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Review

Prevalence and risk factors of hepatitis B vaccine non-response in hemodialysis patients: a narrative review

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Abstract

Hepatitis B virus (HBV) infection poses a significant threat to public health, with hemodialysis patients facing an exceptionally high risk due to their compromised immune systems and exposure to blood products. While vaccination is the cornerstone of HBV prevention, hemodialysis patients often exhibit inadequate immune responses to the vaccine, jeopardizing their protection. This narrative review comprehensively evaluates the prevalence of non-response to HBV vaccination among hemodialysis patients and identifies associated factors. Drawing on data from various sources, the review analyzes demographics, clinical characteristics, and vaccination protocols to shed light on the critical determinants of vaccine failure. The analysis reveals significant variability in vaccine response rates among hemodialysis patients, with factors such as age, comorbidities, dialysis duration, and nutritional status playing pivotal roles. Additionally, vaccine type, dosage, and administration schedule influence immunogenicity. The findings provide critical insights into optimizing HBV vaccination strategies for hemodialysis non-responders by identifying underlying risk factors, thereby contributing to enhanced public health outcomes.

Key words: hepatitis B; HBV; hemodialysis; chronic kidney disease.

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Introduction

Hepatitis B virus (HBV) is a significant global health concern, primarily targeting the liver and potentially leading to severe conditions like cirrhosis and hepatocellular carcinoma [1]. HBV is transmitted through exposure to infected blood or bodily fluids and affects an estimated 257 million people worldwide, causing over 880,000 deaths annually [2]. While the HBV vaccine, introduced in 1981, has been highly effective in the general population, it has a notably diminished response rate in high-risk groups, particularly hemodialysis patients [3].

Hemodialysis patients are particularly vulnerable to HBV infection due to frequent exposure to shared dialysis equipment, repetitive use of blood products to manage anemia, and the invasive procedures required for vascular access [4]. This heightened risk, combined with the economic burden of managing chronic infections, underscores the urgent need to address vaccine non-response in this population [2].

The effectiveness of the HBV vaccine is strikingly lower in hemodialysis patients compared to the general public. Studies have shown that while more than 95% of healthy individuals develop protective immunity after vaccination, the response rate in hemodialysis patients can be as low as 42.3% [5]. A study published in BMC Nephrology found that only 70.5% of 156 dialysis patients responded to the vaccine [6], and another study reported that 30.9% of 6,628 patients were non-responders, defined by an anti-hepatitis B (HB) surface antibody titer of less than 10 mIU/mL [7].

Multiple factors contribute to this reduced vaccine response, including patient age, immune and nutritional status, and the duration and adequacy of dialysis [7,8]. These complex factors highlight the need for specialized vaccination strategies. While various vaccines like Engerix-B and Recombivax HB are available, their efficacy in this population is often limited. Even Heplisav-B, a vaccine designed to enhance immune responses in adults, has not fully solved the issue for hemodialysis patients [3,9].

This review aims to synthesize existing data on HBV vaccine non-response in hemodialysis patients, identify key predictors, and propose strategies to

improve vaccination outcomes and protect this population.

Search strategy and selection criteria

A literature search was conducted in PubMed and Scopus to identify studies on HB in the context of vaccination, hemodialysis, and chronic kidney disease. The search strategy applied the keywords ("Hepatitis B" OR "HBV") AND ("hemodialysis" OR "chronic kidney disease") and was restricted to English language publications from 2015 to 2025. Filters were used in PubMed to include bibliographies, clinical trials, meta-analyses, NIH-supported research, reviews, and systematic reviews; while excluding preprints; which yielded 26 records. The search was refined in Scopus to articles and reviews within the subject areas of medicine, immunology and microbiology, and health professions, resulting in 678 records. In total, 736 articles were retrieved, and after removing 32 duplicates, 704 records remained for screening. Titles and abstracts were assessed for relevance, with full-text review performed when necessary. Additional references were identified through manual searches of bibliographies from key studies to ensure comprehensive coverage of the topic.

Defining non-response: a holistic approach

Non-responsiveness to HBV vaccine among hemodialysis patients presents a complex challenge that requires a multifaceted approach. Various strategies have been proposed, including pre-vaccination testing; monitoring antibody levels with repeat testing at regular intervals; and considering clinical factors such as advanced age, malnutrition, co-infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV), tobacco use, diabetes mellitus, comorbidities, prolonged hemodialysis, and low adequacy of dialysis levels [10]. Hemodialysis patients are known to be persistent non-responders to the HBV vaccine, failing to elicit an antibody response. Non-responders to HBV vaccination are people who do not develop protective levels of anti-hepatitis B (anti-HBs; ≥ 10 mIU/mL) after receiving the standard 3-dose vaccination course. The inadequate immune protection which affects some individuals does not work the same way for everyone since response rates depend on age, immunosuppression status, chronic diseases, and genetic background [11].

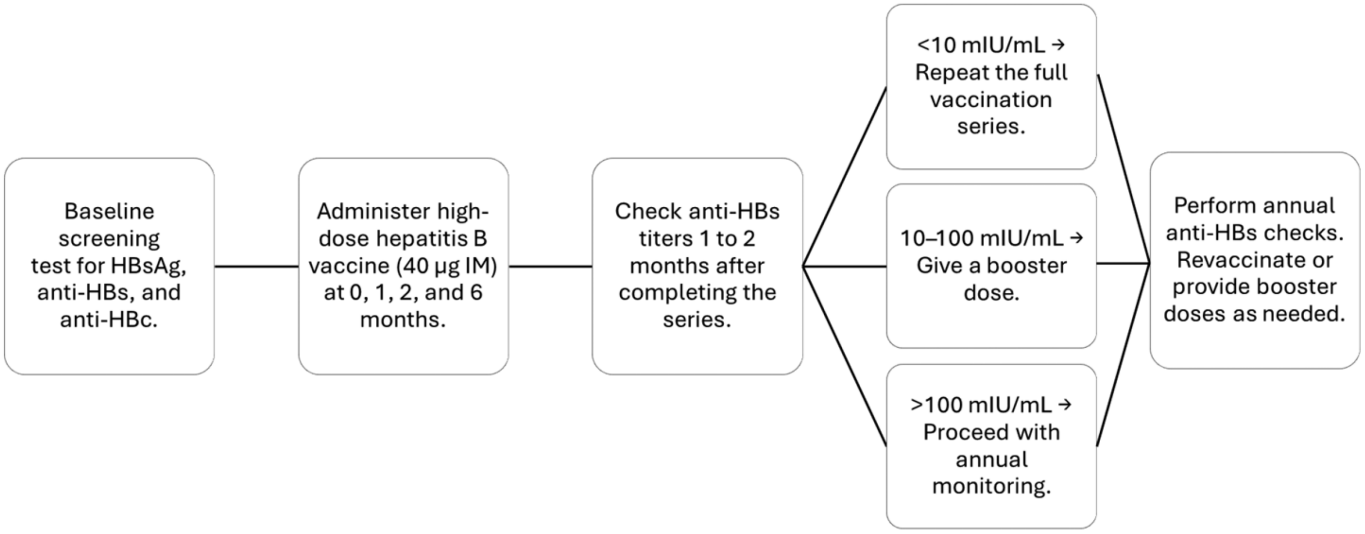
High-risk individuals who do not respond adequately are advised to undergo testing for current or past HBV infection. Pre-vaccination serologic testing is recommended to identify individuals with chronic HBV infection using markers such as HBsAg, anti-HBs, and total anti-HBc; aiming to prevent HBV transmission and provide appropriate care [12]. It is essential to administer the first vaccine dose immediately after collecting the blood sample for serologic testing. Additionally, repeat testing to monitor antibody levels in HBV vaccine non-responders has been proposed [13]. While this approach may help identify waning immunity and guide treatment decisions, it raises concerns regarding cost, psychological burden, and lack of conclusive evidence on clinical practice [14]. Studies evaluating the efficacy of annual HB boosters in primary non-responders among the hemodialysis population have shown limited benefits beyond 3 years, suggesting the need for caution and adherence to universal standards in continuing this practice [15]. Therefore, alternative protocols, such as repeating the primary vaccination with higher vaccine doses or different schedules, should be considered based on individual needs and risk factors (Table 1).

Healthcare providers must prioritize discussions on personalized monitoring and protection against HBV infection in hemodialysis patients (Figure 1) as patients with chronic kidney disease (CKD) often face additional challenges in developing immunity against HB through vaccination [16]. Several factors can hinder their immune response beyond the vaccine itself [16]. Advanced age weakens the immune system's effectiveness, resulting in a weaker response to HBV, especially in individuals aged 60 years and above [11]. Hemodialysis, a common treatment for CKD, can inadvertently remove essential immune factors from the bloodstream, further weakening the immune system's ability to respond to the vaccine [17]. Co-infections

Table 1. Alternative vaccination protocols for hemodialysis patients.

Alternative Protocol	Details	References
High-dose vaccine strategy	40 µg recombinant hepatitis B virus (HBV) vaccine IM at 0, 1, 2, and 6 months	[72]
Accelerated or reinforced schedule	40 µg at 0, 1, 4, and 8 weeks The accelerated arm had higher early seroconversion at 12 weeks, but no guideline endorsement currently exists for hemodialysis (HD) patients	[73]
Booster-based approach	Check anti-HBs 1 to 2 months post-series	[74]
Use of adjuvanted vaccines	Adjuvanted vaccines (CpG 1018 or AS04) show higher seroprotection than standard alum vaccines in open-label trials, cohorts, and reviews, with direct HD data for Heplisav-B (CpG)	[75]
Intradermal vaccination	5 to 10 µg intradermally in multiple doses for persistent non-responders after failed high-dose IM	[76]

Figure 1. Practical monitoring and protection protocol in hemodialysis patients (HBV vaccination).



such as HCV or HIV can overload the immune system, making it less capable of responding effectively to the vaccine [18]. Lifestyle factors like smoking and conditions such as diabetes mellitus and malnutrition also impair immune function, increasing the risk of poor vaccine response [19]. Dialysis adequacy influences vaccine effectiveness, with inadequate dialysis potentially burdening the immune system and making it less responsive to the vaccine. Although the type of dialysis (peritoneal or hemodialysis) does not affect vaccine response, addressing these factors is crucial for healthcare professionals managing HB vaccination in CKD patients [19]. By understanding and addressing these challenges, healthcare providers can ensure that individuals with CKD receive optimal protection against HB.

International organizations like the World Health Organization (WHO) offer evidence-based guidelines for managing HB vaccination programs in high-risk populations. Integrating these guidelines into clinical practice enhances the success of vaccination programs [20]. Healthcare providers should regularly consult national and international guidelines to stay informed about the latest recommendations for identifying non-responders to the HB vaccine. These guidelines define thresholds for non-responsiveness based on serologic markers such as anti-HB levels [20]. National health authorities often provide tailored strategies considering regional variations in prevalence and vaccination protocols. These guidelines may include specific immunization protocols tailored to the unique needs of hemodialysis patients, such as adjustments in vaccine dosage, administration schedules, or adjuvanted vaccines [21]. Comprehensive follow-up strategies for managing non-responders, including booster doses, alternative vaccine formulations, or alternative vaccination schedules, are essential to these guidelines. The frequency and timing of follow-up assessments play a crucial role in ensuring the effectiveness of these strategies.

Furthermore, the implementation of electronic health records (EHRs) proposed by Soi and Soman presents an opportunity to enhance the identification and management of patients requiring HB vaccination and hemodialysis [22]. This project aimed to use EHR to accurately identify all inpatients needing hemodialysis with HBV or occult HBV (OHB). Thus, automating HBsAg testing within 30 days of dialysis initiation and ordering machine disinfection measures via the EHR, can improve adherence and prevent hepatitis transmission. Collaboration with the quality team incorporated the latest hepatitis serology results into dialysis orders for real-time review. Automated HBsAg testing orders were generated if recent results were absent, ensuring timely intervention. This integrated approach showcases the potential of EHR for patient safety and HB management in hemodialysis patients.

Hepatitis B vaccine in hemodialysis patients

Effectiveness in the general population

The HBV vaccine demonstrates significant efficacy in generating protective immunity within the general population. The conventional 3-dose vaccination regimen results in seroconversion rates ranging from 90% to 95% in individuals with optimal health. This indicates that a significant number of recipients attain protective levels on anti-HB antibodies. Young

individuals such as infants, children, and adolescents demonstrate elevated seroconversion rates which are usually between 95% to 98%. It proves that early childhood vaccination serves as a fundamental element of HBV prevention strategies [16]. The ability of the HBV vaccine to provide long-lasting protection is one of the most notable characteristics. Some studies demonstrated that the vaccine provides immunity lasting for 20 to 30 years in vaccinated individuals. Presence of immune memory, facilitated by memory B cells and T cells ensures immediate anamnestic responses upon HBV re-exposure even in low antibody levels [23–26]. This point of view emphasizes the lasting effects of immunity induced by vaccines and lowers the necessity for additional booster doses in immunocompetent individuals.

Global HBV epidemiology has significantly changed as a result of the extensive implementation of HBV vaccination programs. The implementation of universal vaccination policies in various countries has led to a significant decrease in the incidence of HBV infection. In Thailand, the National Immunization Program was conducted by enrolling 6068 participants aged 6 months to 80 years, and showed reduction of HBV infection rates, particularly in younger populations [27]. Taiwan, a country that implemented universal baby vaccination in 1986, had achieved 90% reduction in HBV prevalence among infants and a substantial decline in hepatocellular carcinoma rates within two decades [28]. Other regions have also demonstrated successes which serve as evidence of the capacity of the vaccine to reduce HBV transmission and its associated complications [29,30].

Notwithstanding these obstacles, HB vaccination continues to be an essential preventive strategy for individuals who undergo hemodialysis, adding to the reduction of HBV transmission [3]. Thus, this highlights the crucial function of the vaccine in enhancing disease prevention initiatives and promoting overall public health.

Factors affecting hepatitis B vaccination in hemodialysis patients

Several factors influence the effectiveness of HB vaccination in hemodialysis patients, including vaccine type, formulation, dosing schedule, and individual patient characteristics. These factors play a crucial role in determining both vaccine response rates and the need for adjustments in vaccination strategies. A subset of hemodialysis patients exhibits a diminished immune response to the HB vaccine, a phenomenon known as vaccine non-response. This can be attributed to various factors such as immunosuppression, advanced age, malnutrition, and chronic inflammation [31]. Non-response risk is also influenced by dialysis treatment time: contemporary guidance supports thrice-weekly sessions of at least approximately 4 hours per treatment to achieve adequacy (e.g., spKt/V ≥1.2 or eKt/V ≥1.05); shorter sessions (< 3.5 to 4 hours) can contribute to inadequate clearance and are a plausible modifiable driver of poor vaccine response [32]. Patients undergoing hemodialysis often have compromised immune systems, which reduces their ability to mount an adequate response to the vaccine [33]. Older patients are more likely to be non-responders due to age-related declines in immune function [34]. In dialysis cohorts, seroprotection rates drop markedly after about 60 years of age; many programs treat adults ≥ 60–65 years as a high-risk group and use higher-dose schedules with closer post-series anti-HBs monitoring [35]. Additionally, malnutrition, commonly observed in CKD patients, has been linked to weaker immune responses to vaccination [36]. Persistent inflammation in hemodialysis patients further impairs immune function and hinders vaccine efficacy [37]. Nutritional status also plays a significant role, as malnutrition is prevalent among dialysis patients and is linked to immunosuppression and lower vaccine response rates. Studies have shown that HBV vaccine responders tend to have higher serum albumin levels and better nutritional markers compared to non-responders [38,39]. Furthermore, dialysis adequacy, measured by Kt/V, is another critical factor influencing immune response. Higher solute clearance has been associated with improved HBV vaccine response, with studies indicating that vaccine responders had better dialysis adequacy than non-responders [7]. Synthesized data indicate that responders have modestly higher Kt/V than non-responders, reinforcing dialysis adequacy as a modifiable target. Genetic factors also contribute to vaccine response, as certain human leukocyte antigens (HLA), such as HLA-DR3, have been linked to lower vaccine responses. Research has found that non-responders are more likely to carry this allele, suggesting a genetic predisposition to reduced vaccine efficacy [31]. Beyond DR3 (DRB103), DRB107 and the B8–DR3–DQ2 haplotypes are repeatedly associated with non-response; whereas DRB101, DRB115 and DPB1*04:01 are linked to better responses; these HLA effects are also observed in hemodialysis cohorts [35].

Vaccination strategies for hemodialysis patients often require modifications to enhance efficacy due to the increased risk of non-response. The type and formulation of the vaccine play a significant role in

determining immune response rates. Recombinant HB vaccines containing specific HBV surface antigens are commonly used, and some formulations include adjuvants designed to enhance immune response, making them preferable for immunocompromised individuals [37,40,41]. The dosing schedule is another important factor, as standard HB vaccination involves multiple doses at set intervals. However, hemodialysis patients often require a higher vaccine dose or an alternative schedule to achieve adequate protection [36,41–43]. In the case of adults on hemodialysis, current immunization tables specify 40-µg formulations (Engerix-B 0, 1, 2, 6 months [4-dose] or Recombivax HB dialysis formulation 0,1,6 months [3-dose]); Heplisav-B has limited evidence in hemodialysis, and some authorities do not recommend a dialysis-specific schedule [42]. Additionally, booster doses may be necessary to maintain long-term immunity, as vaccine-induced protection can wane over time in this population [44,45]. Proper vaccine storage, including maintaining appropriate temperatures and protecting the vaccine from light, is also crucial to preserving its immunogenicity and efficacy [44]. When non-response risk is high (e.g., session length <4 hours, Kt/V below target, age ≥ 60 years), optimizing dialysis time and solute clearance before or during the vaccine series and checking anti-HBs 1–2 months after the last dose to guide boosters are pragmatic steps to improve serologic protection [35,46].

Healthcare practitioners must carefully consider these factors when implementing HB vaccination programs for hemodialysis patients. Ensuring the use of the most appropriate vaccine type, adhering to tailored dosing regimens, and monitoring patient immune responses can significantly improve vaccination success rates. Furthermore, patient education on the importance of adherence to vaccine schedules is essential for optimizing protection against HBV infection. Healthcare providers can enhance overall vaccine effectiveness and reduce the risk of HBV transmission in this at-risk population by addressing both vaccine non-response and necessary adjustments for hemodialysis patients. In summary, ensuring session duration ≥ 4 hours and adequacy targets, applying age-stratified dosing/monitoring, and recognizing HLA-linked risk can meaningfully reduce non-response in this high-risk population.

Immunization guidelines for hemodialysis patients

Vaccination is a key component of the healthcare system for the entire population, and it is even more important in immunocompromised individuals, such as patients on hemodialysis. Immunocompromised hemodialysis patients have more chances of infections and complications arising from these infections [47]. To keep these patients safe, we need to follow the current immunization guidelines, which are specifically designed for hemodialysis patients [48,49]. All dialysis patients should undergo pre-vaccination screening for HBsAg, anti-HBc, and anti-HBs to determine their immune status. The reduced immune response in patients undergoing hemodialysis requires a stronger dose (40 µg) HBV vaccine with a 3- or 4-dose administration at 0, 1, 2, and 6 months instead of the regular 3-dose protocol [50].

Serologic tests can be done after vaccinating to check for the formation of antibodies that protect against the disease. The test for anti-HB levels must be within 1–2 months' post-vaccination to determine adequate protection which requires results above 10 mIU/mL. A booster dose should be given when antibody levels drop below the threshold and non-responders need to receive another vaccine series followed by re-testing. HB vaccination is also prescribed for patients and their family members in regions with high endemicity or during outbreaks [51]. The vaccine is given by injection inside muscles in 2-dose series; it is best to provide the second dose 6–12 months after the first dose. The prevention of HB spread requires dialysis units to maintain strict infection control protocols. The guidelines protect patients undergoing hemodialysis because they face an increased risk of HB exposure from repeated blood exposures [22].

Prevalence estimates: non-response to the HBV vaccine in hemodialysis patients

Comprehensive analysis of existing literature

A systematic search was conducted using the PubMed database from 2000 to 2023, employing search keywords 'non-response HB vaccines' and 'non-responsive chronic HB' without language restrictions. Nine references were identified and initially examined based on titles and abstracts. Four studies were deemed suitable for inclusion with the prevalence of response analysis and the risk factors to the unresponsiveness of HBV vaccination in hemodialysis patients. This review encompasses studies with diverse populations explicitly focusing on non-responsive vaccine studies.

Review of studies

Several studies have been dedicated to understanding the underlying causes of vaccine non-responsiveness. Through the review of the studies, the

intention is to provide an all-comprehensive synopsis of the knowledge associated with the lack of response to HB vaccines. Research conducted by Asan *et al.* involved 316 dialysis patients in 7 dialysis centers in Denizli, Turkey. Fifty-two (16.5%) patients had no response to HBV vaccine. From their comparison of statistical analysis to the demographic data, they concluded that unresponsiveness to the HBV vaccination is particularly prevalent in individuals with hepatitis C infection, obesity, elderly, and individuals undergoing a long hemodialysis period [31].

A study was conducted in Boston with a sample size of 132 patients; 87 of them received Engerix-B 40-µg 4-dose at 0, 1, 2 and 6 months; whereas another 2 patients received the Recombivax-HB 40-µg 3-dose at 0, 2 and 6 months. The remaining 43 patients were given an unspecified HBV vaccine. The results showed 69 (52.3%) patients were non-responders to the HBV vaccine. Univariate analysis revealed that HBV vaccination non-responsiveness was substantially correlated with lower serum creatinine and advanced age. However, the unresponsiveness to the HBV vaccine in patients undergoing hemodialysis did not show a correlation with adverse outcomes. The sample size should be increased to evaluate the possible correlation between the response to HBV vaccines and enhanced clinical outcomes [52].

Another study by Cardova and team (2017) assessed the influence of some clinical and laboratory factors on seroconversion rate from the HBV vaccination in hemodialysis patients. Sixty patients were involved in this study. According to the findings, 14% of the patients with arteriovenous fistula, 7% of them with serum albumin levels more than 3.5 g/dL, and 50% of the patients with systemic disease were unresponsive to the vaccine [53]. Thirty out of 71 patients (29.7%) were non-responders in a study conducted by Almueilo [54]. The analysis revealed no significant differences in gender distribution, serum albumin levels, hemoglobin levels, ferritin, parathyroid hormone level, and C-reactive protein level between responders and non-responders. Both groups also showed no significant difference in the prevalence of diabetes mellitus. According to the analysis, younger age is associated with a positive outcome to the HBV vaccine in hemodialysis patients [54].

Table 2 summarizes the prevalence of non-response to the HBV vaccine and the risk factors among hemodialysis patients. In conclusion, this review of studies presents a comprehension of vaccine non-responsiveness. The research findings have shown that variance in non-response to the HB vaccine can be attributed to genetic predisposition, immunological mechanisms, and environmental influences.

Methodological differences and challenges

The critical factor that influences the validity and integrity of research is methodology in study design. The methodology defines the general structure, procedures, and strategies used to conduct a study and tackle research investigations. A well-structured methodology ensures an organized study, replicable methods, and the ability to produce reliable results.

Non-response to the HBV vaccine in hemodialysis patients indicates the inability to develop anti-HBs antibody levels higher or equal to 10 mIU/mL following the completion of the immunization series. Despite some studies assessing non-response vaccines in hemodialysis patients, the results are not consistent. This is primarily due to methodological differences among the studies. Differences in study group sizes were the central issue in these studies. Small group sizes may cause an increment in variability and a reduction in the precision of estimation. Furthermore, the lack of age, gender, and ethnicity-specific risk estimations may create biases in research outcomes. Patient selection bias is a noteworthy obstacle to research as it may significantly affect the validity of the study outcomes. The patient selection bias in the studies above is related to the inclusion of patients with specific characteristics such as high viremia, relative immunotolerance, past non-responsiveness to IFN-γ or other systematic antiviral therapy, and a significant number of patient exclusions due to incomplete full vaccination series or no post-vaccination antibody level check. Hence, taking a thoughtful approach and pre-emptive action is essential to tackle these methodological differences and related challenges.

Table 2. Prevalence and risk factors of hepatitis B (HB) vaccination in published studies.

Year	Prevalence of non-response	Risk factor	Reference
2017	16.5%	Hepatitis C infection, obesity, elderly, long haemodialysis period.	[31]
2023	52.3%	Elderly, lower serum creatinine.	[52]
2017	14% in patients with arteriovenous fistula, 7% in patients with serum albumin levels higher than 3.5 g/dL, 50% in patients with systemic disease.	Elderly, malnutrition.	[53]
2017	29.7%	Elderly	[54]

Strategies to improve vaccine response

Effective viral control measures can be achieved by implementing stringent hygiene protocols within hemodialysis units or clinical settings. However, despite these efforts, the primary means of protection for individuals undergoing dialysis remains a targeted vaccination strategy against HBV. While improvements in medical care quality and hygienic measures within hemodialysis units contribute positively to protection, non-response to the HBV indicates a failure to develop sufficient immune responses among hemodialysis patients following standard vaccination protocols [55]. Though non-response cases represent a small percentage of the population infected with HBV, the implications extend beyond individual vaccination challenges to significant clinical and public health concerns. Accordingly, non-responses among this population may necessitate alternative strategies such as immune globulin administration or novel vaccination approaches with improved regimens, which could be costlier and complex but ultimately offer better seroconversion rates [56]. Moreover, there is a growing need to focus on novel vaccination approaches, including developing new vaccines with improved adjuvant and administration strategies and personalized vaccination strategies tailored to identify high-risk patients and optimize vaccination outcomes.

Novel vaccination approaches

Achieving and maintaining immunity against HB is crucial for the health of individuals with CKD undergoing hemodialysis. However, standard vaccination protocols often fall short in this population due to weakened immune systems. Consequently, researchers have explored various strategies to enhance vaccine response. These include administering vaccines before dialysis, utilizing the intradermal route, providing additional doses, doubling the vaccine dosage, and combining vaccination with immune-modulating agents [13]. These approaches aim to improve immune response and long-term immunity in individuals with chronic diseases or compromised immune systems. Also, increasing vaccine dosage or frequency has shown promise, with studies demonstrating response rates of up to 68% with double dosing in pre-transplant patients [57], and 80% seroconversion with a single high-dose booster in chronic hepatitis C patients [58]. Intradermal vaccine administration has also yielded significantly higher immune responses compared to intramuscular injection, with seroconversion rates ranging from 51% to 69% in non-responsive patients [59]. Efforts to enhance vaccine immunogenicity have focused on incorporating additional antigens or adjuvants into formulations. Vaccines containing pre-S1, pre-S2 particles, or nucleocapsids have shown increased response rates in non-responders [60]. Adjuvants like 3-deacylated monophosphoryl lipid A (3D-MPL) and Delta inulin AdvaxTM have enhanced immunogenicity compared to traditional aluminum-based vaccines [61]. Given that hemodialysis patients often exhibit impaired immune responses, combining HEPLISAV-B™, a TLR agonist-based vaccine, with HBcAg-based vaccines may enhance T-cell and B-cell responses, offering a promising strategy to improve the stronger immune responses [62]. Moreover, alternative routes of administration, including nasal and oral vaccines, have demonstrated promising efficacy and safety profiles in early clinical trials [63]. These approaches offer potential solutions to overcome non-response to standard HB vaccination and improve immunization outcomes in high-risk populations.

Individualized approaches

Tailoring vaccination schedules which involve customizing vaccination schedules for hemodialysis patients is essential to optimize their immune response, considering their immunocompromised condition. Healthcare providers can enhance the likelihood of achieving protective antibody levels against HBV by tailoring vaccination protocols to individual patient needs. This tailored approach allows for adjustments such as administering higher vaccine doses, increasing the frequency of vaccine administration, or utilizing adjuvanted vaccines to stimulate a stronger and more effective immune response. Extended vaccination courses and combination vaccination with other relevant vaccines may further bolster immunity in this susceptible population.

Addressing non-responsive HBV cases among hemodialysis patients requires tailored vaccination strategies to overcome the challenge of inadequate immune response to standard HBV vaccination protocols in this group [7]. Collaboration among healthcare providers, nephrologists, infectious disease specialists, and public health authorities is crucial to optimizing vaccination outcomes and reducing the burden of HBV infection in hemodialysis settings. Personalized vaccination strategies, including tailored vaccination schedules, are paramount in combating this issue. Studies have demonstrated that alternative vaccination schedules, such as increasing vaccine dose or frequency of administration, can enhance immune response [64]. Adjuvanted vaccines have shown

promise in eliciting robust immune responses, potentially enhancing vaccine efficacy in non-responsive individuals [65]. This tailored approach aims to stimulate a stronger and more sustained immune reaction by utilizing adjuvanted HBV vaccines containing immune-enhancing substances, thus improving vaccine effectiveness among non-responders. This strategy underscores the importance of leveraging adjuvants to optimize immunization outcomes in populations with diminished vaccine responsiveness.

Extending vaccination courses and integrating HBV vaccination with other immunizations have been identified as strategies to enhance immunity [54,66]. Individuals are provided with additional opportunities for immune system stimulation by prolonging the duration of vaccination courses, potentially leading to the attainment of protective antibody levels. This approach may involve extending the vaccination schedule or administering booster doses over an extended period, reinforcing the immune response, and optimizing vaccine efficacy. Regular monitoring of antibody levels following vaccination is crucial for evaluating vaccine response and determining the need for further interventions [67]. Additionally, administering HBV vaccines with other vaccines or immunomodulatory agents has been recognized as a strategy to bolster the immune response. Combining HBV vaccination with other vaccines, such as those for hepatitis A or influenza, may elicit synergistic effects and enhance vaccine efficacy. This integrated approach underscores the importance of comprehensive monitoring and strategic combinations to optimize immunization outcomes.

Educating and counselling hemodialysis patients on the importance of vaccination, the risks of HBV infection, and the benefits of tailored vaccination strategies is essential. Patient engagement can enhance adherence to vaccination recommendations and improve outcomes. This educational component, combined with pre-vaccination serological testing, is pivotal in tailored vaccination approaches for non-responsive HBV among hemodialysis patients [68,69]. Regular post-vaccination monitoring of antibody levels allows for the assessment of vaccine response and identifies individuals needing additional interventions, such as booster doses or alternative strategies. Pre-vaccination serological testing identifies those with pre-existing HBV immunity or who may benefit from alternative vaccination approaches, optimizing vaccination efforts and reducing the HBV burden in hemodialysis settings. Overall, a personalized approach, supported by evidence-based strategies, is essential to optimize vaccination outcomes and reduce the burden of HBV infection in hemodialysis settings.

Identifying high-risk patients among hemodialysis individuals infected with HBV involves considering various factors that may impact vaccine efficacy. Firstly, age is a critical determinant, as infants and older adults typically exhibit diminished immune responses to vaccines due to immunosenescence, rendering them more vulnerable to inadequate protection conferred by vaccines, including those targeting HB. Additionally, the presence of underlying health conditions, such as autoimmune disorders or chronic illnesses requiring long-term medication use, may compromise immune function, leading to suboptimal responses to vaccination. Similarly, malnutrition, commonly observed in individuals undergoing hemodialysis, can weaken the immune system and reduce the efficacy of vaccines.

Furthermore, gender plays a significant role in influencing dialysis frequency, thereby impacting the high non-response rate of HB vaccination. A logistic regression and decision tree analysis in China involving hemodialysis patients who received standard or high-dose HB vaccine found male gender and higher dialysis frequency (> 4 times per 2 weeks) as significant risk factors for non-response [10]. Although this study offers insights into personalized vaccination approaches for hemodialysis patients, larger sample sizes and the inclusion of pre-dialysis patients in future research are warranted.

It is crucial to highlight that vaccine administration errors can significantly impact vaccine efficacy. Improper storage, handling, or injection technique can compromise the integrity of the vaccine and diminish its ability to stimulate an immune response effectively. Adherence to strict vaccination protocols, including maintaining proper storage conditions and using appropriate administration techniques, is paramount to ensure optimal vaccine effectiveness and minimize the risk of vaccine failure among hemodialysis patients. Additionally, a comprehensive approach to identifying high-risk patients for HB vaccination among hemodialysis individuals involves considering multiple factors, such as age-related immunosenescence, underlying health conditions affecting immune function, genetic predispositions to vaccine responsiveness, and adherence to proper vaccine administration protocols [70]. Furthermore, recognizing the impact of sleep disturbances and other environmental factors on vaccine response could provide additional insights into optimizing vaccination

strategies for hemodialysis patients and improving HB prevention efforts in this population.

Recently, Han *et al.* explored whether the timing of hemodialysis sessions influences the response to HB vaccination among hemodialysis patients, considering their heightened risk of HB infection and lower seroconversion rates compared to the general population [71]. Their findings from univariate analysis suggested a potential association between early hemodialysis start times and increased HB vaccination response rates. However, this association weakened after adjusting for confounding factors in multivariate analysis, indicating that other variables such as age, gender, and duration of hemodialysis treatment may influence vaccination response.

By considering these various elements, healthcare providers can tailor vaccination strategies to each patient's needs, ultimately enhancing protection against HBV infection.

Conclusion and future directions

Non-response to the HB vaccine, characterized by the failure to develop protective anti-HB antibodies, is a significant issue among hemodialysis patients, the elderly, and immunocompromised individuals. In this context, liposome-based vaccine strategies offer a promising solution by enhancing antigen stability, immune activation, and delivery efficiency. Liposomes can encapsulate the HB surface antigen (HBsAg), protecting it from degradation while improving uptake by antigen-presenting cells, leading to stronger immune responses. Unlike conventional alum-adjuvanted vaccines that primarily stimulate humoral immunity, liposomes can be engineered with immune-stimulating molecules like monophosphoryl lipid A (MPLA) or CpG oligodeoxynucleotides to activate both humoral and cellular immunity. Additionally, liposomes can mimic the HBV viral envelope, improving antigen recognition and ensuring a more robust and sustained immune response. Their ability to provide controlled and prolonged antigen release further enhances immune stimulation, which is particularly beneficial for individuals with weak immune responses. While current HB vaccines such as Engerix-B and HEPLISAV-B do not utilize liposomes, ongoing research explores liposomal formulations as an alternative for non-responders. Future studies should focus on optimizing these formulations, ensuring scalability, and validating their efficacy and safety through clinical trials, as liposome-based HB vaccines have the potential to significantly improve immunogenicity and enhance vaccine responses in high-risk populations. By advancing these research directions, the field can move toward more effective and individualized vaccine strategies, ultimately improving patient outcomes. Addressing these critical gaps will enhance HB protection for these populations, reinforcing the importance of collaborative efforts in patient care and public health.

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Conflict of interest

No conflict of interest is declared.

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