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Real-world effectiveness of hepatitis B vaccination in dialysis patients

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A B S T R A C T

Background: Chronic kidney disease is (CKD) a highly prevalent condition worldwide, with an increasing prevalence in the general population. Effective vaccination strategies are crucial in this population to prevent hepatitis B virus (HBV)-related complications. This study aimed to evaluate the effectiveness of different HBV vaccines in patients with CKD undergoing dialysis, focusing on seroconversion rates and overall immune response.

Methods: A non-concurrent prospective cohort study was conducted on 160 outpatient long-term dialysis patients at the G. Martino Hospital in Messina. Patients were vaccinated with either FENDRIX (HB-AS04), HBVAXPRO 40 mg, or a combination, and their immune responses were assessed one month after the completion of the vaccination course.

Results: The study achieved 100 % vaccination coverage. The overall seroconversion rate was 62.5 %, with mean anti-HBs titers of 604.15 mIU/mL (±437.23 SD) across the cohorts. No significant differences were observed between responders and non-responders concerning demographic, clinical, and biochemical characteristics.

Conclusion: The study confirms the effectiveness of HBV vaccines in patients with CKD, though with a lower and delayed response compared to the general population. Establishing a diagnostic-therapeutic care pathway that integrates vaccination from the early stages of CKD is essential to improve outcomes in this high-risk group.

Keywords
Vaccines
HBV
Dialysis patients
Chronic kidney disease
High-risk group

1. Introduction

Chronic kidney disease (CKD) is a widespread public health issue and a highly prevalent condition globally, with its incidence steadily increasing. It is defined by a sustained reduction in glomerular filtration rate (GFR) to less than 60 mL/min/1.73 m^2 or the presence of renal damage for at least three months. [1]. CKD is a progressive disease that frequently advances to end-stage renal disease (ESRD), a condition associated with markedly increased rates of morbidity and mortality. Cardiovascular diseases and infections are the primary causes, accounting for 50 % and 20 % of total mortality in ESRD patients, respectively [2]. The increased susceptibility to infections in ESRD patients is largely due to alterations in the immune system caused by uremia, which induces a state of immunosuppression. This immunosuppressive state not only increases the prevalence of infections but also their severity, making effective preventive measures, such as vaccination, critically important in this vulnerable group. [3]

Hepatitis B virus (HBV) infection is a significant risk for patients with CKD, particularly those on dialysis, due to their frequent exposure to blood products and compromised immune response. Vaccination is recommended for pre-end-stage renal disease patients before they become dialysis-dependent and for peritoneal and home dialysis patients, as they might require in-center hemodialysis. Specifically, below a GFR of 30 ml/min/1.73 m2, the response is reduced and increases proportionally with the onset of dialysis [5].

In recent years, new HBV vaccines have been developed to address the limitations of standard vaccines in this patient population. Fendrix® (HB-AS04), authorized in Europe in February 2005, is one such vaccine. It contains an adjuvant system that acts as a TLR4 agonist, which

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enhances the immune response by inducing higher levels of B memory cells compared to traditional aluminum-only formulations [6]. This vaccine has shown greater efficacy in pre-dialysis and CKD patients compared to the standard recombinant HBV vaccine, Engerix-B® [7,8]. Another vaccine, HBVAXPRO 40 μg, is adjuvanted with amorphous aluminum hydroxyphosphate sulfate, which serves to accelerate, enhance, and prolong the protective effects of the vaccine [9]. There is concrete evidence in the medical literature that maintenance dialysis patients receiving a complete cycle of recombinant HBV vaccine (i.e., Engerix-B) (four doses at 0, 1, 2, and 6 months, 20 μg each dose intramuscularly) show a seroprotecting rate around 50–60 %. Additionally, anti-HB antibody levels are low and logarithmically decline over time [10,11].

Despite the availability of HBV vaccines, the immunogenicity of these vaccines in CKD patients is often reduced [4]. This is particularly true for patients in advanced stages of the disease, where the immune response to vaccination is weaker compared to the general population. Numerous clinical, demographic, and biochemical parameters have been proposed to explain the poor immunogenicity of HB, including age, sex, overweight, positive serologic status for HCV, HIV infection, history of blood transfusions, interleukin genotypes, possession of the major histocompatibility complex haplotype HLA—B8, SCOI, DR3, and inappropriate nutritional status [11]. According to a report conducted by a single centre, vitamin D deficiency has been linked to a poor response to the HBV vaccine [12]. Failure to complete the entire vaccination cycle against HBV also plays a role [13]. Given the importance of such vaccination practice, considering the lack of response in approximately 50 % of patients, it is necessary to establish a diagnostic-therapeutic care pathway that includes the management of ESRD patients from the early stage, directing them in their chronicity pathway, with a “mandatory” passage through the vaccination clinic, as done in other contexts [14].

This study aims to evaluate the effectiveness of HBV vaccines in a cohort of CKD patients undergoing dialysis. By comparing the seroconversion rates and overall immune responses of patients receiving Fendrix and HBVAXPRO 40 μg with those receiving the standard Engerix-B vaccine, this study aims to determine which vaccine offers the best protection for this high-risk population. The findings will have significant implications for vaccination strategies in CKD patients, potentially leading to improved clinical outcomes and reduced morbidity and mortality in this vulnerable group.

2. Materials and methods

Setting and Study Design: This non-concurrent retrospective cohort study was conducted at the “Azienda Ospedaliera Universitaria” (AOU) G. Martino Hospital in Messina, from September 2023 to March 2025. The study focused on patients undergoing long-term outpatient dialysis. An initial baseline screening was performed to assess the susceptibility of these patients to hepatitis B virus (HBV) infection. Information was retrospectively collected on patients with chronic kidney disease (CKD) who had not been artificially or naturally immunized against HBV and were eligible for inclusion in the study.

Inclusion criteria: Participants were included if they met the following criteria: they were 18 years or older, undergoing regular dialysis (hemodialysis or peritoneal dialysis), had negative serum HBsAg/anti-HBs at baseline, and were able and willing to provide informed consent.

2.1. Eligibility and screening

All chronic kidney disease (CKD) patients undergoing dialysis were screened for eligibility. Screening included medical history, HBsAg, anti-HBs, and anti-HBc testing. Individuals who were HBsAg-positive were excluded, whereas anti-HBc–positive patients were managed as follows:

- anti-HBc–positive / anti-HBs ≥10 mIU/mL: considered immune, no further vaccination.
- anti-HBc–positive / anti-HBs <10 mIU/mL: allocated to vaccination, with tailored monitoring.

Vaccine allocation criteria: Eligible participants were assigned to vaccine groups according to random allocation.

Sample size per group: A total of 160 patients were enrolled:

- Group A: 80 patients
- Group B: 80 patients

Data sources: Clinical and laboratory data were obtained from dialysis unit records, electronic hospital charts, and laboratory information systems. Vaccination data were cross-verified with the regional immunization registry.

Sample size: Primary endpoint. Proportion of seroprotection (anti-HBs ≥10 mIU/mL) one month after completion of the vaccination schedule.

Main comparison. Vaccine A vs Vaccine B (allocation 1:1; $n_1 = n_2 = 80$).

Assumptions and parameters:

- Expected proportion in the reference group: $p_0 = 0.50$ (based on literature in dialysis patients).
- Clinically relevant difference: $\Delta \approx 0.21$ ($p_1 \approx 0.71$ vs $p_0 = 0.50$).
- $\alpha = 0.05$ (two-sided), power = 80 %.
- Two-proportion test with normal approximation and continuity correction (confirmed with χ^2/Fisher’s test).

Sample size adequacy: With 80 participants per arm, the study had ≥80 % power to detect an absolute difference of at least 21 percentage points between groups (corresponding to Cohen’s h ≈ 0.44; formula: h = 2arcsin p1 − 2arcsin p0h = 2\arcsin\sqrt{p_1}-2\arcsin\sqrt{p_0}h = 2arcsinp1 − 2arcsinp0; hcrit = (z1 − α/2 + z1 − β)2/nh_{\text{crit}} = (z_{1-α/2} + z_{1-β})\sqrt{2/n}hcrit = (z1 − α/2 + z1 − β)2/n).

Using a conservative adjustment for two pairwise comparisons (Bonferroni, $\alpha = 0.025$, two-sided), the minimum detectable difference increased to ≈23–24 percentage points ($p_1 \approx 0.73$ vs 0.50).

Overall precision ($n = 160$): For an expected seroprotection rate of ~0.60–0.65, the 95 % confidence interval has a half-width of ≈7–8 percentage points (e.g., for $p = 0.625$, ±7.5 pp), ensuring accurate estimation of the overall prevalence of seroprotection in the cohort.

Software: Calculations were performed using R 4.2.0 (power.prop.test / pwr.2p.test) based on Cohen’s h metric for planning and verified with two-sample proportion tests.

Ethical Considerations: The study followed the ethical principles outlined in the 1996 version of the Helsinki Declaration and Good Clinical Practice guidelines. All patients provided written informed consent before enrollment. The study was notified to the Sicilian Regional Ethics Committee and registered in an ad hoc logbook with the number 511400.

Vaccination Protocol: The study involved the administration of three vaccines: FENDRIX (hepatitis B vaccine, rDNA, adjuvanted and adsorbed), HBVAXPRO 40 ¦ mcg (recombinant DNA) and ENGERIX B (hepatitis B vaccine, rDNA). In the first cohort, patients were administered 4 doses of recombinant vaccine formulated with an improved adjuvant system (HBV AS04, Fendrix), produced by GlaxoSmithKline Biologicals. The HBV AS04 vaccine was administered intramuscularly in a 0.5 ml injection (deltoid muscle) according to a schedule of 0, 1, 2, and 3 months. Each dose of HBV-AS04 contained 20 μg of recombinant HBsAg, 50 μg of MPL (3′-0-desacyl-4′-monophosphoryl lipid A), and 0.5 mg of aluminum salt. In the second cohort, three (0, 1, 6 months) or four doses (0, 1, 2, 12 months) of HBVAXPRO 40 μg/ml adsorbed vaccine were administered, produced by SANOFI PASTEUR MSD SNC. Each dose contained 40 μg of hepatitis B virus surface antigen, adsorbed onto amorphous aluminum hydroxy phosphate sulfate. This vaccine was administered to the contralateral arm of patients with arteriovenous

fistulas for dialysis. In the subgroup of patients on intermittent hemodialysis, the adjuvanted hepatitis B vaccine was administered before the start of hemodialysis sessions or during the interdialytic period. The third cohort was represented by the first two at baseline, first by the administration of a second cycle necessary to improve HBsAb.

A CONSORT-style (STROBE-adapted) flow diagram (Fig. 1) with denominators at each step and per-group outcomes is reported below.

Serum Studies: Blood samples were retrospectively collected at baseline and one month after completing the vaccination schedule. HBV serological markers were tested in all patients at baseline. Hepatitis B surface antigen (HBsAg), antibodies against hepatitis B surface antigen (HBsAb), and hepatitis B core antigen (HBcAb) were tested in plasma samples using enzyme immunoassays. A wide range of demographic, clinical, and biochemical parameters was also collected for each participant.

2.2. Laboratory methods

Serological testing for HBsAg, anti-HBs, and anti-HBc was performed using a chemiluminescent immunoassay (LIAISON®, DiaSorin S.p.A., Saluggia, Italy). All assays were conducted with the same lot number throughout the study period. The lower limit of quantification (LLOQ) for anti-HBs was **3.3 mIU/mL**, with protective immunity defined as anti-HBs ≥10 mIU/mL.

Quality control (QC) was carried out according to the manufacturer's recommendations, with two internal controls (low and high) included in each run. The inter-assay coefficient of variation (CV) was typically **<8 %**, and the intra-assay CV **<5 %**, consistent with the manufacturer's performance specifications.

All serum samples were processed and tested in the same accredited laboratory at [institution name], ensuring consistency and minimizing inter-laboratory variability.

2.3. Safety and reactogenicity

2.3.1. Safety assessment

Solicited local (e.g., pain, redness, swelling) and systemic (e.g., fever, fatigue, myalgia, headache) adverse events (AEs) were collected using standardized diary cards during the 7 days following each vaccination. Events were graded by severity according to a predefined scale: mild (no interference with daily activity), moderate (some interference), and severe (prevents daily activity). Investigators also monitored unsolicited adverse events and serious adverse events (SAEs) throughout the study period.

2.3.2. Causality assessment

The relatedness of each AE to vaccination was determined by the site investigators using prespecified criteria (temporal association, biological plausibility, and exclusion of alternative causes), in accordance with international pharmacovigilance guidelines (CIOMS/WHO). Local symptoms occurring at the injection site were generally considered vaccine-related unless a clear alternative explanation was present.

Statistical Analysis: All statistical analyses were performed using R software (ref. 4.2.0). Descriptive analyses were used to summarize continuous variables as means ± standard deviation and categorical variables as percentages. Normality of quantitative data was tested using the Shapiro-Wilk test. Differences in demographic, clinical, and biochemical characteristics between responders and non-responders to the HBV vaccine were analyzed using Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. The chi-square test was used for the association between immune response to the HBV vaccine (responder/non-responder) and gender.

For statistical significance, *p*-values <0.05 were taken into consideration.

Definitions: A positive vaccine response (seroprotection) was defined

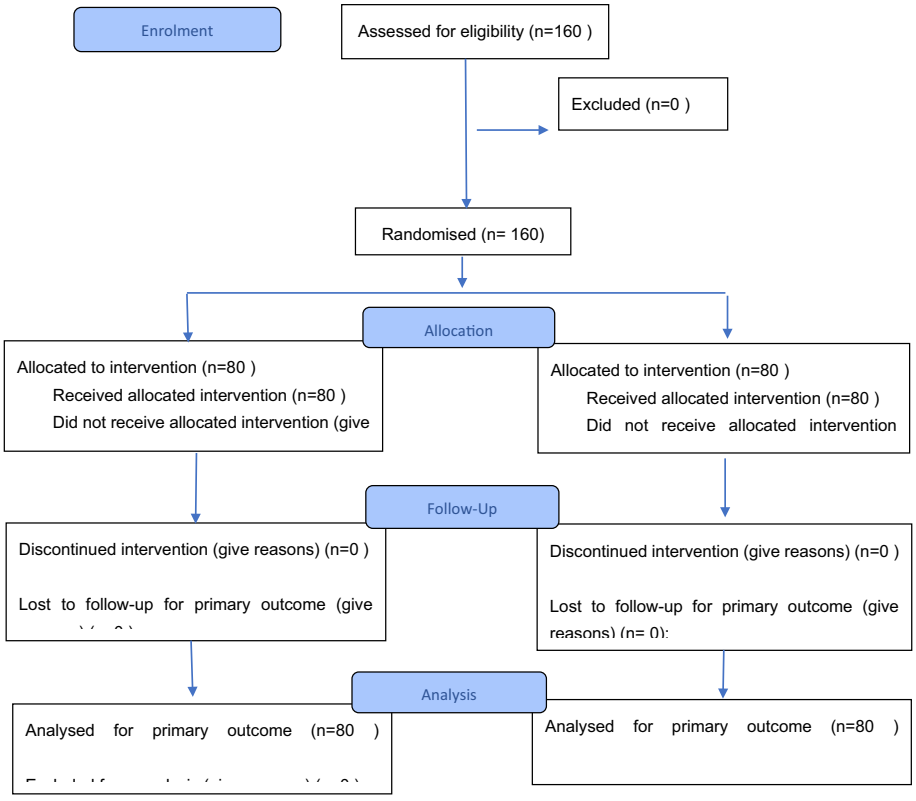

Fig. 1. CONSORT 2025 Flow Diagram [15].
Flow diagram of the progress through the phases of a randomised trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).

as anti-HBs ≥10 mIU/mL. Patients were classified as responsive or non-responsive based on their anti-HBs antibody levels one month after completing the vaccination cycle. Non-responsive patients were those with HBsAb levels <10 IU/L.

Serological Analysis: The following parameters were also collected: white blood cell count, lymphocyte count, transferrin levels, and total proteins. Additionally, the presence of one or more comorbidities was recorded for each participant.

All enrolled patients completed the study protocol without any loss to follow-up, and all planned clinical and serological variables were available. Consequently, no missing data occurred, and no imputation or sensitivity analyses were necessary. Had missing data been present, multiple imputation methods under the assumption of missing at random (MAR) would have been applied."

3. Results

A total of 160 patients were enrolled in the study, and all participants completed the protocol, allowing for a comprehensive per-protocol analysis. The study sample had a mean age of 67.85 (± 21.05 SD). The baseline demographic, clinical, and biochemical parameters of the patients are reported in Table 1. Most patients had Caucasian origin and no cases of HIV infection were reported among the study population.

The study achieved 100 % vaccination coverage for HBV among the participants. The seroprotection rates observed in the three investigated cohorts were 100 % (n = 20), 40 % (n = 12), and 62.1 % (n = 36), respectively. Overall, 62.5 % (100/160) of the patients exhibited an adequate immune response, defined as anti-HBs titers ≥10 mIU/mL, one month after completing the vaccination series to standardize the procedure. The mean seroprotecting antibody titer across all cohorts was 604.15 mIU/mL (±437.23 SD) for all cohorts.

For the three cohorts, the GMT were represented in Fig. 2.

Univariate analysis (Table 2) showed no statistically significant difference between responders (seroprotection, anti-HBs ≥10 mIU/mL) and non-responders concerning a great number of analyzed demographic, clinical, and biochemical characteristics.

No significant differences in seropositivity rates were found when analyzing the patient subgroups by gender, age, transferrin, comorbidity, and white cell count. Infection surveillance was conducted for 1 months following vaccination. Participants underwent regular testing for HBsAg (at months 1), with HBV DNA measured in cases of clinical suspicion. During this period, no new HBV infections were detected. However, given that immunogenicity was assessed only one month after series completion and follow-up was limited in duration, these data should be interpreted as an absence of incident infections during the surveillance window, rather than definitive evidence of long-term vaccine effectiveness.

Multivariate analysis reported the following values of Table 3.

3.1. Adverse events (Table 4).

Solicited local reactions were common across vaccine groups, most frequently pain at the injection site, which was generally mild to moderate and transient. Systemic events such as fatigue, headache, and myalgia were reported at lower frequencies. The majority of solicited AEs were mild (10 %) or moderate (5 %), with severe events being rare (0 %).

No unexpected safety signals were identified. Serious adverse events (SAEs) were infrequent (n = 0, 0 %) and none were judged to be causally related to vaccination.

In line with protocol definitions, local symptoms were presumed to be related to vaccination unless a more plausible cause was documented. Systemic symptoms were assessed case by case.

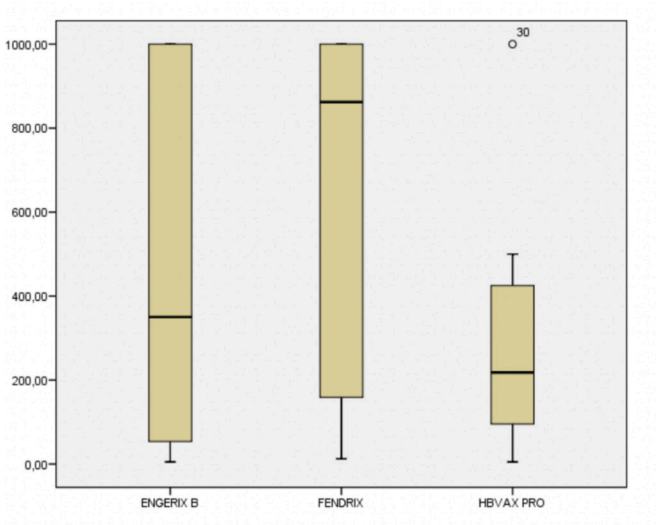

Fig. 2. GMT by vaccine in the three cohorts.

Table 1
Baseline characteristics of study patients.

Gender	Males	70 (43.8)
Age, years	Mean (SD)	67.85 ± 21.05
Diabetes mellitus, *n*		32 (20 %)
Arterial hypertension, *n*		22 (13.75)
White cell count	Mean (SD)	6732.69 (2140.79)
Transferrin, mg/dL	Mean (SD)	178 ± 32.37

Table 2
Baseline characteristics of responder and non-responder patients.

	Responders (n = 100)	Non-responders (n = 60)	*P*
Gender, males	48 (48)	36.7 (22)	0.323
Gender, females	63.3 (52)	52 (38)	
Age, years	68.21 ± 18.68	67.02 ± 23.74	0.804
Transferrin, mg/dl	175 ± 31.12	196 ± 33.99	0.728
Number of comorbidity	2 ± 0.96	2 ± 1.08	0.320
White cell count, number/ul	6000 ± 1828.38	7000 ± 2528.67	0.749

Table 3
Multivariate analysis.

Variable	OR (95 % CI)	*P* value
Age	1.00 (0.96–1.04)	0.862
Sex	0.77 (0.17–3.50)	0.740
Comorbidities	0.88 (0.44–1.78)	0.731
Vaccine type	1.02 (0.48–2.13)	0.968

4. Discussion

In our study, we obtained a total of 100 % of vaccination coverage and a high rate of seroconversion in patients The seroprotecting rates across the three investigated cohorts were 100 % (n = 20), 40 % (n = 12), and 62.1 % (n = 36), with an overall responder rate of 62.5 % (100/160) one month after completing the vaccination course. The mean seroprotective antibody titer across all cohorts was 604.15 mIU/mL (±437.23 SD). These findings are consistent with those reported by Fabrizi et al. [5,12,17] who reported a seroconversion rate of 81.5 % one month after completing the vaccine course. They also noted significant differences in seroprotection rates across various demographic, clinical, and biochemical characteristics, with age showing only a near-significant difference (p = 0.08) [14].

Table 4
Adverse Event Summary. Adverse events are summarized by category, event type, time window, vaccine group, dose, frequency, severity grading, duration, relatedness, action taken, and outcome. If a participant experienced multiple grades of the same event, the maximum grade was reported. SAEs were reviewed separately by an independent safety monitor.

Category	Specific AE	Time Window	Vaccine Group	Dose #	n/N (%)	Severity Grade (1–4)	Median Duration, days (IQR)	Relatedness	Action Taken	Outcome
Local	Pain at injection site	Days 0–7	A (40 μg)	1						
Local	Erythema	Days 0–7	A (40 μg)	1						
Local	Swelling/ induration	Days 0–7	A (40 μg)	1						
Systemic	Fever	Days 0–7	A (40 μg)	1						
Systemic	Fatigue	Days 0–7	A (40 μg)	1						
Systemic	Myalgia	Days 0–7	A (40 μg)	1						
Systemic	Headache	Days 0–7	A (40 μg)	1						
Unsolicited	(specify)	Days 0–28	A (40 μg)	1						
SAE	(specify)	Through EOS	A (40 μg)	1						
Local	Pain at injection site	Days 0–7	B (20 μg)	1						
Local	Erythema	Days 0–7	B (20 μg)	1						
Local	Swelling/ induration	Days 0–7	B (20 μg)	1						
Systemic	Fever	Days 0–7	B (20 μg)	1						
Systemic	Fatigue	Days 0–7	B (20 μg)	1						
Systemic	Myalgia	Days 0–7	B (20 μg)	1						
Systemic	Headache	Days 0–7	B (20 μg)	1						
Unsolicited	(specify)	Days 0–28	B (20 μg)	1						
SAE	(specify)	Through EOS	B (20 μg)	1						

The HBV-AS04 vaccine offers several advantages for long-term dialysis patients. It reduces the need for booster doses, thereby decreasing the frequency of vaccinations and related healthcare visits. This extended protection is particularly crucial for patients awaiting renal transplantation, as it allows for the inclusion of donors who were previously excluded due to prior HBV infection, potentially expanding the donor pool and reducing transplant wait times. Additionally, chronic HBV infection has been associated with the development and progression of CKD in the general population. By providing protection against HBV, the vaccine may help mitigate the risk of kidney damage and related complications in dialysis patients [16].

Patients who test negative for hepatitis B surface antigen (HBsAg) but have protective levels of anti-HBs antibodies can safely undergo hemodialysis even in settings designated for HBsAg-positive patients. This flexibility in patient management allows for better utilization of resources and reduces the need for separate facilities or staffing arrangements solely for HBsAg-positive patients.

However, despite these benefits, it remains essential to implement preventive measures, such as isolating HBsAg-positive carriers within dialysis units, to prevent HBV transmission. Adhering to CDC recommendations for isolation protocols helps safeguard both patients and healthcare staff from HBV transmission within dialysis settings [17].

Another important point to be discussed is that pre-existing renal disease promotes sepsis-induced acute kidney injury and worsens outcomes [18–22]. This underscores the importance of vigilant management of infections and other complications in this patient population.

One limitation of this study is the lack of data on the decay rate of anti-HBs titers following vaccination, which could provide insights into the long-term efficacy of the vaccines. Nevertheless, a notable strength of the study is the large sample size, which enhances the reliability of the findings. Additionally, the study's evaluation of three different vaccine types provides a comprehensive understanding of the effectiveness of HBV vaccination in this high-risk population.

5. Conclusions

This study demonstrated a robust immune response across all three cohorts of immunized patients, providing valuable real-world data on the effectiveness of HBV vaccines in a large sample of patients with CKD. Our findings confirm that patients with CKD exhibit a lower and delayed response to HBV immunization compared to the general population. This reduced response is likely due to various factors associated with CKD, including malnutrition, low hemoglobin levels, uremia, and immunological dysfunction, all of which categorize these patients as immunocompromised. To achieve satisfactory seroconversion in this vulnerable population, it is critical to initiate vaccination during the early stages of CKD (stages 3–4), before the onset of renal replacement therapy, or to utilize adjuvanted vaccines specifically designed to enhance immune responses. Given the importance of such vaccination practices, it is necessary to establish a diagnostic-therapeutic care pathway. This pathway should include early and continuous management of CKD patients, with mandatory integration of vaccination clinics, as has been successfully implemented in other healthcare settings [19–21]. Overall, our study highlights the need for tailored vaccination strategies in CKD patients to improve clinical outcomes and protect this high-risk group from HBV infection.

CRediT authorship contribution statement

Giovanni Genovese: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Elisabetta Genovese:** Investigation, Data curation. **Domenico Santoro:** Visualization, Validation. **Flavia Pennisi:** Writing – review & editing, Writing – original draft. **Giuseppe Trimarchi:** Methodology, Formal analysis. **Raffaele Squeri:** Validation, Supervision, Project administration. **Daniela Lo Giudice:** Visualization, Validation. **Cristina Genovese:**

Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Institutional review board statement

The study was conducted by the Declaration of Helsinki.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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