotection were provided [8,9,19,20]. The effectiveness of immunization programmes is further supported by population level reduction of HBV prevalence after the introduction of universal vaccination [21]. Lack of a substantial increase in pooled fever thus supports, rather than contradicts, the well-known protective effect of vaccination. Therapeutic vaccination is a different use than prophylactic vaccination. Virological, biochemical, and cellular immune response of chronic HBV infection was reported by the NA HSVAC and TG1050 studies [10,11]. Bepirovirsen is not a typical vaccine, but was incorporated into the source literature as an immunotherapeutic approach and demonstrated functional responses in a group of participants [12]. The methods are encouraging but as of yet not an alternative to preventive vaccines and the risk-benefit ratio of each should be assessed in their own right in future syntheses. Vaccine performance is also influenced by host characteristics. Factors that may affect seroconversion and durability include older age, immunosuppressive therapy, autoimmune inflammatory disease, occult infection, and post-transplant immune reconstitution [15,17,18]. Boosters or alternate vaccination schedules are necessary for some patients, and in others, vaccination does not diminish the risk of reactivation. Co-administration of HBV with BCG also demonstrated sex-dependent cytokine effects that point to other possible sex-dependent biological responses [16]. Some of these variations may have driven the evidence base to be somewhat heterogeneous. There are a number of limitations in the study. However, only nine studies and a single adverse event were included in the quantitative analysis, so a thorough safety evaluation was not possible. Enrollment and reporting criteria were not completely uniform in the source thesis, and there was no formal risk of bias table. The older and newer vaccine studies were pooled, definitions of outcomes might have

varied, and some comparisons were based on few events. The number of studies was also not large enough to be able to assess publication bias or meta-regression. Lastly, the pooled fever analysis should not be used as a direct indicator of vaccine efficacy; rather, conclusions about vaccine efficacy are largely based on the qualitative evidence. Although these are its limits, this analysis offers a helpful synthesis of the different pieces of evidence on HBV vaccines. Future reviews should prospectively register a protocol, use a validated risk-of-bias instrument, include only platforms for prophylactic products, harmonize adverse-event definitions, examine seroprotection and antibody titres as separate outcomes, examine special populations as a separate outcome, and examine adverse events as separate outcomes. Individual-participant or stratified analyses can help to explain the impact of age, immune status, vaccine platform, and dosing schedule.

5. Conclusion

Hepatitis B vaccines will continue to be a key priority in the prevention of HBV infection and chronic liver disease. The qualitative evidence in the source thesis backs up the efficacy and immunogenicity of traditional and novel vaccine platforms. For the random effects meta-analysis, there was no significant difference in the frequency of post-vaccination fever between the vaccine and the comparator groups, although the degree of heterogeneity was moderate and the precision was low. Overall, the evidence suggests an acceptable safety profile, but calls for larger, more methodologically consistent trials as well as the need to develop a separate strategy for the evaluation of prophylactic, therapeutic and special population vaccine strategies.

Declarations

Ethics approval: Not applicable; this study analyzed previously published data.

Consent for publication: Not applicable.

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Data availability: All numerical data used in the manuscript were extracted from the submitted thesis document.

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