

Are healthcare workers immunized after receiving hepatitis B vaccination according to recommended guidelines? A systematic review and meta-analysis

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Introduction

Hepatitis B remains one of the most relevant concerns on global public health.^[1-3] Nowadays, it is believed that more than 240 million people worldwide are infected with the hepatitis B virus (HBV), and according to the Global Burden of Disease Study 2010 (GBD 2010), hepatitis associated to its irreversible health-related consequences, represented by hepatic failure, cirrhosis, and hepatocellular carcinoma, already is ranked as 15th cause of human death around of the world.

The HBV is transmitted by percutaneous or mucous membrane exposure to infectious blood and body fluids that contain blood.^[4] Percutaneous exposures that have resulted in HBV transmission also include transfusion of blood or blood products manipulation, contaminated equipment used for therapeutic injections or needle pricks or for endogenous illegal drug application, as well as other healthcare-related procedures such as injuries from sharp instruments sustained by hospital

ABSTRACT

Objectives: Nowadays, it is believed that more than 240 million people worldwide are infected with the hepatitis B virus (HBV), associated with irreversible health-related consequences, represented by hepatic failure, cirrhosis, and hepatocellular carcinoma, and already are ranked as 15th cause of human death around the world.

Methods: A systematic review and a meta-analysis were performed to evaluate the effectiveness of vaccination and immunization on health professionals against HBV. The review was registered at the PROSPERO database (CRD42017075643). A search for cross-sectional studies was performed in PubMed, Scopus, Web of Science, LILACS, BBO, Cochrane Library, and in the gray literature. The Effective Public Health Practice Project Modified Scale was used to evaluate the internal quality of the studies included.

Results: A total of 1865 articles were identified after the removal of duplicates. Of these, 790 studies remained after screening the titles and abstracts. Finally, ten studies remained after full-text reading for qualitative analysis, all of which were used in the meta-analysis. A significant difference was found in the vaccine protocol for health professionals immunized against hepatitis B, compared to those not immunized. The risk ratio was 7.37 (95% confidence interval = 3.92–13.83; $P < 0.00001$).

Conclusion: This study showed that the vaccine protocol is effective in immunizing health professionals against hepatitis B.

Keywords: Health personnel, hepatitis b vaccines, meta-analysis, systematic review

personnel. In addition, occasional outbreaks of hepatitis B have been associated with tattooing and acupuncture.^[5]

This incident places healthcare workers, especially medical, nurse, and dental professionals at higher occupational risk when compared to other common communicable diseases, including human immunodeficiency virus (HIV) and hepatitis C virus.^[6-8] Thus, measures of individual protection and the vaccination of workers who may come into contact with blood or other body fluids, or even with sharp instruments or contaminated surfaces, should be adopted to prevent transmission of hepatitis.^[9] Vaccination is the most persuasive intervention for infectious disease prevention,^[10] and the HBV vaccine is the most currently used measure of disease prevention.^[11] The administration of this vaccine is considered safe, and its efficacy is considered high; its score conversion can be attested by 90–95% of immunocompetent adults.^[12]

However, it should highlight that some individuals who fail to elicit a protective antibody response after hepatitis B

vaccination remains at risk for HBV infection,^[7] but the vast majority of those who do not achieve anti-HBs seroprotective levels respond to a booster vaccine and may be considered protected against HBV.^[13]

After primary immunization received with the hepatitis B vaccine, the titer of antibody to hepatitis B surface antigen (anti-HBs) considered seroprotective is ≥ 10 milli-international units per milliliter (mIU/ml).^[14] However, anti-HBs levels decline as soon as the time period progress, and many previously vaccinated individuals may have anti-HBs below the threshold of protection considered as accepted, attested 10–15 years after the first series of doses.^[15,16] It is noteworthy that a health professional under these circumstances invariably inserted his or her peers and patients at hepatitis risk.

According to these premises, as well as in an endeavor to analyze whether health professionals are or are not immunized against HBV, we performed a systematic review sought to answer the following question: Are healthcare workers immunized after receiving the hepatitis B vaccination according to the recommended guidelines?

Methods

Herein we described the sequence from previously published systematic reviews.^[17-19]

Protocol and registration

This study was conducted from July to December 2017 at University Positivo, Curitiba, Paraná, Brazil. We previously have registered the study at the protocol at the PROSPERO database (CRD42017075643) and followed the recommendations of the MOOSE statement to report this systematic review.^[20]

Information sources and search strategy

The search strategy included indexed terms, such as MeSH terms and loose words in the article appearing in the title and abstract. The strategy was defined based on the study question formed by the acronym PECOS, which stands for:

1. Population (P): Healthcare workers
2. Intervention (E): Effective vaccination
3. Comparison (C): Not effective vaccination
4. Outcome (O): Immunization after being given the hepatitis B vaccination according to the recommended guidelines
5. Study design (S): Observational studies.

This review included trials from the following electronic databases: MEDLINE through PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature database (LILACS), Brazilian Library in Dentistry (BBO), and Cochrane Library. No restrictions were made regarding publication date or language.

We also used other sources to identify a greater number of articles published in literature. We searched the abstracts of annual conferences of the International Association for Dental Research and contacted authors of relevant abstracts for further information. We explored the gray literature using the System for Information on Gray Literature in Europe database, as well as dissertations and theses, using the full texts of the ProQuest Dissertations and Theses database and the Capes Theses database.

We searched the following clinical trial registries to locate unpublished and ongoing trials related to the review question: Current Controlled Trials (www.controlled-trials.com), International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>), ClinicalTrials.gov (www.clinicaltrials.gov), Rebec (www.rebec.gov.br), and EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu>).

Eligibility criteria

We included all studies that identified the number of healthcare workers who were not seropositive after receiving the hepatitis B vaccine. Non-controlled clinical trials, editorial letters, pilot studies, historical reviews, *in vitro* studies, and cohort and descriptive studies, such as case reports and case series, were excluded from the study.

Study selection and data collection process

Primarily, the articles were selected by title and abstract according to a previously described search strategy. Articles that appeared in more than one database were considered only once. Full-text articles were obtained even when the title and abstract had insufficient information to make a clear decision; subsequently, four reviewers classified those which met the inclusion criteria. The data were extracted using customized extraction forms, and the following data were recorded for each study included:

- Details of study methods, including study design and setting.
- Details of the participants, comprising only healthcare workers
- Only studies that included results of anti-HBs blood tests
- Data from publications of unrestricted date – article publication dates were not defined.

If there were multiple reports of the same study (i.e., reports with different follow-ups), the data from all these reports were extracted and included on a single data collection form to avoid data overlap.

Risk of bias of individual studies

The internal quality of the included studies was assessed by two independent reviewers using the Effective Public Health Practice Project (EPHPP) Modified Scale.^[16] This quality assessment tool evaluates the design and quality of observational studies and facilitates the incorporation of

quality assessments into the interpretation of the meta-analysis results, although it is not used as criteria for the inclusion or exclusion of articles.

The quality assessment instrument used herein contains the following components: (1) Selection bias, (2) study design, (3) identification and treatment of confounders, (4) blinding of outcome assessors and of participants, (5) reliability and validity of data collection methods, and (6) withdrawals of consent and dropouts. The components are rated as strong, moderate, or weak, according to a standardized dictionary (http://www.ehph.ca/PDF/QADictionary_dec2009.pdf).^[21]

The overall rating given to the study is determined by assessing the previous six rating components. In the original instrument,^[21] studies having no weak ratings and at least four strong ratings should be considered strong. Those with less than four strong ratings and one weak rating are to be considered moderate. Finally, those with two or more weak ratings should be considered weak.

Strong and moderate studies were included in the review.^[21] We listed the important confounders that should have been taken into consideration in the study: Whether the research used health professionals, the number of relevant participants, the participants' report on whether they followed all or part of the vaccination protocol, and whether the studies reported the results of anti-HBs blood tests. If the article covered two or three of these confounding factors, the study was considered strong; if the article covered only one of the factors, the study was considered moderate, and if the article did not cover any of the factors, the study was considered weak.

The inclusion criteria defined for evaluating the quality of this study consisted of articles that considered only professionals in the health area, that reported completion of the vaccination protocol, with 3 doses as having been administered on 0, 1st, and 6th month, respectively, and that included the anti-HBs test to determine if, in fact, the immunization should be performed earlier than 1 year of age.

Summary measures and synthesis of the results

The RevMan 5.3 program (Review Manager, The Cochrane Collaboration, Copenhagen, Denmark) was used to conduct all the analyses that could be extracted from the study. The data from eligible studies were dichotomous (presence or absence of immunization). Risk ratio effects models were applied to the dichotomous data.

Assessment of the quality of evidence using grading of recommendations: Assessment, development, and evaluation (GRADE)

We graded the quality of the evidence for each pair of comparison across studies and for the ranking of

treatments (body of evidence) using the GRADE (<http://www.gradeworkinggroup.org/>) and following the recommendations for assessment of the quality of evidence for network meta-analysis.

From the initial classification, it is possible to identify and judge the aspects that can reduce or increase the level of evidence. The factors responsible for the reduction in the level of evidence are risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) to possibly downgrade the quality of the evidence (1 or 2 levels). In addition, if the level has not been lowered due to the factors presented above, the evidence from observational studies can be high considering three factors: Great magnitude of effect; dose-response gradient; and residual confounding factors, which increase confidence in the estimate. Each one of these topics was assessed as “no limitations,” “serious limitations,” or “very serious limitations” to allow for categorization of the quality of the evidence for each outcome into high, moderate, low, and very low.

Results

Study selection

The EndNote program was used to refine the search after database screening and removal of duplicates; it identified 1835 studies [Figure 1]. A total of 790 studies remained after title and abstract screening. This number was further reduced to 10 after careful examination of the abstracts.

The characteristics of the included studies^[22-31] and their locations of origin of the studies were: Catalonia, Chile, Costa Rica, United States, India, Israel, Pakistan, Peru, Valencia, and Taiwan. The average age of the participants in 6 articles^[12,13,26,28,30,31] was 37.8 years, the youngest participant being 18 years old, and the oldest is 70 years old. In only one article, the age of the participants was not reported.^[27] In three articles, the authors separated the participants into groups of different age ranges but did not go into details.^[24,25,29]

In eight articles, the percentage of male gender participants was stated: 34.2%^[24-31]. In the other two articles, these data were not mentioned.^[22,23] In relation to the number of participants, a disparity was observed among the studies, ranging from 34 to 2058 participants. The number of participants in the respective studies by Herrer^[22] and Villena^[25] was the same: 211 health professionals. The average number of participants in all the articles was 740.

All the participants were health professionals, but four articles did not report what specific fields these professionals belonged to Racela *et al.*,^[23] Sabido *et al.*,^[24] Yen *et al.*,^[26] Zeeshan *et al.*^[29] In the other six articles, the professional nurses were part of the research. Doctors appeared in four

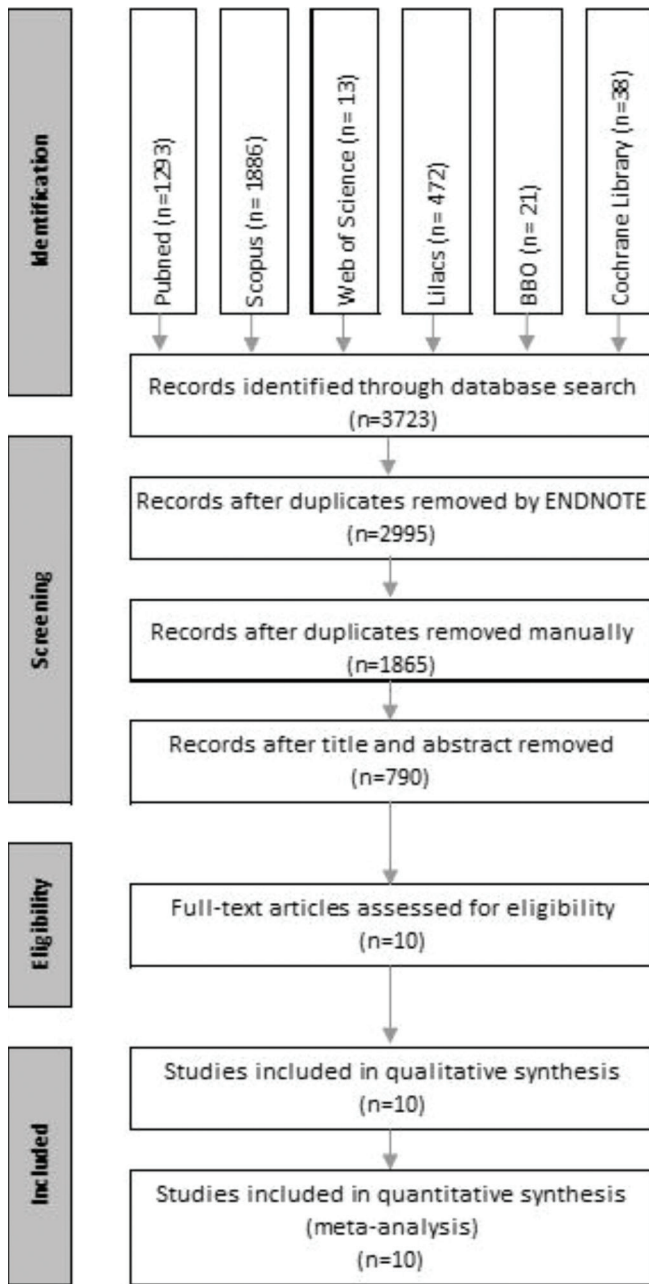


Figure 1: Flow diagram of the studies

articles;^[22,24,27,31] technicians (no particular area mentioned) in three articles;^[22,25,31] laboratorians (no specific field mentioned), in two articles;^[27,30] and dentists, in only one article.^[22]

Three types of vaccines against HBV were applied to the participants: Engerix-B;^[24,26,28-31] Cuban anti-HBV;^[25] and Heptavax-B.^[22,23,27] The interval between the first and second dose was 1 month, while the interval between the second and third dose was 6 months in six articles;^[26-31] in two articles,^[24,25] the interval was 1 month between the first and second dose and 2 months between the second and third dose. In one article,^[22] the interval between the doses was 2 months between the first and the second dose and a variation of 4–6 months between

the second and the third doses. Racela *et al.*^[23] did not report this data.

The anti-HBs test was requested in all the articles, but the time after the third dose and the collection was reported in seven articles.^[23,24,26-30] The period between the third dose and the anti-HBs test was between 6 and 8 weeks,^[29] 6 months,^[22,23] 7 months,^[31] 21–120 days, and 1 month.^[30] The laboratory method for evaluating the anti-HBs test was: Enzyme immunoassay method in six articles,^[25,26,27,28-30] enzyme immunoassay and radioimmunoassay method in one article,^[23] radioimmunoassay method in one article,^[24] immunoradiometric assay in one article,^[22] and quantitative immunoassay in another article.^[31]

In relation to the location of the health service where the surveys were carried out, six articles reported that they were carried out at a hospital;^[22-25,29,31] two at a medical center;^[26,27] two at a laboratory;^[23,30] and only one article did not report the location^[28].

Other data evaluated in some articles were seroconversion, seroprotection, and hyperresponsiveness. These data were computed in five articles^[23-25,28,29].

Assessment of the risk of bias

The studies were evaluated for quality using the EPHPP tools [Table 1]. Ten studies were selected being that six were considered strong,^[23-25,28,30,31] and four were considered moderate,^[22,26,27,29] according to the quality assessment components. For this reason, all the studies were included in the meta-analysis.

Meta-analysis

The meta-analysis was performed on studies classified as strong and moderate, based on the final rating of quality assessment components.

Frequency of individuals immunized against hepatitis B

This analysis was based on 10 studies.^[22-31] The risk ratio of those immunized and those not immunized for HBV was 7.37, with a 95% confidence interval [CI] of 3.92–13.83 ($P < 0.001$). Based on these studies, a significant statistical difference could be identified among the groups [Figure 2]. The data were heterogeneous (Chi-square test, $P < 0.00001$; $I^2 = 98\%$; Figure 2), which means that none of the studies included in the analysis shared a common effect size.

Sensitivity analysis

We sought to identify the factors warranting the heterogeneity observed by considering the local characteristics of where the research was carried out, such as the primary health care

system and the systemic and socioeconomic conditions of the researched populations.

Assessment of the quality of evidence

In the summary of findings in Table 2, the meta-analysis was graded as low in the quality of evidence. The reasons for downgrading the evidence were that all studies are observational, had imprecision with a high 95% CI and statistical heterogeneity (for the meta-analysis). The reason for the increase the evidence was the great magnitude of effect (RR>5).

Discussion

Viral hepatitis resulted in 1.34 million of deaths in 2015, a number similar to the deaths caused by tuberculosis and HIV in the same year. However, the mortality rates for tuberculosis and HIV are declining, whereas hepatitis death rates seem to be increasing.^[27]

All the articles evaluated in the present systematic review have demonstrated that health professionals are mostly immunized against HBV after receiving 3 doses of the vaccine protocol.

Table 1: Quality assessment components and final rating of the studies

Study ID	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals of consent and dropouts	Final rating
Chadha 2000	Strong	Moderate	Strong	Weak	Strong	Strong	Strong
García <i>et al.</i> 2002	Strong	Moderate	Strong	Weak	Strong	Strong	Strong
Herrera <i>et al.</i> 1988	Moderate	Moderate	Strong	Weak	Strong	Moderate	Moderate
Karpuch <i>et al.</i> 1993	Strong	Moderate	Moderate	Weak	Strong	Strong	Moderate
Martinez <i>et al.</i> 1998	Strong	Moderate	Strong	Moderate	Strong	Moderate	Strong
Racela <i>et al.</i> 1986	Moderate	Moderate	Strong	Moderate	Strong	Strong	Strong
Sabido <i>et al.</i> 2007	Moderate	Moderate	Strong	Weak	Strong	Strong	Strong
Villena <i>et al.</i> 2000	Moderate	Moderate	Strong	Moderate	Strong	Strong	Strong
Yen <i>et al.</i> 2005	Moderate	Moderate	Moderate	Moderate	Strong	Moderate	Moderate
Zeeshan <i>et al.</i> 2007	Moderate	Moderate	Moderate	Weak	Strong	Strong	Moderate

Table 2: Summary of findings table

Patient or population: Healthcare workers Exposition: Effective vaccination Comparison: Non-effective vaccination					
Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Immunized	Non-immunized			
Immunization assessed with: Anti-HBs exam	896/1000 (477 to 1681)	104/1000	RR 7.37 (3.92–13.83)	5134 (10)	⊕⊕○○ LOW**

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Imprecision due to the high 95% CI; inconsistency due to the high heterogeneity; and great magnitude of effect (RR>5). GRADE working group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. CI: Confidence interval

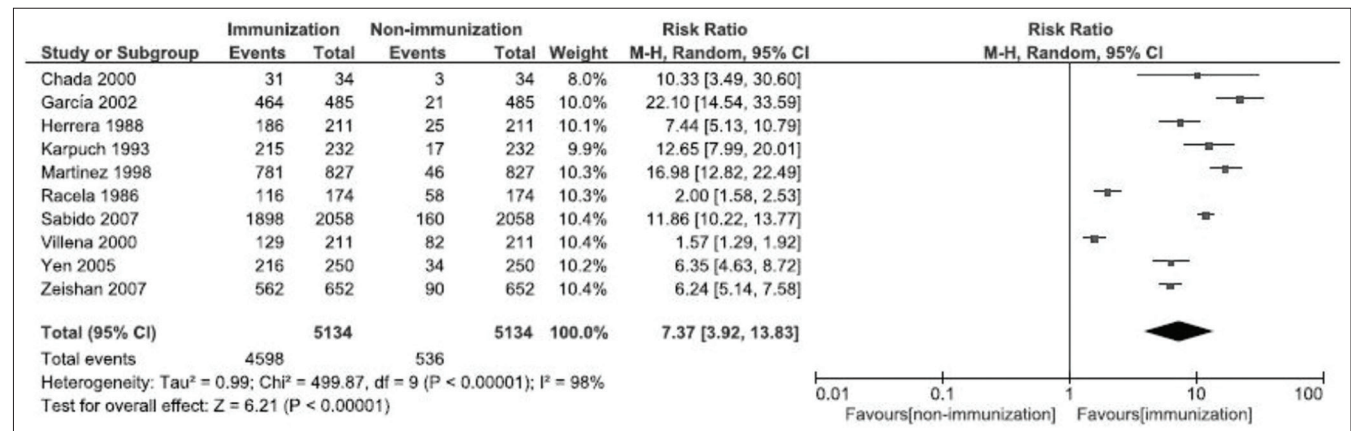


Figure 2: Forest plot of the frequency of immunized and non-immunized individuals

This result agrees with the vast literature on the subject, in which positive rates of antibodies against HBsAg (anti-HBs) is ≥ 10 mIU/mL have been reported to range from 85% to 95% of the vaccines.^[32]

The practice of a health-related activity represents a risk factor for acquiring HBV infection due to the conglomerate of patients with various infectious diseases and the risk of accidents occurring in many procedures.^[33] The risk of HBV transmission to healthcare professionals is 3–5 times higher than to people in general.^[34] Therefore, it is extremely important that health professionals be vaccinated and prove their immunization.^[33] Healthcare workers should be trained to update their knowledge of prevention and control measures.^[35]

The protocol for unvaccinated individuals, or those for which no prior vaccination information is available, consists of a series of 3 doses of hepatitis B vaccine (0, 1, and 6 months), followed by testing for anti-HBs, performed 1–2 months after the last dose to confirm immunity.^[2,36] Positive results for anti-HBs equal to or >10 mIU/mL confirm immunization.^[37] Vaccinated professionals whose anti-HBs level remains below 10 mIU/mL, even after the booster dose, are considered “non-responders.”^[38] They are also regarded as susceptible to infection; therefore, if exposed to HBV, they should be administered anti-hepatitis B immunoglobulin.^[39]

Even though the HBV vaccine is highly effective, some healthy individuals do not respond satisfactorily to vaccination against hepatitis B, ranging from 5% to 10%.^[40] The reasons for this lack of response are not defined, but the authors believe that the leading causes are advanced age (<40 years), male sex, obesity, alcoholism, smoking, genetic predisposition, chronic diseases, and immunosuppressant drug use.^[41]

Another critical factor that should be addressed is the durability of this immunization. Studies show that 77% of health professionals have adequate levels of antibodies even after 18 years of the vaccine protocol.^[42] The maintaining of a long-term antibody response is critical for protective immunity against HBV infection, particularly among healthcare professionals. The age factor may interfere with the durability of antibody maintenance. A study found that a group of participants between 5 and 19 years of age had a better level of anti-HBs (10 mIU/mL) after 22 years of primary immunization compared to other groups.^[43]

Regarding the immune response of health professionals who had inadequate levels of anti-HBs after years of vaccination, it was found that only one booster dose of the vaccine could elicit a rapid response.^[9] Protective levels were developed at 53% on day 7% and 94% on day 21, with an average increase of 100 times the level of antibodies observed in this period. Other studies with a shorter follow-up time also documented a rapid immune response to a booster dose of the vaccine in health workers and other populations.^[15,37,41]

The fast response to one booster administered in health professionals with no anti-HBs or with inadequate levels of it suggests that they will be protected after the re-exposure to HBV, a response called anamnestic response.^[44] These data support current guidelines that contraindicate revaccination for healthy health professionals.^[45]

Regarding the meta-analysis, high heterogeneity was observed among the ten studies included (98%). A sensitivity analysis was performed to verify the possible heterogeneity between the studies. When the studies by Racela^[23] and Villena^[25] were removed because they were deemed as less adequate in observing heterogeneity, the remaining eight studies were heterogeneous at 94%, proving that this heterogeneity occurs at random. One possible explanation may be that the seroconversion evaluations in the Villena^[25] study were performed 30 days after the second dose and 15 days after the third dose. In other articles, the evaluations were mostly performed only after the third dose. In the study of Racela,^[23] the sample was subdivided and evaluated at different times: 0 and 6 months after the third dose, with 41 subjects, 7 and 24 months after the third dose, with 75 subjects. Moreover, two tests were used to evaluate this seroconversion, thus presenting a variation which may have influenced the observance of heterogeneity in the meta-analysis.

Conclusion

This systematic review demonstrated that there was immunization against HBV in health professionals. This positive result indicates that there is awareness, concern, and care on the part of health professionals. However, these results should be interpreted with caution due to the high heterogeneity found and the quality of evidence being considered low.

The large number of articles presented in the literature and researched in this meta-analysis showed the effectiveness of the vaccine protocol in the immunization against hepatitis B for health professionals. New studies that evaluate the effectiveness of hepatitis B vaccination should be conducted to confirm these positive results.

Authors' Declaration Statements

Ethics approval and patients' consent

Not applicable, as no human subjects were involved in this study.

Availability of data and material

Data related to this paper will be made available by the corresponding author upon receiving legitimate requests.

Competing interests

On behalf of both the authors, the corresponding author states that there are no conflicts of interest.

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Authors' Contributions

JLG and LMW conceptualized and designed this study, performed database search, study selection, data abstraction, risk of bias assessment, analysis, and first and final draft of this manuscript. CK, LFAK, PPS, SPB, AFG, and EP contributed to the study selection, data abstraction, risk of bias assessment, and hard editing of the first draft.

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This work was done by the authors independently, and it is not related to their affiliated institutes.

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