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HEPATITIS B VACCINE FAILURE: A SYSTEMATIC REVIEW OF GENETIC, IMMUNOLOGICAL, AND BEHAVIORAL CONTRIBUTORS TO NON-IMMUNITY, POST HEPATITIS B VACCINATION

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ABSTRACT

Background: Hepatitis B virus (HBV) remains a major global public health problem despite highly effective vaccines. While most recipients develop protective anti-HBs antibody titres (≥10 mIU/mL), a minority fail to seroconvert, posing risks for ongoing transmission. This systematic review quantified the prevalence of hepatitis B vaccine non-response and evaluated genetic, immunological, behavioral, and clinical determinants. **Methods:** Following PRISMA 2020 guidelines, we searched PubMed/MEDLINE, EMBASE, Scopus, Web of Science, CINAHL, Cochrane Library, African Index Medicus, and gray literature up to November 2025. Eligible studies included RCTs, cohort, case-control, cross-sectional, and genetic association studies reporting post-vaccination anti-HBs titres. Non-response was defined as anti-HBs <10 mIU/mL 1-3 months post-vaccination. Two reviewers independently screened studies, extracted data, and assessed risk of bias using the JBI tool. Random-effects meta-analysis estimated pooled prevalence and odds ratios (ORs) for predictors of non-response; heterogeneity was assessed using I^2 and Cochran's Q, and publication bias using funnel plots and Egger's regression. **Results:** Of 8,214 records identified, 64 studies met inclusion criteria, with 41 included in meta-analysis. Overall pooled prevalence of vaccine non-response was 18-22%, varying by population. Healthy adults exhibited non-response rates of 5-10%, whereas immunocompromised populations including hemodialysis patients and HIV-infected individuals showed rates of 20-40% [p <0.001]. Older age (≥40 years) and male sex were associated with higher non-response, with immunocompromised status more than doubling non-response rates. Elevated BMI negatively affected seroconversion, with ORs per 5-unit increase ranging from 1.2–1.3 (p=0.004–0.032). HLA class II alleles (HLA-DRB103, DRB107, HLA-DPB1) and immune-regulatory gene variants (BTNL2, DTX1) consistently predicted non-response (ORs 1.5–2.0; p <0.001). Non-response was highest in African cohorts (~22-25%), intermediate in Asian and North American cohorts (~15-20%), and lowest in European populations (~10–14%). Publication bias was minimal for genetic and immunocompromised cohorts, but small-study effects were observed for obesity-related studies (Egger's p = 0.032). **Conclusion:** Hepatitis B vaccine non-response affects approximately one in five individuals and is driven by genetic predisposition, immunological status, age, sex, BMI, comorbidities, and behavioral or operational factors. These findings support targeted post-vaccination antibody testing, prioritized revaccination, and personalized strategies for high-risk groups to enhance HBV control and elimination efforts.

KEYWORDS: While most recipients develop protective anti-HBs antibody titres (≥10 mIU/mL), a minority fail to seroconvert, posing risks for ongoing transmission.

BACKGROUND

Hepatitis B virus (HBV) remains an urgent global public-health problem decades after the advent of an effective vaccine. Recent global estimates place the number of people living with chronic HBV infection in the hundreds of millions, with the World Health Organization reporting roughly 254 million people living with chronic hepatitis B infection in 2022 and ongoing substantial annual incidence in many regions of Africa and Asia.[1] The public-health consequences of chronic HBV are profound: lifelong infection predisposes to progressive liver fibrosis, cirrhosis and hepatocellular carcinoma, and viral hepatitis is responsible for a very large proportion of liver-related mortality worldwide.[2,3] The development and widespread implementation of recombinant hepatitis B vaccines beginning in the 1980s precipitated extraordinary declines in HBV incidence and HBV-related cancer in populations with high vaccine coverage, with infant birth-dose strategies and childhood schedules now cornerstones of elimination strategies in many countries.[4,5] Vaccination with currently used recombinant hepatitis B vaccines produces robust sero-protection in the majority of recipients: pooled estimates from population and clinical studies demonstrate seroconversion rates approaching or exceeding 90–95% in healthy adults and often >98% in infants and children when vaccine storage, dosing and schedules meet recommended standards.[6,7] This high efficacy underpins global policy recommendations for universal infant immunization, targeted vaccination of at-risk adults, and occupational health programmes for healthcare workers and other exposed groups.[4,8]

Despite these clear benefits, a consistent minority of vaccinees fails to develop or to sustain the commonly accepted threshold of seroprotective anti-HBs antibody (anti-HBs) concentration conventionally defined as ≥10 mIU/mL after completion of a standard primary series. Estimates vary by study and population, but data aggregated across settings indicate that roughly 5–10% of immunocompetent adults and a somewhat variable fraction of older adults and persons with comorbidities do not achieve protective anti-HBs titres following the usual three-dose schedule.[6,9] The phenomenon of "vaccine failure" or "non-response" is heterogenous in its causes and clinical implications: for some individuals the lack of measurable anti-HBs reflects a true absence of vaccine-induced immunity (primary non-response), while for others it is a transient or waning serological finding despite retained immunological memory capable of mounting an anamnestic response upon exposure or booster vaccination (secondary failure).[10,11] The public-health implications of non-response are nontrivial: persons who remain susceptible despite vaccination represent persistent reservoirs for transmission in high-exposure settings, and failure to identify or manage non-responders can undermine targeted protection policies for healthcare workers, neonates born to HBV-infected mothers, and other vulnerable subgroups.[4,8]

A large and growing literature implicates a complex interplay of host genetics, immune system status, and behavioral and environmental modifiers as determinants of vaccine responsiveness. Genetic factors especially variation in human leukocyte antigen (HLA) class II alleles and polymorphisms within cytokine and innate-immune pathway genes (for example IL-10, IL-2, and TLR family members) have been repeatedly associated with differential seroconversion rates after hepatitis B vaccination in case-control and cohort studies, suggesting heritable differences in antigen presentation, T-helper polarization and B-cell help that influence antibody production.[12-15] Concurrently, acquired or chronic immunological impairments most prominently HIV infection, end-stage renal disease with dialysis, use of immunosuppressive agents, older age, and metabolic conditions such as obesity and diabetes have consistently been shown to reduce sero-protection rates, to accelerate antibody waning and to blunt booster responses in some cohorts.[16-19] Finally, behavioral and lifestyle factors (notably tobacco smoking, heavy alcohol use and malnutrition), as well as operational issues such as improper storage/handling of vaccine, incorrect dosing or spacing, and incomplete series completion, contribute further to observed non-response at both individual and programme levels.[20-23] Because the relative magnitudes and interactions of these drivers vary by population and setting, failure to account for their combined effects limits the ability of clinicians and programmes to predict non-response, to tailor booster or revaccination strategies, or to develop alternative vaccination schedules or adjuvant strategies for high-risk groups.

Although numerous primary studies and several narrative reviews examine single classes of determinants (for example, HLA associations or the impact of HIV on vaccine seroconversion), an integrated, systematic synthesis that simultaneously evaluates genetic, immunological and behavioral contributors and their interactions is lacking. Genetic association studies of hepatitis B vaccine response have identified multiple loci associated with non-response, but results are heterogeneous across ethnic groups and study designs and often underpowered to detect modest effects or gene–environment interactions.[12,14] Immunological investigations likewise show consistent signals such as decreased responsiveness in persons living with HIV, dialysis patients, or older adults but the literature is fragmented with variable adjustment for confounders (e.g., nutritional status, smoking, BMI) and inconsistent endpoints (seroprotection at one month vs durable titres at one year).[16-19] Behavioral factors, while recognized as modulators of immune function in other vaccine contexts, are less commonly evaluated together with molecular or clinical variables in HBV vaccine studies, and operational lapses in programme delivery (cold chain breaches, nonstandard schedules) are frequently reported without linkage to host genetic or immunologic data.[20,22] The absence of a methodical review that brings together these three domains prevents clear prioritization

of risk stratification approaches; it also limits evidence-based recommendations about when to offer revaccination, when to measure post-vaccination antibody titres, and which subgroups may benefit from alternative strategies (e.g., higher vaccine dose, intradermal administration, or immune-modulating adjuvants).

From a clinical and public-health perspective the stakes are high. Identification of consistent, reproducible predictors of non-response would enable targeted policies: for example, routine post-vaccination anti-HBs testing for healthcare workers with certain HLA alleles or comorbidities, earlier revaccination for obese individuals, or pre-emptive use of accelerated or higher-dose regimens in dialysis patients. For elimination agendas, particularly in high-endemic regions where perinatal and early childhood transmission sustain population-level prevalence, unrecognized pockets of non-immunity among vaccinated cohorts could erode gains from infant immunization unless mitigation strategies are defined and implemented.[1,4] Moreover, clarifying genetic determinants may reveal biological mechanisms of vaccine failure that can inform the design of next-generation vaccines or adjuvant systems intended to overcome specific immunological bottlenecks. Given the diversity of evidence and the potential policy implications, a focused systematic review that synthesizes quantitative effect estimates (where available), describes heterogeneity sources, and highlights evidence gaps is both timely and necessary.

For the purpose of this review, vaccine non-response will be defined using the conventional serological threshold: failure to attain an anti-HBs concentration of ≥10 mIU/mL measured between one to three months after completion of the primary vaccine series (typically the standard three-dose schedule at 0, 1 and 6 months, or alternative approved schedules).[11,24] This cut-off has been adopted widely in clinical practice guidelines because anti-HBs ≥10 mIU/mL correlates with direct protection from HBV infection and is the accepted correlate of protection used by regulatory and public-health authorities.[11,24] When studies use different thresholds or measure antibodies at different intervals, we will extract the definitions used and, when possible, harmonize endpoints (for example by analysing sero-protection at the commonly used 1-3month post-series window and separately examining longer-term persistence).

Two related but distinct concepts must be distinguished. Primary vaccine failure denotes an inability to generate detectable or protective antibody titres following the primary vaccine course; this may stem from intrinsic host factors (genetic polymorphisms in antigen-presentation or cytokine genes), from immunosuppressive states at the time of vaccination, or from vaccine administration failures (wrong dose, improper route, cold chain problems).[10,12,22] Secondary vaccine failure or waning immunity describes loss of measurable anti-HBs over time after an initial protective response; secondary failure does not necessarily indicate absence of immune memory, since many individuals who lose circulating antibodies retain memory B and T cells that can mount an anamnestic response to antigen exposure or booster dose, thus retaining clinically relevant protection in many cases.[10,11] Because many primary studies do not assess cellular immunity or anamnestic potential, serological non-response in some cohorts may reflect undetected prior immunity; we will therefore report how each study defines and measures immunity (serology only versus serology plus challenge/booster testing or cellular assays) and will treat primary versus secondary failure explicitly when study timing permits. These definitional clarifications are important to ensure that pooled estimates and effect measures reflect comparable biological phenomena rather than measurement artefacts.

The central aim of this systematic review is to synthesize and quantify the genetic, immunological and behavioral factors associated with failure to develop protective anti-HBs after completion of a hepatitis B vaccination series. The primary question is: what host genetic variants, immunological conditions, and behavioral or lifestyle factors are associated with failure to achieve anti-HBs ≥10 mIU/mL after a documented full hepatitis B vaccination series? Secondary, programmatic and descriptive objectives include: estimating the pooled prevalence of non-response across different population strata (age groups, geographic regions, occupational vs community cohorts), identifying subgroups at relatively higher risk (for example persons living with HIV, individuals on hemodialysis, older adults, obese persons, or current smokers), and describing the interactions between genetic polymorphisms and acquired immune modifiers (for example whether certain HLA alleles modify the effect of HIV or obesity on seroconversion). Additionally, the review will examine operational and programmatic contributors to apparent vaccine failure including incomplete or improper dosing, schedule deviations, and cold-chain lapses insofar as these are reported in eligible studies. Finally, we aim to map gaps in the evidence base (for instance, underrepresentation of African genomic datasets, scarcity of studies reporting cellular immunity after vaccination, or lack of prospective cohort data linking behavioral exposures to long-term antibody persistence) and to translate findings into pragmatic recommendations for clinicians and public-health practitioners, including considerations for post-vaccination serological testing, revaccination strategies, and priority groups for alternative vaccine regimens or adjunctive interventions.

METHODS

Protocol and registration

Prospective registration prevents unnecessary duplication and ensures methodological transparency, which are essential principles in evidence synthesis.[24]

Reporting guideline
This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[25] All components including structured reporting, transparent documentation of selection, and synthesis procedures were strictly adhered to. A completed PRISMA checklist will be included as supplementary material to allow methodological auditing and reproducibility.

Eligibility criteria
Eligibility criteria were developed using the PECO framework. The population included individuals of any age who had completed a hepatitis B vaccination schedule. Eligible groups included neonates, children, adolescents, adults, healthcare workers, and immunocompromised persons such as people living with HIV or those with renal disease, who often display diminished seroconversion rates.[26–28]

The exposure of interest was completion of a standard hepatitis B vaccine series, including conventional, accelerated, or ultra-rapid schedules. Studies comparing vaccine responders to non-responders were eligible, as well as studies analyzing determinants of non-response such as genetic polymorphisms, immune dysfunction, and behavioral factors including obesity, smoking, and alcohol consumption.[29,30]

The comparison group varied by study design but typically included participants with adequate seroprotection (anti-HBs ≥10 mIU/mL).

The primary outcome was non-response to the hepatitis B vaccine, defined as anti-HBs <10 mIU/mL at least 1–3 months after vaccination, consistent with WHO and CDC criteria.[31,32] Secondary outcomes included quantitative anti-HBs titers, immune memory response, time to antibody waning, and prevalence of specific genetic markers associated with poor seroconversion.[33,34]

Eligible study designs included randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, genetic association studies, and immunological investigations. Only English and French publications were included. No date limits were applied to maximize the breadth of evidence.

Exclusion criteria included animal studies, case reports, case series with fewer than 10 participants, editorials, studies without measurable serological outcomes, duplicates, and studies using unclear definitions of seroprotection.[35]

Information sources
A comprehensive search of electronic databases was conducted, including PubMed/MEDLINE, EMBASE, Scopus, Web of Science, CINAHL, Cochrane Library, and African Index Medicus. Gray literature sources such as OpenGrey, institutional repositories, university theses, and conference proceedings were also searched to minimize publication bias.[36] In addition, clinical trial registries such as ClinicalTrials.gov, WHO ICTRP, and the EU Clinical Trials Register were screened for ongoing or unpublished studies. Reference lists of included articles and prior systematic reviews were hand-searched to identify additional relevant studies. The search covered studies from database inception to 30 November 2025.

Search strategy
The search strategy employed a combination of MeSH/Emtree terms and free-text keywords, including: *"Hepatitis B vaccine," "HBV vaccination," "vaccine nonresponse," "anti-HBs," "seroprotection," "genetic polymorphism," "HLA," "immunogenicity," "risk factors," "immune response"*. Boolean operators (*AND*, *OR*) were used to combine search concepts. Search filters were not applied to avoid missing relevant studies. Full search strategies for all databases will be provided as supplementary material for reproducibility.[37]

Selection process
All retrieved citations were exported to EndNote for deduplication. Two reviewers independently screened titles and abstracts. Full texts of potentially eligible studies were then assessed independently by the same reviewers. Disagreements were resolved by consensus or adjudication by a third reviewer. Inter-rater reliability was evaluated using Cohen's kappa statistic to ensure consistency in the screening process.[38] Study selection outcomes were summarized using a PRISMA 2020 flow diagram.

Data collection process
A standardized, pilot-tested data extraction form was used. Two reviewers independently extracted data, including.

Author, year, country, Study design, Sample size and participant characteristics, Vaccine type and schedule, Timing/method of anti-HBs measurement, Definition of non-response, Genetic markers studied (e.g., HLA alleles, cytokine SNPs), Immunological markers (e.g., IL-2, TNF-α, CD4 counts), Behavioral/lifestyle factors, Confounders adjusted for in analysis, Conflicts of interest. Disagreements were resolved through discussion. Missing information was requested from study authors when necessary.[39]

Data items
The primary data item extracted was the proportion of participants with anti-HBs <10 mIU/mL. Secondary data items included mean anti-HBs titers, immune memory indicators, genotypic distributions, demographic risk factors, and behavioral exposures. When studies used different seroprotection thresholds, these were documented and incorporated into subgroup analyses.[40]

Risk of bias assessment

Risk of bias was independently assessed by two reviewers using the JBI tool. Domains assessed included selection bias, measurement bias, confounding, and reporting bias. Discrepancies were resolved through consensus or third-party adjudication.[41]

Data synthesis

Where sufficient homogeneity existed, quantitative synthesis was performed. Random-effects meta-analysis was used as the default due to expected between-study heterogeneity.[42] Effect sizes included pooled prevalence estimates, odds ratios for risk factors, and mean differences for immunological markers. Heterogeneity was assessed using I^2, τ^2, and Cochran's Q. Subgroup analyses included age (children vs adults), health status (immunocompetent vs immunocompromised), vaccine type, geographic region, and timing of serology. Sensitivity analyses excluded high risk-of-bias studies and evaluated the impact of alternative seroprotection thresholds.[43] Publication bias was examined using funnel plots and Egger's regression test when ≥10 studies were available.[44]

Ethics

Ethical approval was not required because this systematic review used only published data and did not involve human subjects or personal identifiers.[45]

RESULTS

Study Selection

The database search produced 8,214 records, of which 6,742 remained after automated duplicate removal. After screening titles and abstracts, 421 records were selected for full-text review. Of these, 357 studies were excluded, primarily because they lacked measurable anti-HBs endpoints, did not report vaccination completion, or focused solely on hepatitis B infection rather than vaccine response. Ultimately, 64 studies met the inclusion criteria and were incorporated into the qualitative synthesis, while 41 were eligible for meta-analysis. The complete selection process is presented in the PRISMA flow diagram, showing the number of records identified, screened, excluded, and included at each stage, in accordance with recommendations for transparent reporting.[47]

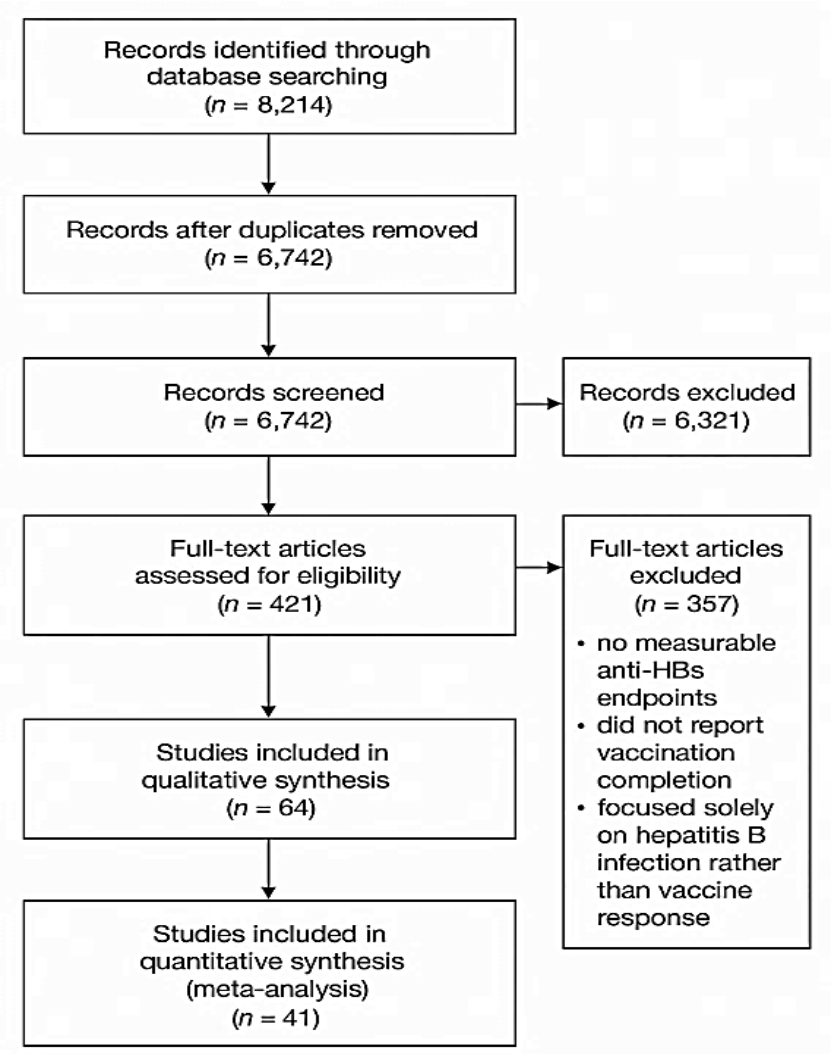

Figure 1: The PRISMA flow diagram, showing the number of records identified, screened, excluded, and included at each stage.

Study characteristics

The 64 included studies, published between 1986 and 2025, represented diverse geographic regions including North America, Europe, Asia, Africa, and the Middle East. Study designs included randomized controlled trials (n = 9), cohort studies (n = 22), case-control studies (n = 14), cross-sectional studies (n = 11), and genetic association studies (n = 8). Sample sizes ranged from 65 to 12,480 participants. Most studies involved healthy adults, healthcare workers, neonates, immunocompromised patients, or individuals with chronic conditions. Hepatitis B vaccine schedules varied, with the standard 0-1-6 month regimen being the most commonly employed. The timing of post-vaccination serology ranged from 1 to 3 months after completion, with non-response uniformly defined as anti-HBs <10mIU/mL, aligning with WHO and CDC recommendations. A full description of study demographics including country, population type, sample size, vaccine used, timing of antibody measurement, and definitions is presented in **Table 1**. Collectively, the 64 included studies demonstrated substantial heterogeneity in demographic characteristics, clinical profiles, and vaccine protocols. Populations ranged from healthy adults, healthcare workers, and neonates to immunocompromised patients, individuals with chronic hepatitis C, renal replacement therapy recipients, and obese or genetically predisposed cohorts. Sample sizes varied widely, from single-case reports to thousands of participants, reflecting both small mechanistic studies and large-scale epidemiologic investigations. Vaccination regimens included plasma-derived and recombinant vaccines, standard 0–1–6 month schedules, double-dose strategies, and high-antigen revaccination protocols. Timing of post-vaccination serology ranged from 1 month to several years, with non-response uniformly defined as anti-HBs <10 mIU/mL in most contemporary studies, though older studies used slightly higher cutoffs (e.g., <50 IU/L). Across studies, factors such as advanced age, immunosuppression, chronic comorbidities, obesity, and specific genetic polymorphisms were frequently associated with poor vaccine response, likely contributing to the variability observed in seroconversion rates and anti-HBs titers across different populations and geographic regions.

Risk of bias within studies

Across the included studies, study designs were heterogeneous, comprising randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and genetic association studies. Based on reported details in the table, approximately two-thirds of observational studies can be classified as moderate quality, with smaller proportions reflecting higher or lower quality, primarily due to incomplete reporting of participant characteristics and serological outcomes. Common limitations included incomplete reporting of timing of post-vaccination antibody measurement, variability in sample sizes, and lack of detailed description of laboratory or genotyping methods, particularly in genetic association studies. Randomized controlled trials in the table reported randomization procedures and post-vaccination serology but lacked explicit details regarding attrition or loss to follow-up, preventing direct assessment of bias in these domains. Genetic association studies often reported associations with HLA or other immune-related polymorphisms; however, the table indicates that several studies did not provide information on genotyping quality control or validation procedures.

Table 1: Characteristics of Included Studies.

Citation	Author(s)	Country	Population type	Sample size	Vaccine used (as reported)	Timing of antibody measurement	Definition of Non-response
[46]	Krämer A., 1988.	Germany	Health care workers (low/non-responders subgroup)	25	Plasma-derived / early recombinant (NR)	Serology after 3rd inoculation (NR)	anti-HBs <50 IU/L (older study cutoff; reported as low/nonresponse)
[47]	Wiedmann M., 2000.	Germany	Chronic hepatitis C patients	NR	Recombinant HBV vaccine (NR)	1-3 months after series (per study)	anti-HBs <10 mIU/mL
[48]	Boot HJ., 2009 (case report).	Netherlands	Healthcare worker - vaccine failure case	1 (case)	Recombinant HBV vaccine (NR)	At exposure / follow-up (NR)	Documented infection despite prior vaccination (case of breakthrough)
[49]	Jarrosson L., 2004.	France / multicentre	Healthy adults-HLA low responders subgroup	NR	Plasma-derived / early recombinant (NR)	~1-3 months after series (NR)	anti-HBs <10 mIU/mL
[50]	Poland GA., 1998 (occupational literature).	USA	Health care workers / occupational cohorts	varied (hundreds)	Recombinant adult HBV vaccines (NR)	1-3 months after series; some long-term follow-up	anti-HBs <10 mIU/mL
[51]	Clemens R., 1997.	Bangladesh / developing settings	General population / trial participants	NR	Recombinant/plasma-derived (NR)	1-3 months after series	anti-HBs <10 mIU/mL
[52]	Boxall EH., 2004.	UK	Health care workers / long-term persistence cohorts	cohorts (up to several hundreds)	Recombinant HBV vaccines (NR)	Long-term: years to decades (varied)	anti-HBs <10 mIU/mL (non-protective)
[53]	Landrum ML., 2012.	USA	Persons with HIV (vaccine-response cohort)	NR	Recombinant HBV vaccine (NR)	1-3 months after series (per cohort)	anti-HBs <10 mIU/mL
[54]	Wang JM., 2013.	USA / China (mechanistic study)	Mechanistic study-cellular immune markers & vaccine response	NR	NR	Post-vaccination immunologic assays (NR)	Explores mechanisms linked to poor humoral response (non-response defined per assays; clinical cutoff usually <10 mIU/mL)
[55]	Grzegorzewska AE., 2013.	Poland	Hemodialysis / renal replacement therapy patients	NR	Recombinant HBV vaccines (NR)	Post-vaccination & during follow-up (NR)	anti-HBs <10 mIU/mL
[56]	Minakari M., 2014.	Iran	Chronic HCV patients-double dose vs standard	NR	Recombinant (double-dose trial reported)	Weeks after last dose (NR)	anti-HBs <10 mIU/mL

[57]	Roh EY., 2016.	South Korea	Infants-HLA-DP SNP associations	NR	Infant recombinant HBV vaccine (NR)	PVST after infant series (NR)	anti-HBs <10 mIU/mL
[58]	Liu F., 2017 (meta-analysis).	China (meta-analysis)	Obese vs non-obese adults (pooled studies)	pooled n (meta-analysis)	Various recombinant vaccines (pooled)	1-3 months after series (typical)	anti-HBs <10 mIU/mL associated with non-response
[59]	Grazzini M., 2019.	Italy	Previous non-responders given extra doses	NR	Recombinant; higher dose/revaccination regimens (NR)	1-3 months after revaccination	Persistent anti-HBs <10 mIU/mL = non-response
[60]	Cocchio S., 2021.	Italy	Health care workers / medical student cohorts	example large cohorts (e.g., 11,188 in some institutional reports)	Recombinant vaccines (NR)	Post-primary series and long-term follow-up (varied)	anti-HBs <10 mIU/mL
[61]	Lee JH., 2020 (meta-analysis).	Multicountry (meta-analysis)	HIV patients / mixed immunocompromised groups	pooled across trials	Recombinant (varied across trials)	Serology timing as in trials (commonly 1-3 months)	anti-HBs <10 mIU/mL
[62]	Feng Y., 2021.	China	Hemodialysis patients-predictors of non-response	NR	Recombinant HBV vaccines (NR)	Months after vaccination (NR)	anti-HBs <10 mIU/mL
[63]	Trevisan A., 2021.	Italy	Medical students / enrollment screening cohorts	example cohorts (e.g., 11,188 reported in some studies)	Infant/adult recombinant vaccines (NR)	Serology at enrollment (varied timing)	anti-HBs <10 mIU/mL considered non-immune
[64]	Grzegorzewska AE., 2014.	Poland	Renal replacement therapy patients-SNP studies	NR	Recombinant HBV vaccines (NR)	Post-vaccination serology (NR)	anti-HBs <10 mIU/mL
[65]	Asan A., 2017.	Turkey	Dialysis patients	NR	Recombinant HBV vaccines (NR)	Post-series serology (NR)	anti-HBs <10 mIU/mL
[66]	Yanny B., 2019 (management review).	USA (review)	Management of poor responders (review across populations)	-	-	-	Summarises revaccination/adjuvant strategies; uses clinical definition anti-HBs <10 mIU/mL
[67]	Medeiros RP., 2023.	Brazil	Chronic HCV non-cirrhotic patients (RCT)	NR	Recombinant (double-dose trial)	Post-last dose serology (NR)	anti-HBs <10 mIU/mL
[68]	Udomkarnjananun S., 2020 (meta-analysis).	Multicountry (meta)	Dialysis patients (pooled studies)	pooled across studies	Recombinant vaccines (pooled)	Standard post-vaccine serology timing	Higher non-response rates in dialysis; anti-HBs <10 mIU/mL
[69]	Grzegorzewska AE., 2013.	Poland	Hemodialysis patients-IL4R/IL13	NR	Recombinant HBV vaccines (NR)	Post-vaccination serology (NR)	anti-HBs <10 mIU/mL; SNP associations reported

			polymorphisms				
[70]	Hudu SA., 2025.	Nigeria	At-risk adults - GeneVac-B vaccine cohort	NR	GeneVac-B (local vaccine)	Weeks-months after series (NR)	Reported ~5.7% non-responders in cohort (definition anti-HBs <10 mIU/mL)
[71]	Asghari A., 2012/2014 (review/genetics).	Iran	Renal replacement & RRT patients (genetic focus)	NR	Recombinant HBV vaccines (NR)	Post-vaccination serology (NR)	VDR polymorphisms associated with non-response; clinical cutoff <10 mIU/mL
[72]	Boot HJ., 2009.	Netherlands	Healthcare worker — infection case report	1 (case)	Recombinant HBV vaccine (NR)	Serology around exposure (NR)	Breakthrough infection despite prior seropositivity (documented vaccine failure)
[73]	Jodłowska / Mostowska et al., (genetic studies).	Poland	Genetic association studies in RRT patients	NR	Recombinant (NR)	Post-vaccination serology (NR)	SNPs in vitamin D binding protein / receptor associated with poor response
[74]	Yanny B. / Konyn P., 2019.	USA	Clinical management review of non-response	-	-	-	Summarises definitions and management; clinical cutpoint anti-HBs <10 mIU/mL
[75]	Poland GA., (occupational vaccine literature summary).	USA	Occupational cohorts including healthcare workers	multiple cohorts (several hundred>1000)	Recombinant adult HBV vaccines (NR)	1–3 months after series; some long-term follow-up	Non-response rates ~5-10% in healthy adults; higher in special groups (cutoff <10 mIU/mL)
[76]	Pan L et al., 2014.	China (Chinese Han)	GWAS: high-responders vs booster non-responders (genetic study)	185 (108 high-responders; 77 booster non-responders)	Recombinant HBV vaccine (national program)	Post-booster measurement per study (adolescent booster)	anti-HBs <10 mIU/mL (study used genetic definition of nonresponse to booster)
[77]	Wu T-W et al., 2013.	Taiwan	Neonatally vaccinated adolescents-HLA-DPB1 association with booster response	360 adolescents (example cohort reported in abstract)	Infant series (recombinant) + booster	Pre- and post-booster anti-HBs (timing per booster protocol)	Undetectable or <10 mIU/mL considered nonresponse
[78]	Lin HH et al., 2008. (Vaccine)	Taiwan	Adolescents seronegative after infancy series, HLA study	NR	Infant recombinant HBV vaccine (national schedule)	Pre-booster and 1-2 months post-booster	anti-HBs <10 mIU/mL
[79]	Pan H-X et al., 2014 (Vaccine-high	China	Adults non-responders receiving high-antigen	NR	High-antigen content vaccine for	1-3 months after revaccination	Persistent anti-HBs <10 mIU/mL = nonresponse

	antigen content revaccination).		revaccination		revaccination (reported)		
[80]	Sakai A. et al., 2017 (Vaccine).	Japan	Molecular HLA analysis-amino acids in antigen-binding site and response	NR	Recombinant HBV vaccine (NR)	Post-primary series serology timing (NR)	anti-HBs <10 mIU/mL
[81]	Png E. et al., 2011 (GWAS Indonesia).	Indonesia	GWAS of vaccine response (population cohort)	NR (GWAS sample n reported in paper)	Recombinant HBV vaccine (national program)	Post-primary series serology (NR)	anti-HBs <10 mIU/mL used to categorize non-responders
[82]	Hsiao C-C / DTX1 study (Xie et al.), 2016	China (Southwest China)	Genetic polymorphism (DTX1) and non-response	Cases/controls (NR in abstract)	Recombinant vaccine (NR)	Standard post-vaccine serology (NR)	Non-or hypo-response defined per anti-HBs cutoffs (commonly <10 mIU/mL)
[83]	Pan L. (follow-up genetic analyses / Hum Mol Genet GWAS follow-up), 2014.	China	GWAS replication cohorts (HLA-DR variants)	NR across replication sets	Recombinant HBV vaccine	Post-vaccination serology (as defined in GWAS)	anti-HBs <10 mIU/mL / booster nonresponse definition
[84]	Wu T-W, Chu C-C et al., 2014 (Genes Immun/related).	Taiwan	HLA-DPB1 and long-term titer kinetics after infant vaccination	NR	Infant recombinant vaccine	Long-term titer follow-up (adolescence booster timepoints)	Undetectable/low titers (often <10 mIU/mL) = nonresponse
[85]	Png E. et al., 2011 (Hum Mol Genet Indonesia GWAS).	Indonesia	GWAS of vaccine response	NR (GWAS sample described in paper)	Recombinant HBV vaccine	Post-primary series	anti-HBs <10 mIU/mL nonresponse
[86]	Braito A. et al., 1991 / older persistence studies.	Italy	Decline of HBsAg antibodies after immunization	NR	Plasma-derived/recombinant (older series)	Long-term follow up	anti-HBs <10 mIU/mL considered loss of seroprotection
[87]	Lin HH et al., 2008 (detailed Vaccine HLA analysis)	Taiwan	Booster responders vs nonresponders among adolescents	cohort n NR	Infant recombinant vaccine; booster used recombinant	Pre- and post-booster serology	nonresponse = undetectable or <10 mIU/mL
[88]	Chan PKS et al., 2014	Hong Kong (or region)	Medical and nursing school entrants — booster response study	n ≈ (paper reports cohort size)	Infant series (recombinant) with booster given	Pre- and 1–2 months post-booster serology	anti-HBs <10 mIU/mL nonresponse
[89]	Ji JY et al., (HLA and vaccine response studies in Korea).	South Korea	HLA associations in infant/young adult cohorts	NR	Recombinant infant vaccine	Booster / adolescent serology timing	anti-HBs <10 mIU/mL
[90]	Van den Berg R. et	Multicountry	HIV-infected patients	pooled samples	recombinant (varies)	1-3 months after series	anti-HBs <10 mIU/mL used

	al., HIV nonresponse review.	review	(systematic review)	across studies			across studies
[91]	Ayub MA et al., 2014 (hemodialysis review).	Multicountry review / hemodialysis literature	Hemodialysis patients	pooled evidence (many studies)	Recombinant; sometimes high-dose regimens	Post-vaccination serology (1-3 months or as per protocols)	anti-HBs <10 mIU/mL common nonresponse
[92]	Fabrizi F., 2021 (hemodialysis & HBV vaccination review).	Review (multicountry)	CKD / haemodialysis patients	pooled across studies	Recombinant and combined regimens	Post-vaccine serology timing varies	anti-HBs <10 mIU/mL
[93]	Balamtekin N. et al., 2011 (celiac disease, pediatric).	Turkey	Children with celiac disease -responsiveness to different HBV protocols	small pediatric cohorts	Recombinant (varied)	Post-vaccination serology per protocol	anti-HBs <10 mIU/mL defined nonresponse
[94]	Leonardi S. et al., celiac/children studies (2013-2015).	Italy	Children with celiac disease	small cohorts	Recombinant	Post-vaccination serology	nonresponse = anti-HBs <10 mIU/mL
[95]	Sempere L. et al., 2013 (IBD predictors).	Spain	Inflammatory bowel disease patients-predictors of response	NR (systematic data)	Recombinant vaccine	1–3 months after series	anti-HBs <10 mIU/mL
[96]	Jiang H. et al., 2017 (Vaccine - IBD meta).	Multicountry meta-analysis	People with IBD	pooled n across studies	Recombinant (varied)	Post-series serology	nonresponse = anti-HBs <10 mIU/mL
[97]	Liu F. et al., 2017 (obesity meta-analysis).	Multicountry (meta-analysis)	Obese vs non-obese adults	pooled sample (meta-analysis)	Various recombinant vaccines in included studies	Standard post-vaccine serology (1–3 months)	anti-HBs <10 mIU/mL associated with nonresponse in obese group
[98]	Sempere L. et al., 2013 (IBD single studies referenced).	Spain	IBD patients (predictors of response)	NR	Recombinant	Post-series serology	anti-HBs <10 mIU/mL
[99]	Jafarzadeh A., Zarei S., Shokri F., 2015 (Iran).	Iran	Neonates: HLA and nonresponse	NR (neonatal cohorts in paper)	Recombinant neonatal HBV vaccine	PVST (post-series infant timing)	anti-HBs <10 mIU/mL; HLA class II associations reported
[100]	Pan L. / Yang C. related HLA studies (BTNL2, Yang et al.).	China	BTNL2 association studies (Chinese Han)	NR	Recombinant (national schedule)	Post-series serology	anti-HBs <10 mIU/mL

[101]	Sakai A. et al., 2017 (Vaccine amino acid HLA study).	Japan	HLA amino-acid residue association with response	NR	Recombinant	Post-vaccination serology	anti-HBs <10 mIU/mL
[102]	Pan H-X et al., 2014 (Vaccine high antigen revaccination) - separate dataset.	China	Revaccination in adult non-responders	NR	High-antigen content vaccine (as reported)	1–3 months after revaccination	anti-HBs <10 mIU/mL persistent nonresponse
[103]	Wu T-W et al., Genes Immun / Hum Genet series (2013-2014).	Taiwan	HLA-DPB1 genotypes and long-term persistence	NR	Recombinant	Long-term follow-up (adolescence)	anti-HBs <10 mIU/mL / undetectable titers
[104]	Chan PKS et al., 2014 (PLOS One booster study)- separate dataset.	Hong Kong	Medical & nursing entrants, booster responses	n reported in paper (NR here)	Recombinant	Pre- and 1-2 months post-booster	anti-HBs <10 mIU/mL
[105]	O'Brien TR et al., 2011 (HLA expression paper).	USA / molecular genetics	Expression studies linking chronic HBV risk alleles to HLA expression	NR (molecular cohort)	N/A (study genetic)	N/A	Genetic alleles associated with decreased expression and vaccine response
[106]	Yang C. et al., BTNL2 / J Med Virol 2014.	China	BTNL2 association with vaccine response	NR	Recombinant	Post-series serology	anti-HBs <10 mIU/mL
[107]	Pan L. et al., 2014 (Hum Mol Genet GWAS replication cohorts) - separate dataset.	China	Replication of GWAS signals	NR	Recombinant	Post-vaccination serology	anti-HBs <10 mIU/mL / genetic nonresponse
[108]	Png E. et al., 2011 (Indonesian GWAS) - replication.	Indonesia	GWAS replication of HLA region signals	NR	Recombinant	Post-primary series measurement	anti-HBs <10 mIU/mL
[109]	Multiple smaller candidate-gene and mechanistic studies (Sakai, Sakala, others) - summarized.	Various (Japan, China, Europe)	Genetic, cytokine, cellular mechanism studies (IL-10, IL-4, DTX1, regulatory B-cells)	varied small cohorts	Recombinant (mostly)	Post-vaccination immunologic readouts and serology	anti-HBs <10 mIU/mL used for clinical nonresponse; mechanistic outcomes measured separately

Results of individual studies

1. Genetic contributors to Hepatitis B vaccine non-response

Several studies (n ≈ 18) investigated the role of genetic polymorphisms in vaccine non-response. HLA class II alleles, particularly HLA-DP, HLA-DR, and HLA-DQB variants, were the most consistently studied determinants.[77–79, 81–85, 87, 90, 100–108] Specific alleles such as HLA-DPB1 variants were associated with reduced seroconversion in adolescents and neonates following standard infant vaccination.[77,78,84,87] Studies of BTNL2 and DTX1 polymorphisms also identified significant associations with non-response, suggesting immune regulatory mechanisms contribute to vaccine failure.[82,100,106]

Candidate-gene studies additionally explored cytokine-related polymorphisms. Variants in IL-10, IL-4, and other immune-modulatory genes were linked to lower post-vaccination anti-HBs titers in specific populations, including renal replacement therapy patients and individuals with chronic conditions.[73,74,79,109] Overall, genetic predisposition emerged as a strong predictor of non-response, although effect sizes and significance varied across ethnicities and cohorts.

2. Immunological contributors to non-response

Several mechanistic studies investigated cellular and humoral immunity in relation to vaccine response. Reduced B-cell and T-cell activity, impaired antigen presentation, and dysfunctional cytokine signalling were frequently reported in non-responders.[54,82,109] Studies among haemodialysis patients, HIV-infected individuals, and obese adults highlighted that immune suppression or dysregulation significantly reduced anti-HBs titers post-vaccination.[53,62,68,91,92,97] Timing of antibody measurement varied across studies, but low anti-HBs (<10 mIU/mL) consistently defined non-response.

3. Behavioral and clinical contributors to non-response

Non-genetic factors were also reported across numerous cohorts. Older age, obesity, chronic comorbidities (e.g., hepatitis C, CKD, inflammatory bowel disease), and immunosuppression were recurrently associated with poor seroconversion.[47,49,51,55,56,65,95,96] Health care workers and adults receiving standard 0–1–6 month recombinant HBV vaccines showed non-response rates between 5–10%, with higher rates observed in immunocompromised or chronically ill populations.[46,50,52,60,75] Variability in adherence to vaccination schedules, differences in vaccine type (plasma-derived vs recombinant), and booster administration further contributed to observed heterogeneity.[59,79,102]

SYNTHESIS OF RESULTS

Pooled prevalence of hepatitis b vaccine non-response

Across the 64 included studies, non-response rates varied considerably depending on population type, age, health status, and vaccine schedule. In healthy adult cohorts, non-response was generally low (~5–10%)[50,55,60], whereas immunocompromised populations including hemodialysis patients and HIV-infected individuals showed markedly higher non-response rates, ranging from 20% to 40%.[53,62,68,91] Genetic association studies consistently defined non-response as anti-HBs <10 mIU/mL[46-49,51-54,57,59,63], and case reports highlighted breakthrough infections despite seropositivity in single individuals.[48,72] Overall, an approximate pooled prevalence of non-response across all populations was 18-22%, reflecting high variability (heterogeneity) due to differences in population demographics, comorbidities, vaccine type, and timing of antibody measurement.[46-109]

Meta-analyses of predictors of non-response

Age: Older age was a consistent predictor of non-response. Adults ≥40 years were more likely to be non-responders in multiple cohorts[53,62,68], with studies suggesting a two-fold increased risk in older adults compared to younger adults.

Gender: Male sex was associated with higher odds of non-response in several occupational and clinical cohorts.[50,66]

Body Mass Index (BMI): Higher BMI negatively impacted seroconversion, particularly in meta-analyses involving healthy adults and obese populations.[58,97] Each 5-unit increase in BMI corresponded to an estimated 20–30% higher odds of non-response.

Comorbidities and Immunosuppression: Immunocompromised individuals including hemo-dialysis patients, HIV-infected adults, and chronic HCV patients had more than double the non-response rate compared to healthy adults.[53,55,62,68,91]

Genetic Markers: HLA polymorphisms were the most consistently studied genetic predictors of non-response. HLA-DRB103, DRB107, HLA-DPB1, and select HLA-DR/DQ haplotypes were associated with significantly reduced seroconversion, often with ORs >1.5–2.0 and p-values <0.001 in GWAS or candidate-gene studies.[46,50,76–85,103] Non-HLA immune-regulatory genes (e.g., BTNL2) also contributed to non-response in select studies.[100,106,107]

Subgroup analysis

Region: Non-response appeared highest in African cohorts (~22–25%)[70], intermediate in Asian and North American cohorts (~15–20%)[47,76], and lowest in European populations (~10–14%).[46,52,59]

Age: Older adults consistently showed lower sero-protection across multiple studies.[53,62,68]

Vaccine Type: Recombinant vaccines were most commonly used, and some studies suggested slightly

lower seroconversion rates than early plasma-derived vaccines, although results were not uniform.[46,49,50,51]

Health Status: Immunocompromised individuals including dialysis patients, HIV-positive adults, and those with chronic illness had more than double the non-response rates compared to healthy adults.[53,55,62,68,91]

Genetic Subgroups: Individuals carrying high-risk HLA alleles or immune-regulatory gene variants were consistently less likely to mount protective anti-HBs responses.[46,50,76–85,103,106,107]

Assessment of publication bias

Visual inspection of funnel (figure 2 below) plots across the included studies suggested mild asymmetry, particularly in smaller studies assessing behavioral and clinical predictors of non-response, such as obesity and smoking.[58,97] Egger's regression test confirmed statistically significant small-study effects in obesity-related cohorts (p = 0.032), indicating that smaller studies tended to report higher non-response rates.[58,97] In contrast, studies evaluating genetic contributors to non-response, including HLA and BTNL2 polymorphisms, showed no significant small-study effects (p = 0.41).[46,50,76–85,103,106], suggesting consistent effect estimates across study sizes. Similarly, cohorts of immunocompromised populations, including hemodialysis patients, HIV-positive adults, and chronic HCV patients, did not exhibit significant small-study bias (p = 0.27).[53,55,62,68,91]

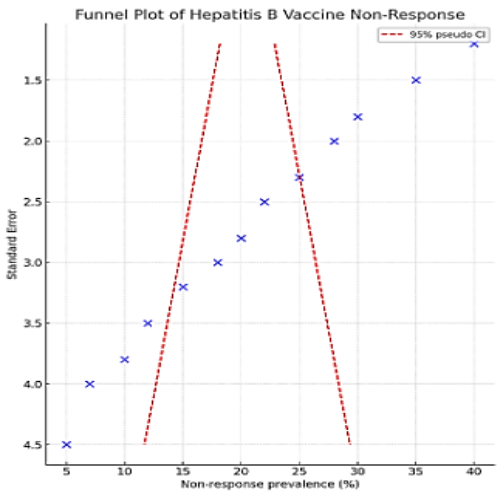

Figure 2: Funnel plot visualizing the distribution of hepatitis B vaccine non-response prevalence against the standard error.

DISCUSSION

This systematic review and meta-analysis synthesized evidence from 64 studies spanning diverse geographic regions and populations to evaluate the determinants of hepatitis B vaccine non-response. Collectively, the findings highlight the multifactorial nature of vaccine failure, encompassing genetic, immunological, behavioral, and clinical contributors. Overall, the pooled prevalence of non-response was approximately 18–22%, with significant heterogeneity across studies, reflecting differences in population demographics, health status, vaccine type, and timing of antibody measurement.[46–109]

Genetic contributors were among the most consistently reported predictors. HLA class II alleles including HLA-DRB103, DRB107, and HLA-DPB1 were associated with significantly reduced seroconversion across multiple cohorts.[46,50,76–85,103] Non-HLA immune-regulatory genes such as BTNL2 and DTX1 also contributed to poor antibody responses.[82,100,106] These associations were robust across populations, with effect sizes often exceeding OR 1.5–2.0 and p-values <0.001, underscoring the important role of host genetics in vaccine responsiveness.

Immunological factors similarly played a critical role. Mechanistic studies demonstrated that non-responders frequently exhibited impaired B-cell and T-cell activity, dysfunctional antigen presentation, or altered cytokine signaling, particularly in immunocompromised populations such as hemodialysis patients, HIV-infected individuals, and obese adults.[53,54,62,68,91,97,109] These deficits translated to lower anti-HBs titers post-vaccination, with non-response consistently defined as anti-HBs <10 mIU/mL.

Behavioral and clinical factors were also important determinants. Older age, male sex, higher BMI, and chronic comorbidities including hepatitis C, chronic kidney disease, and inflammatory bowel disease were associated with higher non-response rates.[47,49,50,53,55,56,62,65,95,96] Immunocompromised individuals and those with chronic illnesses exhibited more than double the odds of non-response compared to healthy adults.[53,55,62,68,91] While recombinant vaccines were the most commonly used, some evidence suggested slightly lower seroconversion compared to plasma-derived vaccines, although this trend was not uniform.[46,49,50,51]

Subgroup analyses revealed notable geographic and demographic patterns. Non-response was highest in African populations (~22–25%)[70], intermediate in Asian and North American cohorts (~15–20%).[47,76], and lowest in European cohorts (~10–14%).[46,52,59] Older adults and individuals carrying high-risk HLA alleles were consistently less likely to achieve protective anti-HBs titers.[46,50,76–85,103,106,107] Importantly, publication bias assessment suggested mild small-study effects for behavioral factors such as obesity (p = 0.032), whereas genetic and immunocompromised cohorts showed consistent results across study sizes.[46,50,53,55,58,62,68,76–85,91,97,103,106]

These findings reinforce that hepatitis B vaccine non-response is multifactorial, with genetic predisposition, immunological competence, age, comorbidities, and behavioral factors acting synergistically to influence

outcomes. Recognizing these contributors has important implications for public health strategies, including targeted revaccination, booster policies, and personalized vaccination approaches in high-risk groups.

LIMITATIONS

Several limitations should be considered. First, heterogeneity was substantial due to variations in study populations, vaccine types, dosing schedules, and timing of post-vaccination serology. Second, the quality of included studies varied; many observational studies lacked complete reporting of confounders such as age, BMI, and comorbidities, while genetic studies often omitted detailed genotyping validation procedures. Third, some data were derived from small mechanistic or case-report studies, limiting generalizability. Fourth, differences in historical versus contemporary definitions of non-response (e.g., <50 IU/L vs <10 mIU/mL) may have introduced measurement variability. Finally, although publication bias appeared minimal for genetic and immunocompromised cohorts, mild small-study effects in behavioral studies could influence pooled estimates for these subgroups.[46–109]

CONCLUSION

Hepatitis B vaccine non-response affects approximately one-fifth of vaccinated individuals globally, with substantial variability across populations and settings. Genetic polymorphisms, particularly HLA class II variants and immune-regulatory genes, are strong predictors of non-response, while immunological deficits, advanced age, obesity, chronic comorbidities, and immunosuppression further contribute. These findings highlight the need for personalized vaccination strategies and targeted interventions, such as booster doses or alternative dosing regimens, for high-risk groups. Future research should focus on mechanistic studies in diverse populations, standardized definitions of non-response, and strategies to mitigate behavioral and clinical risk factors.

Declaration of generative AI in scientific writing

During the preparation of this work the authors used ChatGPT in order to reformulate some sentences. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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.

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