

# The role of new hepatitis B vaccines in South Africa

G U van Zyl,<sup>1</sup> FCPATH (SA) Virol, PhD; T Maponga,<sup>1</sup> MSc, PhD; H Rabie,<sup>2</sup> MMed, PhD; J Taljaard,<sup>3</sup> MMed (Intern), DTM&H

<sup>1</sup> Division of Medical Virology, Department of Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa

<sup>2</sup> Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; Tygerberg Children's Hospital, Cape Town, South Africa

<sup>3</sup> Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; Tygerberg Academic Hospital, Cape Town, South Africa

**Corresponding author:** G U van Zyl (guzv@sun.ac.za)

Vaccination is key to eliminating hepatitis B virus infection in South Africa (SA). Despite introducing immunisation in 1995, as part of the expanded programme of immunisation (EPI), hepatitis B virus infection remains endemic, and EPI vaccine coverage is incomplete. In addition to infants, non-immune adults at risk of infection through their occupation or with behavioural risk factors should receive vaccination. SA has many individuals with diabetes mellitus (a prevalence of almost 13%), obesity, HIV (8.45 million) or older age (5 million >60 years old), associated with a poorer vaccine response. Recently two new hepatitis B vaccines have been licensed: HEPLISAV-B includes an adjuvant that improves immunogenicity and has shown improved vaccine response in individuals with HIV, old age or diabetes mellitus. PreHevbrio, which includes three hepatitis B surface protein domains, instead of one, may also be more immunogenic, although clinical study data are still limited. These two novel vaccines have not yet been investigated in children and licensed in SA. Should HEPLISAV-B become available in SA, it may be particularly valuable to target high-risk groups in the country, such as people living with HIV, who show a poor response to the currently licensed vaccine.

*S Afr Med J* 2024;114(2):e1473. <https://doi.org/10.7196/SAMJ.2024.v114i2.1473>

Despite universal hepatitis B virus (HBV) vaccination since 1995, HBV remains endemic in South Africa (SA), with gaps in the prevention programme. In this review we will review progress and gaps towards HBV elimination, and discuss the potential role of novel vaccines in HBV prevention.

## Hepatitis B infection status and epidemiology in South Africa

In SA, there are ~8 million people living with HIV (PLWH),<sup>[1]</sup> and of around 260 000 pregnancies in 2022, 8 000 children became infected despite a prevention of mother-to-child transmission (PMTCT) programme.<sup>[2]</sup> SA also still has endemic HBV infection, with an estimated 3% of the population having chronic HBV infection.<sup>[3]</sup> However, there is an absence of nationally representative seroprevalence studies to confirm HBV seroprevalence, or the rate of co-infection of HBV and HIV in SA. A Western Cape Province study based on 2008 antenatal samples found a similar prevalence of ~3% in pregnant women with or without HIV.<sup>[4]</sup> Another study using seroincidence samples from 2009 from KwaZulu-Natal Province showed a HBV surface (S) antigen (HBsAg) prevalence of 16/215 (7.4%) among individuals with HIV compared with 14/29 (4.8%) among those without, which was not statistically significant, but 6 of the 16 with HIV had hepatitis B e-antigen (HBeAg), and none without HIV ( $p=0.0185$ ). Since HBeAg is a marker of infectivity, this suggests a much higher transmission risk of HBV when infants are born to mothers with HIV.<sup>[5]</sup>

## Progress towards hepatitis B virus elimination in South Africa

Vaccination is the most important intervention to prevent HBV infections and protect individuals at high risk of infection. Initially referred to as the Australia antigen, HBV was shown to be the cause of hepatitis in 1966.<sup>[6]</sup> The characterisation of the virus and its surface

antigen resulted in the production and licensing of vaccines. The first vaccine was a purified and inactivated HBsAg product from the plasma of patients with chronic hepatitis B infection.<sup>[7]</sup> This was followed by the production of a recombinant HBsAg vaccine in yeast cells.<sup>[7,8]</sup> Although HBV vaccines have been available internationally since 1982, it was only introduced in the SA expanded programme of immunisation (EPI) in 1995.<sup>[9]</sup> Universal HBV vaccination, as part of the EPI, given to children at 6, 10 and 14 weeks of age and at 18 months since 1995, has resulted in a significantly lower prevalence of chronic hepatitis B in subsequent birth cohorts: from 8/622 (1.29%) born before 1995 to 0/572 (0%) in a study of pregnant women from the Western Cape Province and from 7.4% to <4.1% in birth cohorts born before or after 1995<sup>[10]</sup> in a large laboratory-based study of >100 000 samples from Gauteng Province.<sup>[11]</sup> A national measles rash surveillance study showed that only 0.4% of residual samples from children from the post-1995 birth cohort had evidence of current HBV.<sup>[12]</sup> In an investigation of low-risk blood donors, the prevalence of HBV was 0.84% in samples in individuals born before 1995, decreasing to 0.14% in individuals born after 1995.<sup>[13]</sup>

Another factor that could potentially reduce HBV transmission is the antiretroviral rollout programme. Most HIV-infected adults and older children receive tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) or lamivudine (3TC) as part of antiretroviral treatment. TDF or TAF provide durable suppression of HBV replication in infected patients, reducing the transmission risk,<sup>[14]</sup> whereas 3TC, when used long-term as a single agent, is associated with the emergence of drug resistance.<sup>[15]</sup> TDF has also been used for PMTC of hepatitis B<sup>[16]</sup> or to prevent viral reactivation in cases of iatrogenic immune suppression.<sup>[17]</sup> TDF as part of antiretroviral therapy (ART) may therefore protect non-immune hepatitis B-uninfected individuals, either through suppressing HBV replication in infected individuals or as pre-exposure prophylaxis.<sup>[18]</sup>

## Gaps in eliminating HBV in South Africa

Vaccination has unfortunately not eliminated HBV, and the prevalence is higher in PLWH and male sex.<sup>[19]</sup> Individuals who have not been vaccinated, due to being born prior to 1995, or who did not access vaccination,<sup>[9]</sup> or who were perinatally exposed before being vaccinated,<sup>[20]</sup> may be at risk of chronic hepatitis.<sup>[12,13,21]</sup> Despite several years of routine infant vaccination starting in 1995, local studies indicate that HBV is far from eliminated in the post-vaccine cohort, with incomplete vaccine coverage (estimated to be only 71% for 3 doses as part of EPI in 2015),<sup>[9,22,23]</sup> and despite study heterogeneity, there is an overall higher prevalence in PLWH: 1.7% of children with HIV from Gauteng Province compared with none in HIV-negative children from a vaccinated birth cohort,<sup>[21]</sup> and 13% of children with HIV, compared with 7.5% from KwaZulu-Natal Province infants being HBV DNA positive in 2011.<sup>[24]</sup>

Apart from childhood EPI vaccination, the SA National Guidelines for the management of viral hepatitis advise that the following at-risk individuals should also be vaccinated: healthcare workers, residents and workers of facilities for the mentally disabled, emergency service workers, household contacts of HBsAg-positive persons, men who have sex with men, sex partners of HBV-infected individuals, intravenous drug users, persons with end-stage kidney disease, patients who require organ transplants or have chronic liver disease and those with HIV infection.<sup>[25]</sup> Despite these guidelines, there is no adult HBV vaccination programme. Vaccination of high-risk individuals is also inadequate, as a study at an academic centre showed that less than half of healthcare workers had been vaccinated.<sup>[26]</sup> Testing of key populations such as pregnant women is also not incorporated into programmes. Identifying mothers with hepatitis B is key to preventing mother-to-child transmission. Moreover, despite guidelines advising this, and the option of using rapid tests, there is currently no national strategy to test pregnant women for HBsAg.<sup>[25]</sup> Although SA adopted the World Health Organization recommendation of HBV birth dose vaccine as part of the EPI vaccination schedule in 2019, it has not yet been implemented.<sup>[27,28]</sup>

Based on the estimated number of patients with HIV and the hepatitis B prevalence in HIV-infected patients, one could assume that at least 300 000 cases would be coinfecting.<sup>[28]</sup> As HBV may reactivate in patients with HIV, these individuals may be a source of ongoing horizontal or mother-to-child hepatitis B transmission<sup>[28]</sup> when not on treatment.<sup>[29]</sup> Moreover, PLWH who disengage from care would not have the benefits of treatment.

There is also concern that infant vaccination-induced antibodies may have waned by the time individuals are at risk of sexual transmission.<sup>[30]</sup> Nevertheless, data suggest that in settings with a low HIV prevalence, the risk of chronic HBV infection in individuals remains low, despite waned antibody levels, implying that an immune memory response remains protective.<sup>[31]</sup> Of 55 children with HIV on ART in a study from Thailand who had at least three doses of hepatitis B vaccination in early childhood, only one had sufficient HBV immunity at a median age of 9.6 years.<sup>[32]</sup> A review article reported response rates of children with HIV of between 25% and 35% after three vaccine doses.<sup>[33]</sup> PLWH or individuals with other causes of immune suppression are at higher risk of developing chronic HBV infection should they be exposed to HBV compared with HIV-uninfected patients. This is because PLWH are not able to clear HBV as easily as immune-competent individuals.<sup>[34]</sup> Moreover, HIV and HBV share similar transmission routes. PLWH are therefore at increased risk of chronic HBV infection and may require screening for HBV immunity irrespective of birth cohort, and should they not be immune, receive a course of HBV vaccination. Whereas >90% of healthy adults would show seroprotection after a three-dose vaccine

course with the currently available aluminum hydroxide adjuvanted recombinant S-antigen vaccine,<sup>[35]</sup> it is much lower in PLWH, with the pooled response rate of vaccination being 71.5% in a meta-analysis.<sup>[36]</sup> In another meta-analysis, the relative risk of non-response was 1.47 for smokers v. non-smokers, and 1.48 for patients with a body mass index of  $\geq 25$  v.  $< 25$ , and 1.30 for age  $\geq 60$  years v. lower age.<sup>[35]</sup> In a randomised controlled trial, only 65.1% of individuals with diabetes mellitus responded to a three-dose vaccine of Engerix B.<sup>[37]</sup> The diabetes mellitus prevalence in SA was estimated to be 12.7% in 2019,<sup>[38]</sup> and that of obesity 30.8% in 2015. An estimated 5 million people in SA are  $> 60$  years old,<sup>[39]</sup> and 13.7% of adults are living with HIV.<sup>[1]</sup> Using the currently available vaccines, a poor response rate could therefore be expected in older HIV-1 infected individuals born before 1995 should they be enrolled into a vaccination programme.

Unlike HIV, there is a lack of representative seroprevalence studies for hepatitis B. Information is necessary to determine whether the waning of anti-hepatitis B surface (HBs) levels in HIV-exposed and HIV-infected children translates to increased HBV infections to inform further interventions. However, longitudinal follow-up in cohort studies is expensive. There is a need for prevalence studies of birth cohorts after the introduction of universal hepatitis B vaccination, investigating differences in rates of HBV infection and immunity in HIV-infected and uninfected individuals. Vaccine-induced protection is detected by assessing seroprotection. HBV seroprotection is defined as having, or previously having had, an anti-HBs concentration of  $\geq 10$  mIU/mL. Nevertheless, relying on anti-HBs alone as evidence of immunity to HBV has limitations. Individuals who may be misclassified as requiring HBV vaccine include 3 groups: (i) anti-HBs negative individuals who have chronic hepatitis B and who therefore would not benefit from vaccination; (ii) individuals who have natural immunity to HBV with waning anti-HBs; and (iii) individuals who had a seroprotective vaccine response but whose anti-HBs have waned to  $< 10$  mIU/mL. Previous exposure to natural HBV infection could be elucidated by detecting hepatitis B core total antibodies (total anti-HBc). In the case of individuals with waned vaccine immunity, an immune memory response can be detected by providing a single vaccine dose and by showing a fast protective response by retesting anti-HBs 7 - 10 days later.<sup>[40]</sup> However, this is seldom regarded as feasible. A more practicable approach, often preferred, is to revaccinate individuals who do not have evidence of seroprotection with a full vaccine regimen, followed by testing for anti-HBs, 1 - 2 months after the last dose.<sup>[41]</sup> Apart from general seroprevalence data and data on vaccine response, considering their high prevalence and association with vaccine non-response, linked data on diabetes and obesity should also be collected.<sup>[42]</sup> An opportunity may be to add HBV to existing seroprevalence studies of HIV and syphilis. Such prevalence studies would provide current information on the differential risk related to HIV infection, and other associations with poor vaccine response and the likely necessity to change the approach to vaccinating these individuals.

## The potential role of novel hepatitis B vaccines

Recently, more immunogenic vaccines have been internationally licensed. One is a yeast recombinant S-antigen vaccine with a cytosine-phosphate-guanosine oligodeoxynucleotide (CpG) adjuvant,<sup>[37,43]</sup> which has been licensed in the USA<sup>[44]</sup> and Europe,<sup>[45]</sup> but not yet approved by the SA Health Products Regulatory Authority (SAHPRA)-approved or available in SA. This vaccine has been shown to be effective in vaccine non-responders and immune-suppressed individuals. Another benefit of this vaccine is that it induces a high level of protection in immune-competent individuals after a course of just two vaccine doses,<sup>[46]</sup>

whereas four doses provide a high proportion of seroprotection in haemodialysis patients.<sup>[43]</sup> When three vaccine doses were given, it resulted in seroprotection of all 68 previously unvaccinated PLWH.<sup>[47]</sup> This CpG adjuvant vaccine, marketed as HEPLISAV-B, may increase the seroprotection rates in SA HIV-infected patients, should it become available.<sup>[48]</sup> Other priority groups for a more immunogenic vaccine may be individuals with diabetes mellitus, due to its high burden in SA, and their lower vaccine response rates. However, data on the safety and efficacy of this vaccine in children are still lacking.

Another novel three-antigen vaccine (pre-S1 and pre-S2 and S-antigens expressed in mammalian cells to assure native glycosylation), marketed as PreHevrio, has also been licensed in the USA,<sup>[49]</sup> and as PreHevri in the European Union,<sup>[50]</sup> and appears potentially more immunogenic in individuals  $\geq 45$  years old, and may therefore have value in vaccine non-responders, as it provides additional B-cell epitopes.<sup>[51]</sup> However, data on its value in other patients with a high risk of vaccine non-response, including HIV-infected individuals, are lacking, and it has also not been investigated in children.

While these novel vaccines are unavailable, alternative strategies for the management of vaccine non-responders, including higher vaccine dose or intradermal injection,<sup>[52]</sup> must be explored.

Should HEPLISAV-B or PreHevrio become available in SA, their role will depend on the following: is it safe and efficacious in children? Is it affordable to the public sector, and in the case of HEPLISAV-B, can a two-dose HEPLISAV-B vaccine schedule administered to infants or immune-competent individuals replace the current three-dose vaccine schedule? Would HEPLISAV-B be safe and effective when the first dose is given at birth to prevent perinatal transmission? Could the new vaccines be included in co-formulated preparations with other childhood vaccines? Clinical trials in different SA patient groups and implementation research are needed to establish whether there is a role for these novel vaccines in reducing hepatitis B prevalence, and ultimately in eliminating hepatitis B infection in SA. Should these new vaccines be introduced, this should also be accompanied by public awareness campaigns on the safety and benefits in order to limit the spread of disinformation.

**Declaration.** None.

**Acknowledgements.** None.

**Author contributions.** GvZ drafted the first version, and TM, JTT and HR provided inputs and edits. All authors approved the final manuscript version.

**Funding.** None.

**Conflicts of interest.** None.

- South African National Government. People of South Africa. Pretoria: SA government; 2023. <https://www.gov.za/about-sa/people-south-africa-0> (accessed 1 November 2023).
- Joint United Nations Programme on HIV/AIDS. Fact sheet. Latest global and regional statistics on the status of the AIDS epidemic. Geneva: UNAIDS, 2022. [https://www.unaids.org/en/resources/documents/2022/UNAIDS\\_FactSheet](https://www.unaids.org/en/resources/documents/2022/UNAIDS_FactSheet) (accessed 18 November 2022).
- Maepa MB, Ely A, Kramvis A, et al. Hepatitis B virus research in South Africa. *Viruses* 2022;14(9):1939. <https://doi.org/10.3390/v14091939>
- Andersson MI, Maponga TG, Ijaz S, et al. The epidemiology of hepatitis B virus infection in HIV-infected and HIV-uninfected pregnant women in the Western Cape, South Africa. *Vaccine* 2013;31(47):5579-5584. <https://doi.org/10.1016/j.vaccine.2013.08.028>
- Thumbiran NV, Moodley D, Parboosing R, Moodley P. Hepatitis B and HIV co-infection in pregnant women: Indication for routine antenatal hepatitis B virus screening in a high HIV prevalence setting. *S Afr Med J* 2014;104(4):307-309. <https://doi.org/10.7196/SAMJ.7299>
- Blumberg BS. Australia antigen and the biology of hepatitis B. *Science* 1977;197(4298):17-25. <https://doi.org/10.1126/science.325649>
- Blumberg BS. Hepatitis B virus, the vaccine, and the control of primary cancer of the liver. *Proceedings of the National Academy of Sciences* 1997;94(14):7121-7125. <https://doi.org/10.1073/pnas.94.14.7121>
- Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. *JAMA* 1984;251(21):2812-2815.
- Burnett RJ, Kramvis A, Dochez C, Meheus A. An update after 16 years of hepatitis B vaccination in South Africa. *Vaccine* 2012;30:C45-C51. <https://doi.org/10.1016/j.vaccine.2012.02.021>
- Joseph Davey D, Hsiao N-Y, Wendy Spearman C, et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: Implications for oral pre-exposure prophylaxis roll out. *BMC Infect Dis* 2022;22(1):a719. <https://doi.org/10.1186/s12879-022-07697-5>
- Mbenenge N, Subramoney K, Gascua Adu-Gyamfi C, Treurnicht FK. Hepatitis B virus immunity gap: A six-year laboratory data review of hepatitis B serological profiles in Gauteng Province, South Africa. *Adv Virol* 2023;2023:6374874. <https://doi.org/10.1155/2023/6374874>
- Prabdi-Sing N, Makhathini L, Smit SB, et al. Hepatitis B sero-prevalence in children under 15 years of age in South Africa using residual samples from community-based febrile rash surveillance. *PLoS ONE* 2019;14(5):e0217415. <https://doi.org/10.1371/journal.pone.0217415>
- Vermeulen M, Swanevelder R, Van Zyl G, Lelie N, Murphy EL. An assessment of hepatitis B virus prevalence in South African young blood donors born after the implementation of the infant hepatitis B virus immunisation program: Implications for transfusion safety. *Transfusion* 2021;61(9):2688-2700. <https://doi.org/10.1111/trf.16559>
- Lacombe K, Gozlan J, Boelle P-Y, et al. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. *AIDS* 2005;19(9):907-915. <https://doi.org/10.1097/01.aids.0000171404.07995.5c>
- Hamers RL, Zaaijer HL, Wallis CL, et al. HIV-HBV coinfection in Southern Africa and the effect of lamivudine- versus tenofovir-containing cART on HBV Outcomes. *J Acquired Immune Defic Syndr* 2013;64(2):174-182. <https://doi.org/10.1097/QAI.0b013e3182a607d>
- Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: A systematic review and meta-analysis. *Lancet Infect Dis* 2021;21(1):70-84. [https://doi.org/10.1016/S1473-3099\(20\)30586-30587](https://doi.org/10.1016/S1473-3099(20)30586-30587)
- Buti M, Manzano ML, Morillas RM, et al. Randomized prospective study evaluating tenofovir disoproxil fumarate prophylaxis against hepatitis B virus reactivation in anti-HBc-positive patients with rituximab-based regimens to treat hematologic malignancies: The Preblin study. *PLoS ONE* 2017;12(9):e0184550. <https://doi.org/10.1371/journal.pone.0184550>
- Mizushima D, Takano M, Aoki T, et al. Effect of tenofovir-based HIV pre-exposure prophylaxis against HBV infection in men who have sex with men. *Hepatology* 2023;77(6):2084-2092. <https://doi.org/10.1097/HEP.0000000000000384>
- Samsunder N, Ngcapu S, Lewis L, et al. Seroprevalence of hepatitis B virus: Findings from a population-based household survey in KwaZulu-Natal, South Africa. *Int J Infect Dis* 2019;85:150-157. <https://doi.org/10.1016/j.ijid.2019.06.005>
- Andersson MI, Rajbhandari R, Kew MC, et al. Mother-to-child transmission of hepatitis B virus in sub-Saharan Africa: Time to act. *Lancet Glob Health* 2015;3(7):e358-e359. [https://doi.org/10.1016/S2214-109X\(15\)00056-X](https://doi.org/10.1016/S2214-109X(15)00056-X)
- Amponsah-Dacosta E, Lebelo RL, Rakgole JN, Burnett RJ, Selabe SG, Mphahlele MJ. Evidence for a change in the epidemiology of hepatitis B virus infection after nearly two decades of universal hepatitis B vaccination in South Africa. *J Med Virol* 2014;86(6):918-924. <https://doi.org/10.1002/jmv.23910>
- Tsebe KV, Burnett RJ, Hlungwani NP, Sibara MM, Venter PA, Mphahlele MJ. The first five years of universal hepatitis B vaccination in South Africa: Evidence for elimination of HBsAg carriage in under 5-year-olds. *Vaccine* 2001;19(28):3919-3926. [https://doi.org/10.1016/S0264-410X\(01\)00120-7](https://doi.org/10.1016/S0264-410X(01)00120-7)
- Breakwell L, Tevi-Benissan C, Childs L, Mihigo R, Tohme R. The status of hepatitis B control in the African region. *Pan Afr Med J* 2017;27(Suppl 3):S17. <https://doi.org/10.11604/pamj.supp.2017.27.3.11981>
- Mdlalose N, Parboosing R, Moodley P. The prevalence of hepatitis B virus infection in HIV-positive and HIV-negative infants: KwaZulu-Natal, South Africa. *Afr J Lab Med* 2016;5(1):283-287. <https://doi.org/10.4102/ajlm.v5i1.283>
- South African National Department of Health. National Guidelines for the Management of Viral Hepatitis. Pretoria: NDOH, 2019.
- Razwiedani LL, Mogale NM, Mawela MPB. Hepatitis B vaccination coverage amongst healthcare workers in a tertiary academic hospital in Gauteng province, South Africa. *South Afr J Infect Dis* 37(1):a393. <https://doi.org/10.4102/sajid.v37i1.393>
- World Health Organization. Hepatitis B vaccines: WHO position paper – recommendations. *Vaccine* 2010;28(3):589-590. <https://doi.org/10.1016/j.vaccine.2009.10.110>
- Solomon-Rakiep T, Olivier J, Amponsah-Dacosta E. Weak adoption and performance of hepatitis B birth-dose vaccination programs in Africa: Time to consider systems complexity? A scoping review. *Trop Med Infect Dis* 2023;8(10):474. <https://doi.org/10.3390/tropicalmed8100474>
- Spearman CW, Afihene M, Ally R, et al. Hepatitis B in sub-Saharan Africa: Strategies to achieve the 2030 elimination targets. *Lancet Gastroenterol Hepatol* 2017;2(12):900-909. [https://doi.org/10.1016/S2468-1253\(17\)30295-9](https://doi.org/10.1016/S2468-1253(17)30295-9)
- Whittle H, Jaffar S, Wansbrough M, et al. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. *BMJ* 2002;325(7364):569-573. <https://doi.org/10.1136/bmj.325.7364.569>
- Mendy M, Peterson I, Hossin S, et al. Observational study of vaccine efficacy 24 years after the start of hepatitis B vaccination in two Gambian villages: No need for a booster dose. *PLoS ONE* 2013;8(3):e58029. <https://doi.org/10.1371/journal.pone.0058029>
- Siriaksorn S, Puthanakit T, Sirisanthana T, Sirisanthana V. Prevalence of protective antibody against hepatitis B virus in HIV-infected children with immune recovery after highly active antiretroviral therapy. *Vaccine* 2006;24(16):3095-3099. <https://doi.org/10.1016/j.vaccine.2006.01.045>
- Catherine F-X, Piroth L. Hepatitis B virus vaccination in HIV-infected people: A review. *Hum Vaccin Immunother* 2017;13(6):1304-1313. <https://doi.org/10.1080/21645515.2016.1277844>
- Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. *J Infect Dis* 1991;163(5):1138-1140. <https://doi.org/10.1093/infdis/163.5.1138>
- Yang S, Tian G, Cui Y, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. *Sci Rep* 2016;6(1):27251. <https://doi.org/10.1038/srep27251>
- Tian Y, Hua W, Wu Y, et al. Immune response to hepatitis B virus vaccine among people living with HIV: A meta-analysis. *Front Immunol* 2021;12:745541. <https://doi.org/10.3389/fimmu.2021.745541>
- Champion CR. Heplisav-B: A hepatitis B vaccine with a novel adjuvant. *Ann Pharmacother* 2021;55(6):783-791. <https://doi.org/10.1177/1060028020962050>
- Grundlingh N, Zewotir TT, Roberts DJ, Manda S. Assessment of prevalence and risk factors of diabetes and pre-diabetes in South Africa. *J Health Popul Nutr* 2022;41(1):7-19. <https://doi.org/10.1186/s41043-022-00281-2>
- Statistics South Africa. SA's elderly population increasing steadily. Pretoria: Stats SA, 2023. <https://www.statssa.gov.za/?p=16280> (accessed 1 November 2023).
- Jan C-F, Huang K-C, Chien Y-C, et al. Determination of immune memory to hepatitis B vaccination through early booster response in college students. *Hepatology* 2010;51(5):1547-1554. <https://doi.org/10.1002/hep.23543>
- Yanny B, Konyan P, Najarian LM, Mistry A, Saab S. Management approaches to hepatitis B virus immunization nonresponse. *Gastroenterol Hepatol* 2019;15(2):93-99.
- Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014;103(2):137-149. <https://doi.org/10.1016/j.diabres.2013.11.002>
- Awad AM, Ntoso A, Connaire JJ, et al. An open-label, single-arm study evaluating the immunogenicity and safety of the hepatitis B vaccine HepB-CpG (HEPLISAV-B) in adults receiving hemodialysis. *Vaccine* 2021;39(25):3346-3352. <https://doi.org/10.1016/j.vaccine.2021.05.003>
- US Food and Drug Administration. HEPLISAV-B. FDA, 2023. <https://www.fda.gov/vaccines-blood-biologics/vaccines/heplisav-b> (accessed 1 November 2023).

45. European Medicines Agency. Heplisav B. EMA, 2020. <https://www.ema.europa.eu/en/medicines/human/EPAR/heplisav-b> (accessed 1 November 2023).
46. Jackson S, Lentino J, Kopp J, 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. <https://doi.org/10.1016/j.vaccine.2017.12.038>
47. Marks KM, Kang M, Umbleja T, et al. Immunogenicity and safety of hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HEPLISAV-B) in HBV vaccine-naïve people with HIV. *Clin Infect Dis* 2023;ciad201. <https://doi.org/10.1093/cid/ciad201>
48. Khaimova R, Fischetti B, Cope R, Berkowitz L, Bakshi A. Serological response with Heplisav-B in prior hepatitis B vaccine non-responders living with HIV. *Vaccine* 2021;39(44):6529-6534. <https://doi.org/10.1016/j.vaccine.2021.09.050>
49. Talbird SE, Anderson SA, Nossov M, Beattie N, Rak AT, Diaz-Mitoma F. Cost-effectiveness of a 3-antigen versus single-antigen vaccine for the prevention of hepatitis B in adults in the United States. *Vaccine* 2023;41(23):3506-3517. <https://doi.org/10.1016/j.vaccine.2023.04.022>
50. European Medicines Agency. PreHevbri. EMA, 2022. <https://www.ema.europa.eu/en/medicines/human/EPAR/prehevbri> (accessed 1 November 2023).
51. Vesikari T, Finn A, van Damme P, et al. Immunogenicity and safety of a 3-antigen hepatitis B vaccine vs a single-antigen hepatitis B vaccine: A phase 3 randomized clinical trial. *JAMA Netw Open* 2021;4(10):e2128652. <https://doi.org/10.1001/jamanetworkopen.2021.28652>
52. Raven SFH, Hoebe CJPA, Vossen ACTM, et al. 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. [https://doi.org/10.1016/S1473-3099\(19\)30417-7](https://doi.org/10.1016/S1473-3099(19)30417-7)

*Accepted 21 November 2023.*