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Post-Universal HBV Vaccination and Breakthrough Infections in Saudi Arabia: Three Decades of Evidence

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Abstract: In Saudi Arabia, universal hepatitis B virus (HBV) vaccination was introduced in 1989, resulting in large declines in HBV endemicity over the last three decades. This structured narrative review evaluates the published evidence (1989-2025) on long-term vaccination outcomes, breakthrough infections, occult hepatitis B infection (OBI), and future elimination challenges in Saudi Arabia. Relevant studies were identified from PubMed, Scopus, Embase, Web of Science, and regional grey literature sources and narratively synthesized. Available evidence shows a decline in HBsAg prevalence from about 8% pre-universal vaccination to <1% in vaccine-era populations, confirming the significant public health impact of the national immunization program. However, HBV DNA positivity and occult infections are still being reported, particularly in blood donors, hemodialysis patients, healthcare workers, and other high-risk groups. Suggested contributors include waning of anti-HBs immunity, host immunogenetics, the predominance of genotype D, and vaccine-escape mutations. Current evidence also highlights important gaps in national molecular surveillance and sequencing data. While mass vaccination continues to be a very effective strategy for preventing chronic HBV infection, sustainable control will depend on improved molecular surveillance, targeted surveillance of high-risk groups, and evidence-based booster strategies. This review discusses the success of HBV vaccination in Saudi Arabia and the emerging post-immunization challenges pertinent to the goal of HBV elimination.

Key Words: Infections, Hepatitis B, Occult HBV, Saudi Arabia,Vaccine Effectiveness

INTRODUCTION

Hepatitis B virus (HBV) is a long-term and widespread problem in global public health, according to the World Health Organization (WHO); nearly 254 million persons are afflicted with chronic infection, which causes an estimated 1.1 million deaths, mostly from cirrhosis and hepatocellular carcinoma [1,2]. The advent of safe and effective HBV vaccines represented a major public health milestone in infectious disease prevention. Over the past four decades, national vaccination policies shifted from targeting specific risk groups to universal infant programs, leading many settings into what researchers describe as the post-universal infant vaccination era [3,4]. This phase is characterized not only by a substantial reduction in incidence rates among vaccinated populations but also by the emergence of new scientific questions. The growing population of long-term vaccinated individuals has led to recognition of phenomena such as breakthrough infections and occult HBV infection (OBI). Breakthrough infections, defined as a positive test for HBV DNA or surface antigen in someone who has previously completed the HBV vaccination series, raise the question of whether seroprotection confers lifelong immunity or whether complete sterilizing immunity is maintained long term [5,6]. Understanding the complexity of these challenges is essential to tailor global strategies further and achieve the WHO 2030 elimination goals.

Saudi Arabia added the hepatitis B vaccine to the national infant immunization schedule on 1 October 1989, and a universal birth-dose vaccination (dose at month 0) is documented in subsequent national practice; GCC countries, including Saudi Arabia, had adopted a timely (≤24 h) birth dose by around 2001[7,8]. Saudi Arabia continues to maintain high vaccination coverage rates, including timely birth-dose administration. Such an early nationwide vaccination

strategy led to a major public health impact, enabling the country to move from an intermediate endemicity (8%) to less than 1% among post-vaccination populations and to successfully achieve control of mother-to-child transmission, with early signals of reduced chronic liver disease morbidity [9,10]. This marked early reduction in childhood infection rates must be balanced against the situation with a now-aging vaccinated population. The duration of vaccine-induced protection, the actual incidence and mechanisms of breakthrough infections, and the silent OBI burden in the Saudi setting need to be thoroughly studied to determine whether current guidelines remain applicable.

Despite the major success of universal HBV vaccination, important uncertainties remain regarding long-term immune protection, occult HBV persistence, vaccine-escape mutations, and the public health significance of breakthrough infections in Saudi Arabia. This review addresses three key questions: (1) how HBV epidemiology has changed following universal vaccination in Saudi Arabia, (2) what mechanisms contribute to breakthrough and occult infection, and (3) what surveillance and policy strategies may support HBV elimination goals.

Evidence Acquisition

This study was undertaken as a structured narrative review with a systematic literature search and thematic evidence synthesis to evaluate the long-term impact of the universal hepatitis B virus (HBV) vaccination in Saudi Arabia, with special interest in breakthrough infections, occult hepatitis B infection (OBI), vaccine escape, and post-vaccination public health challenges. Relevant literature published between January 1989 and March 2025 was identified through searches of PubMed, Scopus, Embase, and Web of Science databases in addition to grey literature sources that include reports from the World Health Organization (WHO), the WHO Eastern Mediterranean Regional Office (EMRO), the Saudi Ministry of Health, and Gulf Cooperation Council (GCC) public health publications.

Search terms included combinations of: “hepatitis B,” “HBV,” “Saudi Arabia,” “vaccination,” “universal immunization,” “breakthrough infection,” “occult hepatitis B,” “OBI,” “HBV DNA,” “vaccine escape mutation,” “genotype D,” “anti-HBs,” “immune memory,” “blood donors,” “hemodialysis,” and “healthcare workers,” using Boolean operators (“AND” and “OR”) as appropriate. Reference lists of eligible articles were also manually screened to identify additional relevant studies.

Studies were considered eligible if they reported data on HBV epidemiology, vaccine-induced immunity, occult or breakthrough infection, molecular characteristics, vaccine-escape mutations, or HBV-related public health policy relevant to the Saudi population. Priority was given to Saudi-based epidemiologic, immunologic, molecular, and surveillance studies. International studies were included where they provided important mechanistic or comparative context relevant to post-vaccination HBV control. Case reports, animal studies, conference abstracts without sufficient data, and studies unrelated to HBV vaccination outcomes were excluded.

Two reviewers independently screened titles and abstracts and assessed full-text articles for potential relevance. Discrepancies were resolved by discussion to reach a consensus. Due to significant heterogeneity in study design, laboratory methods, populations, and outcome reporting across the included literature, findings were synthesized narratively rather than via formal meta-analysis. Ethical approval was not required because the review used only previously published literature and publicly available data sources.

Post-Vaccination Epidemiological Landscape

Introduction of universal hepatitis B virus (HBV) vaccination in Saudi Arabia in 1989 markedly changed the epidemiology of HBV infection throughout the Kingdom. Prior to vaccine implementation, Saudi Arabia was classified as a region of intermediate endemicity, with HBsAg prevalence estimates exceeding 8% in the general population and considerable rates of childhood transmission. Early integration of HBV vaccination into the national Expanded Program on Immunization represented one of the earliest nationwide HBV control strategies in the Gulf region and was followed by progressive declines in HBV transmission and chronic carriage [11].

Initial post-vaccination surveillance studies demonstrated a marked reduction in HBV infection among vaccinated children. Eight years after implementation of the national immunization program, the prevalence of HBsAg among Saudi children aged 1–12 years declined from approximately 6.7% before vaccination to nearly 0.3%, confirming the substantial effectiveness of universal infant immunization in reducing chronic HBV carriage [9]. Long-term follow-up studies later showed the persistence of vaccine-induced protection and continued low HBsAg prevalence among vaccinated cohorts, with evidence of sustained immune memory despite a gradual decline in anti-HBs antibody titers [12,13].

Later epidemiologic investigations consistently found lower prevalence of HBV exposure markers in populations during the vaccine era. As the prevalence of anti-HBc declined among children, adolescents, and young adults, evidence emerged of a substantial interruption in viral transmission following the widespread implementation of immunization [14,15]. Studies among Saudi health college students and medical trainees also found that most persons vaccinated during infancy retained either detectable anti-HBs antibodies or an anamnestic immune response after booster exposure, consistent with persistence of immunologic memory beyond the decline of measurable antibody [15-18]. Conversely, higher HBV seroprevalence persisted among older, previously unvaccinated adults, reflecting the historical pattern of exposure before the introduction of universal vaccination [19,20].

Table 1: Epidemiologic Trends of HBV Infection Following Universal Vaccination in Saudi Arabia

Study/Reference	Population	Region	Key Marker Assessed	Major Findings
Al-Faleh *et al.* [9]	Children aged 1–12 years	National cohort	HBsAg prevalence	Decline in HBsAg prevalence from approximately 6.7% pre-vaccination to 0.3% following universal vaccination
Al-Faleh *et al.* [12]	Vaccinated adolescents	Saudi Arabia	Anti-HBs persistence	Sustained immune memory despite declining anti-HBs titers
Alrowaily *et al.* [19]	General population	Saudi Arabia	HBsAg prevalence	Continued decline in HBV endemicity after universal immunization
Hudu *et al.* [13]	Vaccinated individuals	Institutional cohorts	Anti-HBc positivity	Low but measurable evidence of prior HBV exposure and possible occult infection
Lingawi and Afifi [16]	Healthcare trainees	Najran region	Anti-HBs seroprotection	Majority retained protective immunity or immune memory
Mahallawi [17]	Medical students	Southwestern Saudi Arabia	Anti-HBs titers	Declining antibody levels observed in some vaccinated individuals
Alghamdi *et al.* [19]	Adult population	Saudi Arabia	HBsAg prevalence	Higher HBV prevalence persisted among older unvaccinated populations
WHO and global elimination reports [24,27]	National estimates	Saudi Arabia	HBV control indicators	Saudi Arabia approaching regional HBV elimination targets

HBsAg: Hepatitis B surface antigen, anti-HBs: Antibody to hepatitis B surface antigen, anti-HBc: Antibody to hepatitis B core antigen

The epidemiologic transition also shifted the dominant modes of HBV transmission in the Kingdom. Prior to the advent of universal vaccination, vertical and early childhood transmission were important contributors to chronic HBV infection. The implementation of routine birth-dose vaccination and improved maternal-child preventive measures resulted in a significant reduction in mother-to-child transmission and early-life acquisition of infection [7,20,21]. As a consequence, the remaining HBV burden gradually moved to older age groups and high-risk adult groups such as those with occupational exposure, repeated healthcare contact, or immunocompromising conditions.

Saudi Arabia's experience parallels reports from other early adopters of universal HBV vaccination, especially Taiwan and South Korea, where sustained reductions in HBsAg prevalence and childhood HBV-related liver disease have been observed with long-term immunization programs [22,23]. Within the Gulf region, Saudi Arabia achieved comparatively earlier and broader vaccine implementation, contributing to major reductions in HBV endemicity among younger generations. More recent national surveillance studies continue to demonstrate low HBsAg prevalence among vaccinated cohorts and indicate that Saudi Arabia remains on track to achieve regional HBV elimination targets [19].

Despite these major public health achievements, emerging evidence suggests that low-level HBV persistence, occult infection, and breakthrough HBV DNA positivity may still occur in selected populations, particularly as vaccinated cohorts age and long-term immune dynamics evolve. These results underscore the importance of continued epidemiologic monitoring, molecular surveillance, and targeted assessments of high-risk populations in the postuniversal vaccination era. Key epidemiologic studies demonstrating the long-term impact of universal HBV vaccination in Saudi Arabia are summarized in Table 1.

Mechanisms of Breakthrough Infection, Immune Waning, and Vaccine Escape

Breakthrough hepatitis B virus (HBV) infection in vaccinated individuals is a multifactorial process involving interactions between host immunity, viral evolution, and long-term immunologic dynamics. Although universal HBV vaccination has substantially reduced chronic infection and clinical disease worldwide, vaccine-induced protection is not always sterilizing, and low-level viral persistence or occult infection may persist in selected individuals over time [28,29].

Post-vaccination HBV-related outcomes are generally categorized into primary vaccine failure, secondary vaccine failure, and true breakthrough infection. Primary vaccine failure refers to failure to achieve protective anti-HBs antibody levels (≥10 mIU/mL) following completion of the primary vaccine series, whereas secondary vaccine failure describes a gradual decline of initially protective antibody titers over time [28]. In contrast, breakthrough infection is characterized by the detection of HBV DNA, with or without HBsAg positivity, in a previously vaccinated individual, indicating viral replication despite prior immunization [30]. Importantly, transient low-level HBV DNA positivity may not always represent clinically significant vaccine failure, whereas persistent viremia or occult HBV infection (OBI) may carry greater long-term clinical and public health implications [31]. The major interacting mechanisms contributing to breakthrough infection and occult HBV persistence are summarized in Figure 1. These mechanisms include viral escape mutations, waning humoral immunity, and impaired cellular immune responses, all of which may collectively influence long-term vaccine effectiveness and post-vaccination viral persistence.

One of the principal mechanisms underlying breakthrough infection is waning humoral immunity. Although anti-HBs antibody concentrations progressively decline after vaccination, immunologic memory mediated by memory B cells and T cells often persists for decades and continues to provide protection against severe disease and chronic infection [29,32]. Nevertheless, reduced antibody levels may permit transient viral replication following exposure, particularly in settings of high viral inoculum, immunosenescence, or immunosuppression. Longitudinal studies suggest that persistence of immune memory varies between individuals and may weaken over time in the

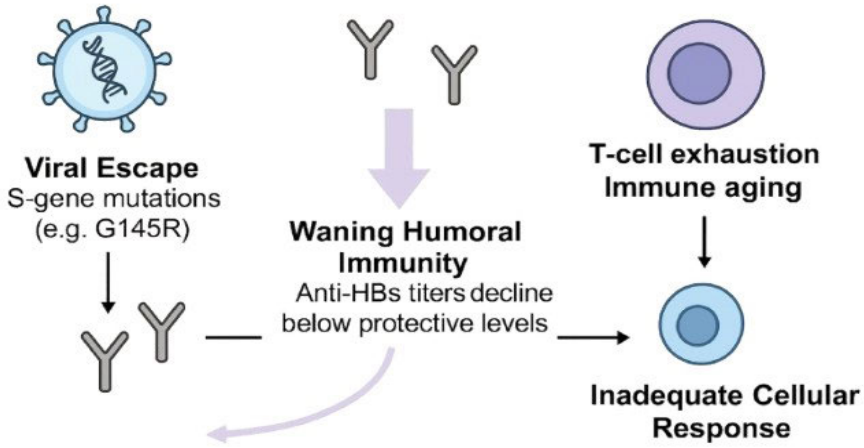

Figure 1: Schematic Illustration of the Major Mechanisms Contributing to Hbv Breakthrough Infection Following Vaccination, Including Viral Escape Mutations, Waning Humoral Immunity, and Impaired Cellular Immune Responses

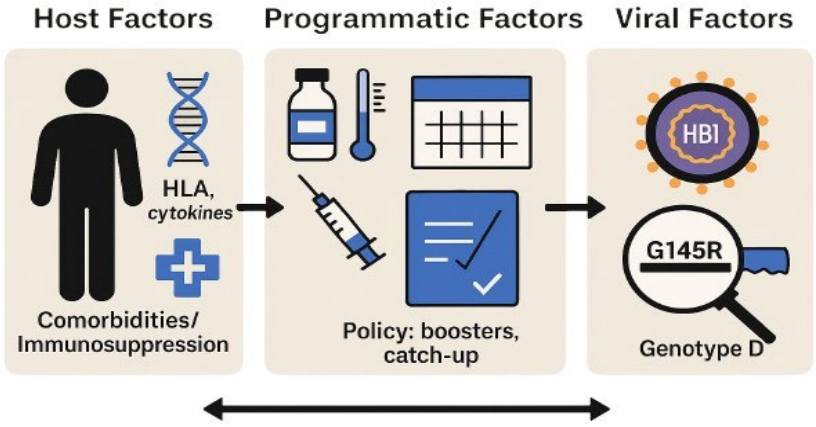

Figure 2. Summary of Host, Programmatic, and Viral Factors Associated with HBV Vaccine Breakthrough and Non-Response

absence of natural antigenic boosting [33]. As illustrated in Figure 1, declining anti-HBs titers below protective thresholds may reduce viral neutralization capacity and increase the risk of breakthrough infection.

Host genetic and immunologic factors also contribute significantly to vaccine responsiveness and long-term protection. Variations in human leukocyte antigen (HLA) alleles, particularly within HLA-DR and HLA-DQ regions, have been associated with hypo-responsiveness or non-response to HBV vaccination by affecting antigen presentation and T-cell activation pathways [34,38]. In addition, polymorphisms involving immunoregulatory cytokines such as IL-10, IFN-γ, and TNF-α may influence the magnitude and durability of vaccine-induced immune responses [37]. Other host-related factors, including advanced age, diabetes mellitus, chronic kidney disease, smoking, and immunosuppressive conditions, may further impair the development or maintenance of protective immunity [38,39]. Figure 1 further highlights the role of impaired cellular immunity, including T-cell exhaustion and immune senescence, in limiting clearance of infected hepatocytes and facilitating persistence of low-level infection.

Viral factors represent another important contributor to post-vaccination HBV persistence. Universal vaccination exerts selective immune pressure on circulating HBV strains, potentially favoring the emergence of vaccine-escape mutants. These variants commonly involve mutations within the “a” determinant region of the HBV surface antigen (HBsAg), the principal target of vaccine-induced neutralizing antibodies [40,41]. Among these, the G145R substitution is the most extensively studied vaccine-escape mutation and has been associated with altered antigenicity, reduced antibody binding, and potential diagnostic escape [40]. As demonstrated in Figure 1, these surface-gene mutations may alter HBsAg structure sufficiently to reduce recognition by vaccine-induced antibodies, thereby permitting viral persistence despite prior immunization.

The predominance of HBV genotype D in Saudi Arabia may also have mechanistic relevance in the post-vaccination

setting. Genotype D has been associated with greater genetic variability within the surface gene and may demonstrate increased propensity for immune escape compared with some other HBV genotypes [42-45]. However, national sequencing data on vaccine-escape variants in Saudi Arabia remain limited, and current evidence remains insufficient to determine the true epidemiologic burden of these mutations at the population level [45-51].

Occult HBV infection likely represents the combined effect of these interacting mechanisms. In many individuals, strong but incomplete host immune control suppresses viral replication below conventional HBsAg detection thresholds, while low-level HBV DNA persists within hepatocytes or in the circulation [47,48]. In other cases, viral surface mutations may alter antigen recognition and reduce assay detectability, creating overlap between occult infection and vaccine-escape phenomena [45,49-56]. Consequently, breakthrough infection, occult persistence, waning immunity, and viral evolution should not be viewed as isolated processes but rather as interconnected outcomes within the long-term host–virus equilibrium established after universal HBV vaccination.

Determinants of Breakthrough Infection and Vaccine Non-Response

Breakthrough HBV infection and vaccine non-response are influenced by a complex interactions among host-related, programmatic, and viral factors that collectively affect long-term vaccine effectiveness. As illustrated in Figure 2, these determinants do not act independently but interact dynamically to influence susceptibility to HBV infection despite prior vaccination. Understanding these overlapping mechanisms is important for identifying populations at increased risk of waning immunity, occult infection, or incomplete vaccine protection.

Host factors include age, genetic variants, and immunosuppression; programmatic factors include cold-chain integrity, dosage regimen, and booster policy; and virologic factors include S-gene mutations and genotype D diversity.

Host-related factors play a major role in determining both the initial immune response to vaccination and the durability of long-term protection. Age is one of the most consistently recognized predictors of reduced vaccine responsiveness, as immune function gradually declines with advancing age because of immunosenescence [38]. Similarly, chronic medical conditions including diabetes mellitus, chronic kidney disease, malignancy, and immunosuppressive disorders may impair the development or persistence of protective immunity following vaccination [39]. Figure 2 further highlights the contribution of host genetic variability, particularly polymorphisms involving human leukocyte antigen (HLA) alleles and immunoregulatory cytokines, which may influence antigen presentation, T-cell activation, and antibody production [34-39]. These factors may contribute to primary vaccine non-response, reduced anti-HBs persistence, or increased susceptibility to breakthrough infection over time.

Programmatic and operational factors also substantially influence vaccine effectiveness. As shown in Figure 2, adherence to the recommended vaccination schedule, timely administration of the birth dose, and maintenance of cold-chain integrity are critical determinants of successful immunization. Delayed or incomplete vaccination may compromise development of durable immune memory, particularly in high-risk infants and vulnerable populations. In addition, improper vaccine storage conditions, including exposure to excessive heat or freezing, may reduce vaccine potency and immunogenicity [57]. Although recombinant HBV vaccines have substantially improved vaccine safety and consistency, minor differences in immunogenicity between vaccine formulations may still influence long-term antibody responses in some individuals.

The role of booster vaccination in the post-universal immunization era remains an important area of ongoing discussion. Current WHO recommendations do not support routine booster doses for fully vaccinated immunocompetent individuals because immune memory generally persists despite declining antibody titers. However, Figure 2 illustrates how waning immunity, repeated occupational exposure, and immunocompromising conditions may increase the risk of breakthrough infection in selected populations. Consequently, targeted anti-HBs monitoring and selective booster administration may be beneficial for healthcare workers, hemodialysis patients, and other high-risk groups with increased exposure risk or impaired immune protection [16-18].

Viral factors represent another important determinant of breakthrough infection and reduced vaccine effectiveness. Mutations within the HBV surface gene, particularly within the “a” determinant region of HBsAg, may alter viral antigenicity and reduce recognition by vaccine-induced neutralizing antibodies [40-41]. Among these, the G145R mutation remains one of the best-characterized vaccine-escape variants and has been associated with immune escape and potential diagnostic failure [31,40,45,58]. Figure 2 further demonstrates the contribution of viral genetic diversity, particularly the predominance of genotype D in Saudi Arabia, which has been associated with increased surface-gene variability and potential immune escape in some studies [42-45]. Although available Saudi molecular data remain limited, emerging evidence suggests that continued circulation of genetically diverse HBV strains may exert selective immune pressure favoring persistence of escape-associated variants [43,44].

Collectively, the determinants summarized in Figure 2 emphasize that HBV breakthrough infection and vaccine non-response are multifactorial phenomena shaped by interactions between host susceptibility, vaccine implementation factors, and viral evolution. These findings support the need for integrated long-term surveillance strategies that combine immunologic monitoring, molecular epidemiology, and targeted public health interventions to sustain the long-term success of universal HBV vaccination programs in Saudi Arabia.

Table 2: Reported Occult Hepatitis B Virus Infection (OBI) in Selected Saudi Populations Following Universal HBV Vaccination

Study/Reference	Population	Region/Setting	OBI Definition/Detection Method	Reported OBI Prevalence	Key Findings
Hudu *et al.* [40]	Vaccinated healthy individuals	Mixed vaccinated cohorts	Isolated anti-HBc positivity with or without detectable HBV DNA	Rare but measurable	Suggested possible occult exposure or low-level viral persistence after vaccination
Alqahtani *et al.* [42]	Healthcare workers and trainees	Najran region	Anti-HBc and anti-HBs serologic assessment; limited molecular testing	Low prevalence of overt HBV with evidence of waning immunity	Suggested ongoing occupational exposure risk and declining long-term immunity in some individuals
Alshayea *et al.* [59]	Blood donors	Central Saudi Arabia	HBsAg-negative, HBV DNA-positive using NAT/PCR	Low but detectable OBI prevalence	Confirmed occult HBV among seronegative blood donors, supporting molecular screening in transfusion settings
Im *et al.* [60]	Immunocompromised and high-risk populations	International comparative data	HBV DNA detection in HBsAg-negative individuals	Higher prevalence in immunocompromised populations	Demonstrated increased OBI burden among high-risk groups
Kwak and Kim [61]	Chronic liver disease and immunocompromised populations	International comparative data	Molecular detection of occult HBV	Variable prevalence across risk groups	Highlighted mechanisms and persistence of occult infection
Takuissu *et al.* [47]	Blood donors	Global comparative meta-analysis	NAT combined with serologic testing	Variable prevalence globally	Reinforced transfusion-related importance of occult HBV
Alrezaihi *et al.* [46]	Blood donors	Saudi Arabia	NAT-confirmed HBV DNA positivity in HBsAg-negative donors	Variable prevalence depending on donor characteristics	Demonstrated continued occurrence of OBI despite routine serologic screening
Al Saran *et al.* [53]	Hemodialysis patients	Riyadh tertiary-care centers	HBV DNA detection among HBsAg-negative patients	Approximately 4.4–4.9%; up to 17% among anti-HBc-positive patients	OBI prevalence substantially higher among dialysis patients than blood donors

OBI: Occult hepatitis B infection, defined as detectable HBV DNA in individuals negative for hepatitis B surface antigen (HBsAg); NAT: Nucleic acid testing; PCR: Polymerase chain reaction; anti-HBc: Antibody to hepatitis B core antigen; anti-HBs: Antibody to hepatitis B surface antigen. Reported prevalence estimates should be interpreted cautiously because of heterogeneity in study populations, diagnostic methods, and geographic coverage

Occult HBV Infection and Vaccine-Escape Variants

Occult hepatitis B virus infection (OBI) represents one of the most important emerging challenges in the post-universal vaccination era because it reflects persistence of HBV DNA in individuals who remain negative for hepatitis B surface antigen (HBsAg). In many cases, OBI is clinically silent and detectable only through molecular assays, particularly nucleic acid testing (NAT). The persistence of low-level HBV DNA despite apparent serologic recovery or vaccination has important implications for blood safety, immunosuppression-related reactivation, and long-term liver disease surveillance [47,48].

The epidemiology of OBI in Saudi Arabia remains incompletely characterized, as most available evidence derives from regional or institution-based studies rather than from coordinated national surveillance programs. Nevertheless, published Saudi data consistently confirm the presence of occult HBV infection in blood donors, hemodialysis patients, and other high-risk populations, although prevalence estimates vary considerably according to population type, diagnostic methods, and geographic location (Table 2).

Among blood donors, several Saudi studies have demonstrated the presence of detectable HBV DNA in HBsAg-negative individuals during routine donor screening. Molecular surveillance studies conducted in central Saudi Arabia identified occult HBV infection among seronegative blood donors, underscoring the limitations of serology-only screening approaches [59]. More recent donor-based studies similarly reported measurable OBI prevalence among apparently healthy donors, further supporting the importance of integrating NAT into routine transfusion safety programs [46]. These findings are consistent with international evidence demonstrating that occult HBV infection remains a persistent transfusion-related concern even in countries with successful vaccination programs [34].

The burden of OBI appears substantially higher among immunocompromised and repeatedly exposed populations. Hemodialysis patients, in particular, represent a major high-risk group because of recurrent blood exposure, impaired immune function, and prolonged healthcare contact. Saudi studies have reported OBI frequencies ranging from approximately 4% to 5% among dialysis populations, with even higher prevalence among anti-HBc-positive individuals [53]. Similar patterns have been observed globally, where occult infection occurs more frequently in patients with chronic kidney disease, HIV infection, hematologic disorders, or other immunosuppressive conditions [47,48].

The persistence of occult HBV infection may result from several overlapping mechanisms. Strong host immune control may suppress viral replication to levels below conventional HBsAg assay detection thresholds while

covalently closed circular DNA (cccDNA) persists within hepatocytes. In addition, mutations within the HBV surface gene may alter antigenicity and reduce detectability by commercial HBsAg assays, creating overlap between occult infection and vaccine-escape phenomena [45,49-56]. Surface-gene mutations involving the "a" determinant region, particularly G145R, have been associated with altered antibody recognition and possible immune escape [40,41].

The predominance of HBV genotype D in Saudi Arabia may have additional implications for occult infection and vaccine escape, as genotype D has been associated with greater genetic diversity within the surface gene and an increased frequency of escape-associated mutations in some studies [42,43-45,58]. However, national molecular surveillance data remain limited, and current evidence is insufficient to determine the true prevalence and geographic distribution of vaccine-escape variants within the Kingdom [43,44].

From a public health perspective, OBI remains clinically important despite its frequently asymptomatic nature. Individuals with occult infection may serve as potential sources of transmission through blood transfusion or organ transplantation and remain at risk of viral reactivation during immunosuppressive therapy. Furthermore, persistent low-level HBV infection may contribute to chronic liver inflammation and long-term hepatocellular carcinoma risk even in HBsAg-negative individuals. As summarized in Table 2, available Saudi evidence supports the need for expanded molecular surveillance, particularly among blood donors, dialysis patients, and other high-risk populations.

High-Risk Populations in the Post-Vaccination Era

Despite the marked decline in hepatitis B virus (HBV) transmission following the introduction of universal vaccination in Saudi Arabia, some groups remain vulnerable to occult infection, breakthrough HBV positivity, and declining vaccine-induced immunity. These risks are unevenly distributed across the population and are shaped by factors such as repeated healthcare exposure, immunosuppression, occupational contact, and underlying medical conditions. Current evidence suggests that hemodialysis patients, blood donors, healthcare workers, and immunocompromised individuals constitute the principal high-risk groups requiring ongoing surveillance and targeted preventive measures.

Among these groups, patients undergoing hemodialysis appear to carry the greatest burden of occult HBV infection (OBI). Frequent vascular access, repeated exposure to blood products, prolonged interaction with healthcare settings, and impaired immune function all contribute to their increased susceptibility. Studies from Saudi Arabia have reported OBI prevalence rates of approximately 4%–5% in dialysis cohorts, with substantially higher rates among individuals who are anti-HBc positive [53]. Comparable findings have been documented internationally, where chronic kidney disease and dialysis-associated immunosuppression are recognized as important risk factors for persistent occult infection and viral reactivation [47,48]. Together, these findings highlight the importance of periodic molecular screening and closer monitoring of vaccine-induced immunity in dialysis populations.

Blood donors represent another critical surveillance population because occult HBV infection can escape detection when screening relies solely on HBsAg testing. Saudi studies involving blood donors have identified HBV DNA positivity in individuals who were seronegative by conventional screening, confirming the persistence of low-level occult infection despite widespread vaccination and declining national endemicity [46,59]. Although the overall prevalence among donors remains lower than that observed in dialysis patients, the public health implications are considerable, as undetected OBI may still lead to transfusion-related transmission. For this reason, incorporating nucleic acid testing (NAT) into routine donor screening has become an essential component of blood safety programs in the Kingdom.

Healthcare workers and healthcare trainees also remain an important occupational risk group in the post-vaccination era. While vaccination coverage among healthcare personnel is generally high, studies from Saudi Arabia indicate that anti-HBs antibody levels may decline over time in some individuals, potentially increasing vulnerability after repeated occupational exposure [15-18,62]. Most vaccinated individuals continue to retain immunologic memory even when measurable antibody levels decrease; however, breakthrough exposure may still occur, particularly among those with incomplete vaccine responses, waning immunity, or frequent contact with blood and body fluids. These observations support periodic anti-HBs monitoring and consideration of selective booster strategies for higher-risk occupational groups.

Additional immunocompromised populations, including patients with malignancies, HIV infection, chronic liver disease, or those receiving immunosuppressive therapy, may also face a heightened risk of occult infection and HBV reactivation. In these individuals, impaired cellular immunity can allow low-level HBV replication to persist despite prior vaccination or apparent recovery from infection [47,48]. International studies consistently report higher rates of OBI and HBV reactivation in immunosuppressed populations, although molecular data from Saudi Arabia remain limited. As the use of immunomodulatory therapies and transplantation services continues to expand within the region, these populations are likely to become an increasingly important focus of future surveillance efforts.

Overall, the available evidence suggests that residual HBV risk in post-vaccination Saudi Arabia is now concentrated largely within specific vulnerable populations rather than the general vaccinated community. As summarized in Table 2, the burden of occult and breakthrough HBV infection appears highest among hemodialysis and immunocompromised patients, moderate

among healthcare workers with repeated occupational exposure, and comparatively lower among routine blood donors. These findings support a more focused surveillance strategy that incorporates molecular screening, long-term assessment of vaccine-induced immunity, and risk-based booster approaches tailored to vulnerable populations in the post-universal vaccination era.

Policy and Public Health Implications

The substantial decline in hepatitis B virus (HBV) endemicity following universal vaccination has positioned Saudi Arabia among the leading countries in the region for HBV control. Nevertheless, the persistence of occult HBV infection (OBI), waning immunity, and possible vaccine-escape variants highlights the need for a more integrated long-term surveillance strategy. As illustrated in Figure 3, future progress toward HBV elimination in Saudi Arabia will likely depend on coordinated interaction between integrated health data systems, advanced molecular surveillance, and targeted booster strategies.

The framework integrates vaccination and public health databases, molecular surveillance, and targeted booster strategies to support long-term HBV control and elimination goals.

The World Health Organization (WHO) viral hepatitis elimination targets aim for a 90% reduction in new chronic HBV infections and a 65% reduction in hepatitis-related mortality by 2030 [24-27]. Saudi Arabia has already achieved substantial reductions in HBsAg prevalence among younger vaccinated populations, reflecting the long-term success of the national immunization program [19]. However, residual HBV transmission risk persists within selected high-risk populations, emphasizing the importance of strengthening surveillance beyond conventional serologic monitoring alone.

Figure 3 summarizes a proposed strategic framework for advancing HBV elimination efforts in Saudi Arabia. The first pillar involves integration of vaccination records,

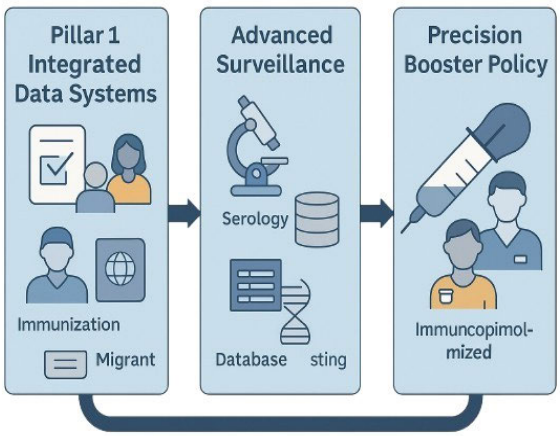

Figure 3: Proposed Framework for Strengthening HBV Surveillance and Elimination Strategies in Saudi Arabia

maternal-child health systems, migrant health screening, and public health surveillance databases into a unified national monitoring platform. Such integration may improve identification of missed birth-dose vaccination, incomplete immunization, and high-risk exposure groups while supporting long-term continuity of care. Strengthening the linkage between immunization registries and maternal-child healthcare programs is particularly important for maintaining low rates of mother-to-child transmission [22].

The second pillar highlighted in Figure 3 is the expansion of molecular and epidemiologic surveillance. Current evidence demonstrates that reliance on HBsAg-based screening alone may underestimate the burden of occult infection and low-level HBV persistence [46,59]. Therefore, broader incorporation of nucleic acid testing (NAT), targeted HBV DNA screening, and molecular characterization of circulating strains may improve detection of occult infection and vaccine-escape variants. Figure 3 further emphasizes the importance of establishing a national HBV sequencing and mutation surveillance framework capable of monitoring the distribution of genotypes and the emergence of surface-gene escape mutations over time.

The third pillar involves targeted boosters and long-term immunity strategies for selected high-risk groups. Although routine booster vaccination is not currently recommended for fully vaccinated immunocompetent individuals, accumulating evidence suggests that some populations may benefit from periodic anti-HBs monitoring and selective booster administration. As shown in Figure 3, healthcare workers, hemodialysis patients, and immunocompromised individuals represent priority groups for risk-based booster policies because of increased exposure risk or impaired immune protection [53,60,61,62]. Such targeted approaches may provide a more practical and resource-efficient strategy than universal booster implementation.

Importantly, the framework presented in Figure 3 should be viewed as a phased public health strategy rather than an immediate nationwide implementation model. Expansion of molecular surveillance and integrated digital health systems will require progressive strengthening of laboratory infrastructure, sequencing capacity, healthcare workforce training, and national data coordination mechanisms. Nevertheless, the long-term integration of epidemiologic surveillance, molecular monitoring, and targeted prevention strategies may substantially improve Saudi Arabia's ability to address emerging post-vaccination HBV challenges while supporting progress toward regional elimination goals.

Future Directions and Research Priorities

The unique situation in Saudi Arabia, a country where universal hepatitis B vaccination has been consistently implemented nationwide for over 30 years, makes it a valuable long-term public health setting for studying vaccine effects over extended periods in real-world settings. The extensive databases created by this long-term vaccination program offer an important opportunity to shift from reactive

descriptions of outcomes to an integrated long-term surveillance framework. This approach calls for the development of a National HBV Immunogenomics Registry. This centralized, comprehensive repository will link detailed vaccination histories with host genetic data, longitudinal serology results, and, when available, viral genomes from breakthrough cases. Such a registry would serve as a research platform for researchers to thoroughly investigate the complex host-pathogen interactions that cause vaccine failure and non-response at the population level. By correlating specific HLA haplotypes and cytokine gene polymorphisms with immune responses across the entire population, the registry could generate enough evidence to replace a one-size-fits-all vaccination strategy with a risk-based prevention strategy.

The immunogenomics registry is most effective when linked to secondary databases and other next-generation public health tools. Molecular epidemiology data, which show how genotypes and vaccine-escape mutants spread, need to be seamlessly integrated with the registry to provide a complete view of the evolving public health situation. This should, in turn, guide a flexible, reactive booster dose policy that can target high-risk groups and the small number of people with specific genetic backgrounds that make them more vulnerable to immunity loss. Additionally, by utilizing the Kingdom's current investments in e-health, this entire system should be integrated into a single digital vaccination record. From a public health standpoint, the ability to access a person's full immunization record at any time— including serology history and booster suggestions—would fill critical gaps in care and help ensure lifelong protection.

These complementary innovations may help shape the future of HBV control through a more advanced and integrated public health approach that is a core part of targeted public health surveillance in the Gulf region. Saudi Arabia has a unique opportunity to lead this change by showing how integrated epidemiologic and molecular data can be used to address long- standing health challenges. Such an approach may shift the national response from reactive management of breakthrough infections toward earlier identification of individuals at increased risk of waning immunity or occult HBV persistence, who need additional protection. By emulating that model, Saudi Arabia can become a regional contributor to HBV control strategies and introduce a scalable, sustainable approach to controlling and even eliminating hepatitis B. Such targeted surveillance and prevention strategies may improve long-term HBV control.

Limitations

This review has several limitations that should be considered when interpreting the findings. First, the study was conducted as a structured narrative review rather than a systematic review or meta-analysis; therefore, formal pooled quantitative estimates and risk-of-bias analyses were not performed. Second, the included studies showed substantial heterogeneity in study design, sample size, laboratory methods, diagnostic criteria, and reporting approaches, which limited direct comparison across studies and prevented formal quantitative synthesis.

In addition, much of the available Saudi evidence derives from institution-based or regional studies rather than nationally representative surveillance programs. Consequently, the true national burden of occult HBV infection, breakthrough infection, and vaccine-escape variants may be under- or overestimated. Geographic coverage across the Kingdom also remains uneven, with limited long-term data from some regions and high-risk populations.

Another important limitation relates to temporal variability in laboratory diagnostics over the three decades covered by this review. Improvements in assay sensitivity, introduction of nucleic acid testing, and evolving molecular techniques may have influenced reported prevalence estimates and detection rates across studies. Furthermore, national sequencing data on HBV genotypes and vaccine-escape mutations remain limited, restricting conclusions regarding the epidemiologic significance of viral evolution in the Saudi setting.

Finally, although international studies were included to provide mechanistic and comparative context, some interpretations regarding immune escape, occult infection, and long-term vaccine dynamics may not fully reflect Saudi-specific epidemiologic conditions. Therefore, the findings and policy implications presented in this review should be interpreted within the context of the currently available evidence base.

CONCLUSIONS

Universal HBV vaccination has substantially altered the epidemiology of HBV infection in Saudi Arabia, leading to major reductions in HBsAg prevalence and interruption of early-life transmission across vaccine-era populations. The national immunization program has contributed substantially to HBV control within the region and has positioned Saudi Arabia favorably toward long-term elimination goals. However, evidence accumulated during the post-vaccination era indicates that occult infection, waning immunity, and possible breakthrough HBV infection continue to occur in selected high-risk populations, including blood donors, hemodialysis patients, healthcare workers, and immunocompromised individuals. These findings highlight the evolving complexity of long-term HBV control despite sustained vaccination success. Current evidence also underscores important gaps in national molecular surveillance, sequencing data, and long-term epidemiologic monitoring of vaccine-escape variants and occult infection.

This review suggests that future HBV control efforts in Saudi Arabia may benefit from a more integrated surveillance approach combining epidemiologic monitoring, molecular testing, targeted screening of high-risk groups, and risk-based booster strategies. Expansion of HBV DNA surveillance and sequencing capacity may further improve

understanding of post-vaccination viral persistence and immune escape within the Kingdom. Nevertheless, the available evidence remains limited by heterogeneous study designs, uneven geographic coverage, and the predominantly institution-based nature of current data. Future multicenter longitudinal studies integrating molecular epidemiology, immunologic surveillance, and vaccine-response profiling will be important to better define long-term HBV control strategies in Saudi Arabia.

Competing Interests

The authors declare no competing interests

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