HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2473222
https://doi.org/10.1080/21645515.2025.2473222

Taylor & Francis
Taylor & Francis Group

ARTICLE COMMENTARY

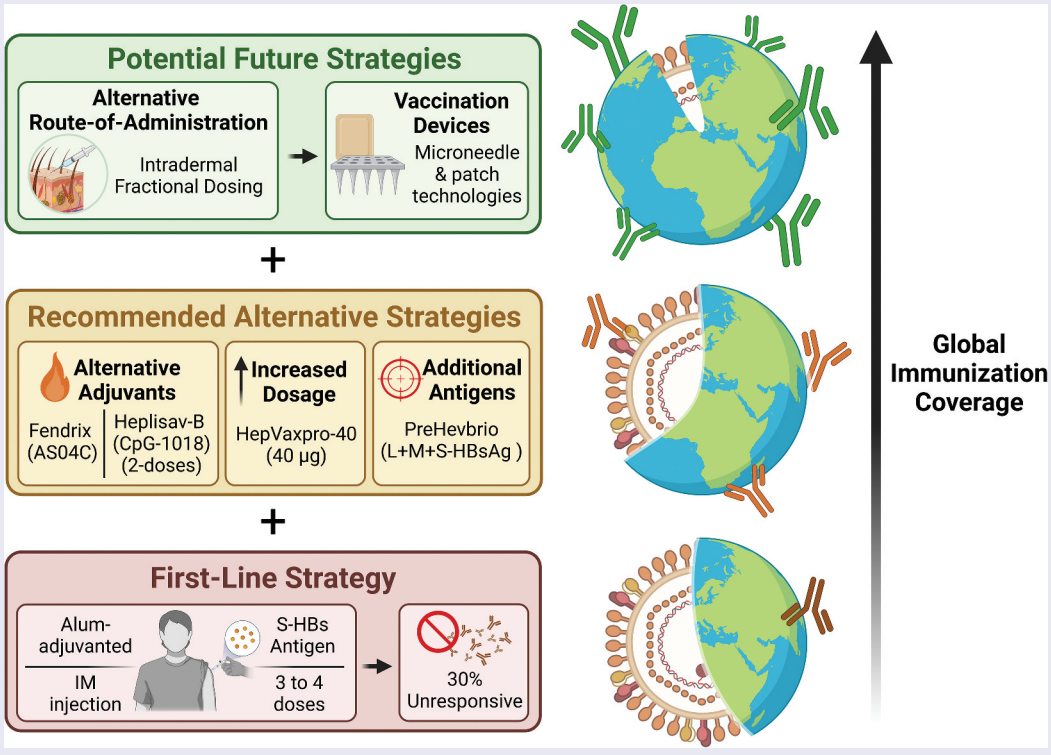
Mission 2030: Toward universal hepatitis B immunization

Elias Broeckhoven* and Kai Dallmeier

KU Leuven Department of Microbiology, Immunology & Transplantation, Rega Institute, Virology, Antiviral & Vaccine Research Group, Molecular Vaccinology & Vaccine Discovery (MVVD), Leuven, Belgium

ABSTRACT

Despite the availability of efficacious and safe vaccines for more than 40 years, the rate of new hepatitis B virus (HBV) infections remains high, leaving large populations at risk of developing chronic hepatitis B, liver cirrhosis and cancer. The WHO aims at reducing the number of cases by 90% as part of its *Immunization Agenda 2030*. While legacy vaccines and established immunization protocols will play a significant role in achieving this goal, challenges such as an inconvenient multi-dose regimen and a reduced efficacy in adults persist. Novel vaccines with improved adjuvants, alternative antigens, and innovative administration routes show promise in overcoming these hurdles. However, achieving universal immunization requires increased vaccine coverage, likely by development and validation of two-dose vaccines for children, and the endorsement and implementation of such new approaches in future immunization policies. By addressing these challenges, the goal of controlling HBV globally through immunization becomes attainable.



ARTICLE HISTORY
Received 23 January 2025
Revised 17 February 2025
Accepted 25 February 2025

KEYWORDS
HBV vaccination; universal immunization; non-responders; vaccine uptake; vaccine formulation

Main text

Hepatitis B virus (HBV) remains a major global health threat, with an estimated 286 million people living with chronic hepatitis B (CHB) who are at risk of developing detrimental sequelae such as liver cirrhosis and hepatocellular carcinoma, resulting in 1.1 million deaths annually. Additionally, despite ongoing efforts to decrease global burden through prevention and therapy, new cases still reached 1.23 million in 2022.[1,2] In 2020, the WHO launched the *Immunization Agenda 2030*, an ambitious yet crucial plan to reduce global infectious disease

CONTACT Kai Dallmeier kai.dallmeier@kuleuven.be KU Leuven Department of Microbiology, Immunology & Transplantation, Rega Institute, Virology, Antiviral & Vaccine Research Group, Molecular Vaccinology & Vaccine Discovery (MVVD), BE-3000 Leuven, Belgium.
*lead author.

incidence and mortality.[3] One goal is to reduce the number of CHB cases by 90%. However, as prevalence remains high and a functional cure for CHB remains yet to be established, current efforts should focus on global diagnostic and prophylactic strategies to break the transmission cycle. Since 1992, the WHO has recommended including hepatitis B vaccination in the *Expanded Programme on Immunization* (EPI), advising first dose vaccination at birth to prevent perinatal transmission. To reach and sustain the 90% goal, blocking vertical transmission is particularly important, given that the risk of developing CHB is 10- to −50-fold higher when infection occurs early in life compared to adulthood; with an estimated likelihood of up to 95%. Nevertheless, currently, less than half of the children born today receive a timely dose to prevent mother-to-child transmission.[2] Whilst we have the tools at hand, universal immunization remains difficult to achieve through current approaches, emphasizing the need for new and improved vaccination strategies to avert infections.

First-generation recombinant small HBV surface antigen (S-HBsAg) vaccines adjuvanted with alum have been widely used, resulting in a significant decline in HBV cases worldwide. The impact of childhood vaccination on the long-term incidence of CHB cannot be underestimated, as shown by real-world effectiveness through the decline of HBsAg-prevalence in children under 5 years in regions with historically high transmission rates such as China or Ghana.[4] Targeting the pediatric population is hence an obvious way to reduce CHB rates in the future.[5] However, these vaccines generally require a three-dose baseline regimen spread over six months. Such extensive regimens limit immunization in areas where patient compliance and healthcare infrastructure pose a major challenge. Nevertheless, when used in a pediatric setting, these vaccines achieve seroprotective antibody titers (anti-HBs antibody, HBsAb ≥ 10 mIU/ml) in 95% of cases upon completion of the 3-dose schedule. However, standard-dose monovalent alum-adjuvanted vaccines show a marked decline in efficacy in adult and elderly patients, with up to 30% of healthy adults failing to mount a sufficiently strong antibody response (HBsAb < 10 mIU/ml) to vaccination. Various factors leading to unresponsiveness have been identified, such as patient behavior like smoking, age at vaccination, or genetic variations regarding HLA or interleukin types.[6] Taken together, this presents a significant hurdle in reaching universal immunization and the ultimate goals of reducing global CHB burden. These inadequately immunized individuals remain susceptible and may become potential HBV reservoirs even when formally vaccinated. Hence, to confirm an appropriate immunization status, HBsAb determination is often performed. However, implementing and rolling out HBsAb serosurveillance at scale comes at a significant cost, increasing dependency on healthcare infrastructures and potentially competing with other public health needs such as managing malaria, tuberculosis, or HIV in resource-limited settings.

When identified as a non-responder, a variety of vaccination strategies can be employed to overcome this issue. Typically, additional doses are administered in the hope to elicit a stronger immune response. Alternatively, Raven et al. compared various approaches, such as double-dosing with two shots of Engerix-B (20 µg small (S)-HBsAg) or a single higher dose vaccine like HBVaxpro-40 (40 µg S-HBsAg), or using alternative-adjuvanted hepatitis B vaccines such as Fendrix, an AS04C-adjuvanted vaccine.[7] Interestingly, all these strategies show a marked increase in seroconversion rates in previous non-responders and should be considered when striving for universal hepatitis B immunization.

Historically, alum was the adjuvant of choice. Fendrix was the first non-alum-adjuvanted HBsAg vaccine to receive market approval. In their studies, Raven et al. and Hoebe et al. showed improved seroconversion rates compared to alum-adjuvanted vaccines like Engerix-B.[7,8] This demonstrates the potential of combining legacy antigens like the S-HBsAg with novel adjuvants to enhance immunization. As of 2017, the FDA approved the use of Heplisav-B (Dynavax), a next-generation prophylactic HBV vaccine using CpG1018 as an adjuvant. This vaccine became the first CpG-adjuvanted human vaccine to receive regulatory approval. The use of CpG1018, a TLR-9 agonist, results in a Th1-biased immune response and has proven to elicit a faster, more potent immune response compared to alum-adjuvanted products.[9] Notably, Heplisav-B is the first HBV vaccine that requires only two doses, limiting the vaccination regimen to a simplified one-month schedule, possibly increasing accessibility where medical interventions are not a given. However, the use of Heplisav-B is currently limited to adults, primarily targeting non-responders to alum-adjuvanted vaccines, immunocompromised individuals, and adults who received no or an incomplete childhood vaccination regimen. Despite its recent approval, Girndt et al. demonstrated in a long-term 34-month follow-up study that Heplisav-B vaccinated individuals showed significantly higher antibody titers and a slower decline of HBsAb compared to the legacy alum-adjuvanted Engerix-B vaccine. Therefor Heplisav-B seems to be immunologically and practically advantageous while preserving a similarly favorable safety profile.[10] Currently, additional dosing is recommended in many countries to cope with waning seroprotection in exposure-prone populations. To combat this, more widespread use of such potent new-generation vaccines may decrease the reliance on both antibody determination through serology and the need for boosting, reducing the burden on healthcare systems and costs.

Besides the use of novel adjuvants, the addition of other HBs-derived HBV antigens has been explored. PreHevbri, or PreHevbrio, which included the PreS1- and PreS2-containing large (L)- and middle (M)-HBs antigens on top of the common small (S)-HBsAg, was the first, and only, 3-dose triple-antigen prophylactic HBV vaccine to be approved and marketed for adult use. Besides an enhanced immunogenicity in previous non-responders, this more complex vaccine formulation induced markedly higher seroconversion rates (efficacy of 91%) than alum-adjuvanted Engerix-B (76%) upon completion of the full 3-dose regimen.[11] Moreover, four weeks after just two doses the triple vaccine achieved already 50% seroprotection, twice that obtained by two doses of Engerix-B.[11,12] However, hesitancy to substitute legacy vaccines and resistance to change established vaccination policies can be inhibitory for the market entry and uptake of new products. Likewise, PreHevbri has been discontinued at the end of 2024, despite these obvious advantages, yet serving as a valuable example of

the potential of alternative or additional antigens to overcome barriers in HBV immunization.

Besides the use of increased dosages, additional HBsAg antigens, or non-alum adjuvanted vaccines, alternative routes of administration have been investigated to address the issue of non-responders. Already in 1983, Miller et al. published on the improved immunogenicity of intradermal (ID) injection of one of the first HBV vaccines, Heptavac-B, in patients who proved to be non-responders to intramuscular (IM) injection.[13] This set the stage for using the skin as a novel site for HBV immunization. Over the past decades, ID vaccination using alum-adjuvanted HBV vaccines has been employed with mixed results in terms of efficacy. However, some reports show improvements in HBsAb and overall seroconversion rates by 12% to 23% compared to IM injection, even in populations which are notoriously difficult to vaccinate for HBV, such as HIV-infected individuals or hemodialysis patients, respectively.[14,15] Regardless, even if not fully consistent, a lack of safety concerns warrants the use of this alternative vaccination route in those who are more difficult to immunize. Additionally, in previously non-vaccinated individuals, ID vaccination offers the potential of fractional dosing, requiring a smaller dose while still reaching seroprotective antibody titers, simply by switching the site of immunization.[16] However, comparing low-dose ID (frequently 2 µg HBsAg, i.e., one-fifth of a standard IM dose) to full-dose IM vaccination sets a high bar. Nevertheless, fractional ID dosing reaches on average seroprotective antibody titers in more than 88% of vaccines, showcasing minimal, if not non-inferiority to standard IM vaccination.[17] Therefore, fractional dosing regimens may be considered in settings where vaccine supply is scarce, choosing a slightly lower efficacy of low-dose ID over no vaccine at all, to increase global population-wide vaccine coverage.

While unresponsiveness to vaccination affects all levels of society, costs of vaccination remain a secondary yet crucial factor contributing to immunization inequity in low-income regions. For pediatric HBV vaccination alum-adjuvanted HBV vaccines (e.g., pediatric Engerix-B and HBVaxPro) remain the method of choice, either as monovalent or as part of a multivalent formulations. As these pediatric regimens share a similar efficacy, comparable price and timeline, their cost-effectiveness is equally favorable. However, for individuals that suffer from poor responsiveness, cost to achieve seroprotection is critically influenced by vaccine potency. While alum-adjuvanted vaccines such as Engerix-B are currently available for the lowest cost per dose, a relatively high rate of primary vaccine failure requires additional booster doses and costly companion serodiagnostics. For example, Vilajeliu et al. assessed the overall expenses to reach seroprotection in patients with chronic kidney disease. In such a notoriously difficult to immunize target population, use of alternatives to Engerix-B was calculated to be only marginally more expensive (HBVaxPro by 3%), or even more cost saving (Fendrix by 10%).[18] This, despite the cost per dose being 40% and 30% higher than Engerix-B, respectively. Dosing schedules using alternative vaccines for specific patient groups can thus be cost-saving when one considers the expenditures associated with repeated doctor's visits and serological follow up. In line, Kuan et al. and Rosenthal et al. compared a 3-dose Engerix-B to a 2-dose Heplisav-B vaccination strategy and conclude that latter may reach a higher cost-effectiveness and cost-saving thanks to its superior efficacy and shorter regimen.[19,20] As intradermal (fractional) dosing is not common practice, cost-effectiveness analyses remain scarce. Regardless, by stretching vaccine stocks and using thus fewer material, it is apparent that costs can be further suppressed through combining strategies. Besides actual costs of immunization, cost-effectiveness should also been seen in light of the global savings associated with prevention of HBV infection and disease. Seen the high morbidity and mortality of CHB, it is obvious and well established that HBV vaccination is cost-effective compared to no vaccination at all.[21] Nevertheless, though more cost-effective in the long term, higher costs per dose may represent a challenge for decision-makers who need to select new vaccines for field use; along with the necessity to revise established immunization policies. Hereby funding mechanism such as the GAVI procurement system may play an important role in supporting the roll-out of new modalities.[22] And when available, healthcare workers should make informed decisions on which vaccine to use to achieve protection in the most efficient and effective way possible, beyond a historically established one-size-fits-all approach and based on a patient's individual medical background.

Despite widespread use, current HBV vaccination faces critical bottlenecks, such as unresponsiveness to vaccination and limited access to vaccines. Researchers have developed new ways to overcome these shortcomings, including new vaccines with more immunogenic adjuvants, antigens and alternative routes of immunization. However, there is still a long way to go, especially considering the increasing mortality, which rose by 30% between 2020 and 2022 according to the most recent *World Hepatitis Report*.[2] Further efforts are required to halt this upward trend. Widespread vaccination remains the most effective HBV prophylaxis. Increasing vaccination coverage, particularly vaccination at birth, and the universal use of second-generation vaccines in unvaccinated people is undoubtedly a strategy to strive for. Developing 2-dose vaccines like Heplisav-B for use in children could streamline and facilitate pediatric vaccination programs, decreasing reliance on patient compliance and healthcare infrastructures. However, this would require additional safety and efficacy assessments for regulatory approval, and implementation in multivalent pediatric vaccines which currently contain the alum-adjuvanted HBsAg vaccine. Additionally, ID vaccination could help stretch available vaccine stocks through fractional dosing and, in combination with novel microneedle and vaccination patch technologies, allow for more widespread vaccination, potentially even self-administration. Vaccine industries and sponsors of such new developments should be incentivized, driven by endorsement and rapid implementation into national immunization programs. By combining these strategies, universal immunization becomes attainable, striving toward a world in control of HBV.

Acknowledgments

E.B acknowledges personal funding by the Flemish Research Foundation (FWO) under grant 1S00525N and Trainee Award *'Bright Sparks in Vaccinology'* from the International Society for Vaccines (ISV) for attendance of the 2024 ISV conference. K. D. acknowledges personal funding by FWO Excellence of Science (EOS) Program under grant 40007527; VirEOS2, and KU Leuven under grants IDN/20/011, C3/19/059 and iBOF/23/005. The content of this commentary represents the opinions of the authors, and does not reflect the views or policies of their corresponding institution or funding agencies.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The work was supported by the Fonds Wetenschappelijk Onderzoek [1S00525N]; Fonds Wetenschappelijk Onderzoek [40007527]; KU Leuven [IDN/20/011, C3/19/059, iBOF/23/005].

Notes on contributors

Elias Broeckhoven graduated as MSc in Biochemistry & Biotechnology in 2022 and is currently a PhD student in Prof. Kai Dallmeier's group of Molecular Vaccinology & Vaccine Discovery at KU Leuven. His research focuses on hepatitis B and D virus infections, particularly the establishment of animal models for chronic and acute infections, aimed at therapy development and unraveling host-pathogen interactions. Additionally, he is working on novel vaccination devices to improve the efficiency and accessibility of HBV vaccination strategies in lower-resource settings.

Kai Dallmeier, PhD, is Research Associate Professor of Virology at the University of Leuven (KU Leuven), Belgium, leading the Laboratory of Molecular Vaccinology & Vaccine Discovery (MVVD) at the KU Leuven Rega Institute. In a multidisciplinary approach and using the live-attenuated yellow fever vaccine as platform, he and his team develop vaccines for emerging infections (such as Zika, Ebola and COVID-19) as well as therapeutic vaccines (for instance for chronic hepatitis B). Thermostable and easy to manufacture plasmid-launched versions thereof aim to tackle vaccine shortage and unmet public health needs faced by people living in LMIC. For deeper mechanistic insight in virus replication and virus-induced disease, this translational work on vaccines is complemented by the study of viral infections in a range of cell culture and animal models, e.g. by introducing a hamster model of COVID-19 immune pathogenesis which in the meantime is widely used for the preclinical assessment of antiviral drugs and vaccines. Dr. Kai Dallmeier studied Microbiology, Biochemistry and Biophysics at the University of Bremen, Germany and obtained a PhD in Molecular Virology from the University of Freiburg, Germany. He is a co-founder of the KU Leuven spin-off company AstriVax.

ORCID

Elias Broeckhoven http://orcid.org/0000-0002-9758-684X
Kai Dallmeier http://orcid.org/0000-0002-8117-9166

Ethics statement

All experiments and research mentioned herein obtained approval from the appropriate local ethics committee or Institutional Review Board as stated in their respective publications.

References

1. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol. 2023;20(8):524–537. doi:10.1038/s41575-023-00760-9.
2. World Health Organization (WHO). Global hepatitis report 2024: action for access in low- and middle-income countries. 2024 [accessed 10 Jan 2025]. https://www.who.int/publications/i/item/9789240091672.
3. World Health Organization (WHO). Immunization agenda 2030. 2021 [accessed 10 Jan 2025]. https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030.
4. Sheena BS, Hiebert L, Han H, Ippolito H, Abbasi-Kangevari M, Abbasi-Kangevari Z, Abbastabar H, Abdoli A, Abubaker Ali H, Adane MM, et al. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet Gastroenterol Hepatol. 2022;7(9):796–829. doi:10.1016/S2468-1253(22)00124-8.
5. de Villiers Mj, de Villiers E, Nayagam S, Hallett TB, de Villiers MJ. Direct and indirect effects of hepatitis B vaccination in four low- and middle-income countries. Epidemics. 2024;49:49. doi:10.1016/J.EPIDEM.2024.100798.
6. Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, Xu K, Ren J, Yao J, Li Y, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. Sci Rep. 2016;6(1):1–12. doi:10.1038/srep27251.
7. Raven SFH, Hoebe CJPA, Vossen ACTM, Visser LG, Hautvast JLA, Roukens AHE, van Steenbergen JE. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2020;20(1):92–101. doi:10.1016/S1473-3099(19)30417-7.
8. Hoebe CJPA, Vermeiren APA, Dukers-Muijrers NHTM. Revaccination with Fendrix® or HBVaxPro® results in better response rates than does revaccination with three doses of Engerix-B® in previous non-responders. Vaccine. 2012;30(48):6734–6737. doi:10.1016/J.VACCINE.2012.08.074.
9. Jackson S, Lentino J, Kopp J, Murray L, Ellison W, Rhee M, Shockey G, Akella L, Erby K, Heyward WL, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine. 2018;36(5):668–674. doi:10.1016/J.VACCINE.2017.12.038.
10. Girndt M, Houser P, Manllo-Karim R, Ervin JE, Charytan C, Chow S, Symonian-Silver M, Lehrner L, Linfert D, Shemin D, et al. Long-term immunogenicity and safety of the hepatitis B vaccine HepB-CpG (HEPLISAV-B) compared with HepB-eng (engerix-b) in adults with chronic kidney disease. Vaccine. 2023;41(20):3224–3232. doi:10.1016/J.VACCINE.2023.04.028.
11. Vesikari T, Langley JM, Segall N, Ward BJ, Cooper C, Poliquin G, Smith B, Gantt S, McElhaney JE, Dionne M, et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. Lancet Infect Dis. 2021;21(9):1271–1281. doi:10.1016/S1473-3099(20)30780-5.
12. Vesikari T, Langley JM, Spaans JN, Petrov I, Popovic V, Yassin-Rajkumar B, Anderson DE, Diaz-Mitoma F. The persistence of seroprotective levels of antibodies after vaccination with PreHevbrio, a 3-antigen hepatitis B vaccine. Vaccine. 2023;41(24):3584–3588. doi:10.1016/J.VACCINE.2023.05.010.
13. Miller KD, Mulligan MM, Gibbs RD, Nutman TB, Francis DP. Intradermal hepatitis B virus vaccine: immunogenicity and side-effects in adults. Lancet. 1983;2(8365–66):1454–1456. doi:10.1016/S0140-6736(83)90800-0.
14. Launay O, Van Der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, De Verdière NC, Slama L, Martin K, Lortholary O, Carrat F. Safety and immunogenicity of 4 intramuscular double

doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA. 2011;305(14):1432–1440. doi:10.1001/JAMA.2011.351.
15. Chanchairujira T, Chantaphakul N, Thanwandee T, Ong-Ajyooth L. Efficacy of intradermal hepatitis B vaccination compared to intramuscular vaccination in hemodialysis patients. J med assoc thail. 2006 [Accessed 2025 Jan 20]. 89 Suppl 2):S33–40. https://mahidol.elsevierpure.com/en/publications/efficacy-of-intradermal-hepatitis-b-vaccination-compared-to-intra.
16. Zoulek G, Lorbeer B, Jilg W, Deinhardt F. Evaluation of a reduced dose of hepatitis B vaccine administered intradermally. J Med Virol. 1984;14(1):27–32. doi:10.1002/JMV.1890140105.
17. Sangaré L, Manhart L, Zehrung D, Wang CC. Intradermal hepatitis B vaccination: a systematic review and meta-analysis. Vaccine. 2009;27(12):1777–1786. doi:10.1016/J.VACCINE.2009.01.043.
18. Vilajeliu A, Sequera VG, García-Basteiro AL, Sicuri E, Aldea M, Velasco C, Bayas JM. Immunogenicity and immunization costs of adjuvanted versus non-adjuvanted hepatitis B vaccine in chronic kidney disease patients. Hum Vaccin Immunother. 2016;12(9):2317–2321. doi:10.1080/21645515.2016.1168955.
19. Rosenthal EM, Hall EW, Rosenberg ES, Harris A, Nelson NP, Schillie S. Assessing the cost-utility of preferentially administering heplisav-B vaccine to certain populations. Vaccine. 2020;38(51):8206–8215. doi:10.1016/J.VACCINE.2020.10.067.
20. Kuan RK, Janssen R, Heyward W, Bennett S, Nordyke R. Cost-effectiveness of hepatitis B vaccination using HEPLISAV^{TM} in selected adult populations compared to Engerix-B® vaccine. Vaccine. 2013;31(37):4024–4032. doi:10.1016/J.VACCINE.2013.05.014.
21. Hall EW, Weng MK, Harris AM, Schillie S, Nelson NP, Ortega-Sanchez IR, Rosenthal E, Sullivan PS, Lopman B, Jones J, et al. Assessing the cost-utility of universal hepatitis B vaccination among adults. J Infect Dis. 2022;226(6):1041–1051. doi:10.1093/INFDIS/JIAC088.
22. Njuguna HN, Hiebert L, Gupta N, Ward JW. Status of HBV birth dose vaccination in Africa: the impact of COVID-19 and Gavi support on policy development. Lancet Gastroenterol Hepatol. 2023;8(6):502–503. doi:10.1016/S2468-1253(23)00071-7.