Lesotho National Immunization Technical Advisory Group

Recommendation on the introduction of a Hepatitis B vaccine birth dose in Lesotho

VACCINE POLICY /STRATEGY ADVICE REQUESTED BY THE MOH

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Table of Contents

List of tables

PREAMBLE

The Lesotho National Immunization Technical Advisory Group (LES-NITAG) was established by the Ministry of Health, Principal Secretary of Health through a decree on the 26th of July 2018 to provide recommendations on vaccine policy in accordance with the National Health Strategy and the National EPI Policy Guidelines.

It is a body of national experts empowering the Ministry of Health and advising on all technical and scientific topics related to vaccines and immunization. The advisory group is technical, and the recommendations made are evidence-based and independent of political and industry influence.

The group does not implement activities or supervise immunization programmes, but instead provides technical advice on policy analysis and strategy formulation for all vaccine-preventable diseases and guides the MOH on identifying and monitoring important data and the latest scientific immunization recommendations and advancements. This document contains Les-Nitag's independent advice and recommendations which are based on the best, current available evidence. Les-Nitag will continue to monitor scientific developments related to hepatitis B and hepatitis B vaccines and will update these recommendations as the evidence evolves.

Abbreviations

AEFI	Adverse events following immunization
Anti-HBc	Antibody against hepatitis B core antigen
Anti-HBs.	Antibody against hepatitis B surface antigen
CFR	Case fatality rate
EPI	Expanded program on immunization
GHSS	Global health sector strategy
GOL	Government of Lesotho
HB-BD	Hepatitis B birth dose
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
MOH	Ministry of health
PLHIV	People living with HIV
SDG	Sustainable development goals
TWG	Technical working group
WHO	World Health Organization

Executive summary

Hepatitis B is an infection of the liver that is caused by the hepatitis B virus (HBV), a Hepadnaviridae that belongs to the genus Orthohepadnavirus. HBV is transmitted by exposure of mucosal membranes or non-intact skin to infected blood or other specific body fluids. HBV infection is highly variable in both presentation and severity. Some people clear the infection spontaneously, while others suffer a lifetime of chronic complications. Perinatally acquired infections and infections acquired early in life are more likely to lead to chronic complications that include hepatitis, cirrhosis and hepatocellular carcinoma (HCC) which carry a high mortality.

Hepatitis B has been targeted for elimination by 2030. This has been outlined in the Global Health Sector Strategy of 2022-2030. The feasibility of hepatitis B elimination and its prioritization as a public health goal is supported by the following factors: the absence of non-human reservoirs, a long incubation time that allows for amnestic immune responses in persons who have been vaccinated, the availability of a safe and effective vaccine that induces long lasting immunity, and the availability of antiviral therapy that lowers HBV replication and reduces liver injury, disease progression and infectivity in the chronically infected.

Vaccination strategies that have been proven to be effective in interrupting hepatitis B transmission include the administration of the hepatitis b vaccine to all newborn infants ideally within 24 hours of life to limit perinatal transmission followed by the administration of two or three hepatitis B vaccine doses to complete the primary series, catch up vaccination for unvaccinated cohorts and vaccination of adults at risk of hepatitis B infection.

Lesotho is currently only offering the hepatitis B vaccine to infants at the ages of 6, 10 and 14 weeks and is yet to include the vaccination of newborn infants at birth. The consideration for inclusion of the birth dose into the routine immunizations schedule was therefore warranted.

Recommendations on the introduction of a hepatitis B vaccine birth dose in Lesotho were done following; (1) Burden of disease; (2) Vaccine and immunization characteristics, (3) Economic and operational considerations and (4) Health policy and programmatic issues review. Technical working groups were formed and looked at the different elements agreed upon in the recommendation framework.

In the presentation of the evidence the following vaccine and immunization characteristics were considered: firstly, hepatitis B vaccines when given at birth were shown to have a favorable safety profile. Adverse events were shown to be predominantly minor and included local pain at injection site, myalgia and transient fever. Secondly, hepatitis B vaccines have also been shown to be immunogenic and effective in reducing perinatal transmission when given alone or in combination with hepatitis b immunoglobulin (HBIG). Thirdly, the administration of the HB-BD is cost-effective and can leverage on existing delivery platforms

and lastly, community and health care worker engagement were shown to be critical to the success of the HB-BD vaccination program.

Based on the findings of this review, it is recommended that:

- *A HB-BD is included in the routine immunization schedule to prevent perinatal transmission of hepatitis B. The HB-BD should be administered to all newborns including those with low birth weight or those born prematurely. The HB-BD may however be deferred in severely ill hepatitis B unexposed newborns, where the benefit of early (within 24hours) vaccination is minimal.*

- *When administration of the HB-BD within 24 hours is not feasible, the vaccine should still be offered at the first contact with the health care worker, up to 14 days after delivery.*

- *The HB-BD should be followed by three doses of the hepatitis B containing vaccine at 6, 10 and 14 weeks according to the routine immunization schedule.*

- *All pregnant women should be tested for hepatitis B infection at least once during their pregnancy. This would allow for a better estimation of the prevalence of hepatitis B infection in this population and the impact of the HB-BD on perinatal transmission.*

- *Antivirals therapy should be offered to all pregnant women who are HBeAg positive or those with high viral loads.*

- *HBIG should be offered to infants born to mothers who are HBeAg positive or those with high viral loads within 24 hours of life.*

- *Strategies to ensure high HB-BD uptake are adopted, including the integration of HB-BD into the essential newborn care package, outreach services for those delivering at home, offering vaccination services daily and ensuring that health care workers are adequately trained on HB-BD administration.*

- *Robust social mobilization and demand creation to be conducted with the use of messaging that adequately addresses issues of safety and misconceptions and that come from trusted endorsers.*

- *The strengthening of surveillance systems for monitoring of the disease and adverse events following immunization.*

I. Introduction

This report presents recommendations on the introduction of a hepatitis B vaccine birth dose (HB-BD) in Lesotho. To achieve this, it firstly presents the context of the question and general information about hepatitis B disease. Then, it presents the methodology used to formulate recommendations and presents evidence to support recommendations for the introduction of a HB-BD). Lastly, this report presents its overall recommendations concerning the introduction of the HB-BD.

Context of the question

Hepatitis B infection is a global health concern largely due to its long-term consequences of chronic infection that leads to cirrhosis and hepatocellular carcinoma. Infection acquired in the perinatal period and the first five years of life are more likely to lead to chronic hepatitis B and its complications [1]. The Global Health Sector Strategy (GHSS) of 2022 - 2030 aims to eliminate viral hepatitis as a public health threat by 2030 and it includes the mother to child transmission (MTCT) of hepatitis B virus (HBV) [2].

In Lesotho, the hepatitis B vaccine was included in the routine immunization schedule in 2003, and it is currently available in a pentavalent formulation with antigens like diphtheria and pertussis. It is given to infants at the ages of 6, 10, and 14 weeks. The coverage of the third dose of the pentavalent vaccine ranged from 92% in 2022 to 90% in 2023 in Lesotho [3]. The vaccine is also available in a monovalent formulation and is offered to laboratory personnel. The HB-BD is yet to be included in the routine schedule.

The effectiveness of the HB-BD and other interventions in reducing perinatal transmission has been demonstrated in other settings [4]. The availability of this intervention and its cost-effectiveness warrants its consideration for inclusion in the immunization schedule.

It is against this background that the Ministry of Health formally requested the development of these recommendations as part of preparations for the introduction of the HB-BD in Lesotho.

General information on the issue

The pathogen

The HBV is a partially double-stranded enveloped DNA that belongs to the family of hepadnaviruses. Hepatocytes are the primary site for the replication of HBV. Humans are the only known reservoir for human HBV genotypes. Hepatitis B viruses occur in 10 different genotypes (A to J) with a DNA variation of >8% between genotypes. Genotypic distribution varies geographically. There are approximately 40 HBV sub genotypes which differ by >4%. HBV genotypes are associated with variable courses of disease, severity of liver disease, and treatment outcomes. The genotypes found on the African continent include A, D, F, and G [1,5].

HBV contains three important antigens: c, e and s. The c antigens (anti-HBc) are readily formed at high titres during the course of infection but are not protective. The presence of e antigens (HBeAg) in the blood indicates that HBV replication is highly active and that the blood and other body fluids (saliva, semen and vaginal fluids) are highly contagious. The presence of the s antigen (HBsAg) is an indicator of acute infection and its serological prevalence reflects the endemicity of active hepatitis B virus infection in each population[1].

HBsAg prevalence of ≥8% defines highly endemic areas, prevalence of 5%–7% defines high intermediate, 2%–4% low intermediate, and <2% defines low endemic areas [1].

Transmission

Transmission can occur perinatally from mother to child. Infants born to mothers who are positive for both HBsAg and HBeAg are at a higher risk of acquiring the infection. In sub-Saharan Africa, among HBeAg-positive women, the pooled risk of MTCT was 38.3% (95% CI: 7.0–74.4%) without prophylaxis, which was significantly lower than the lower bound of 70–90% risk in the literature (P = 0.007). Among HBeAg-negative women, the pooled risk was 4.8% (95% CI: 0.1–13.3%) without prophylaxis, which lays within the lower range of the 5–30% risk in Asia. [6]
Health care workers are also at increased risk of hepatitis B infection because of frequent exposure to blood and other body fluids [1].

Among adolescents and adults major routes of infection are sexual transmission by contact with semen or vaginal fluid, and percutaneous transmission through the use of contaminated needles such as in injection drug use [1].

The disease

The time between exposure to the virus and the appearance of the first symptoms (incubation period) is about 75 days. The liver injury that occurs is immune driven. The risk factors for severe disease include age, sex, genetic factors, co-infection with other viruses, other co-morbid conditions and the use of certain medications. The clinical picture ranges from asymptomatic which accounts for 50% of adults while the remaining 50% of patients may present with abdominal pain, nausea, vomiting, fever, jaundice, loss of appetite, joint pain, dark urine and pale stools. Symptoms of acute hepatitis can last between 6 weeks to 6 months [1,7].

The course of acute hepatitis B infection ranges from full recovery (90% of adults) with acquisition of immunity to future infection in adults to fulminant hepatitis in 1-2% of patients often caused by co-infection with HIV/HCV/HDV, alcohol use and aflatoxins. Chronic hepatis B infection occurs in 80 – 90% of infants infected perinatally and is associated with increased risk of cirrhosis and hepatocellular carcinoma [1,8].

Diagnosis and treatment

The serological diagnosis of acute hepatitis is based on the evidence of the presence of HBsAg, HBcAb (IgM) and HBeAg (present during the high replication phase). Chronic Hepatitis is defined as the persistence of HBsAg for more than 6 months with or without active viral replication or hepatocellular damage. Antibody against hepatitis B surface antigen (anti-HBs) indicates immunity to HBV infection either after recovery from HBV infection or in response to hepatitis B vaccination [1,7,8].

The management of acute hepatitis B is mostly supportive. Tenofovir and Entecavir are antivirals that have been used in the management of chronic hepatitis B infection. While not curative, these antivirals have been shown to suppress hepatitis B viral loads and can prevent or delay the progression to cirrhosis or hepatocellular carcinoma [1,7,8].

II Methodology

This section on methodology focuses on the establishment of working groups, and the recommendation framework used. It also presents considerations related to burden of disease, vaccine, and immunization characteristics as well as economic and operational considerations.

Establishment of a working group

Technical Working Groups (TWGs) were tasked by the Les-Nitag chair to review evidence on the different elements and draft recommendations for full LES- NITAG consideration.

Recommendation framework

The elements that informed the recommendation framework were:

- Burden of disease
- Vaccine and immunization characteristics
- Economic and operational considerations
- Health policy and programmatic issues.

Burden of Disease

- Epidemiology of hepatitis B.
- Morbidity and mortality due to hepatitis B.

Vaccine and immunization characteristics

- Safety
- Efficacy and effectiveness

Economic and operational considerations

- Vaccine related costs
- Vaccine availability
- Vaccine affordability

Health policy and programmatic issues

- Acceptability and equity

- Feasibility
- Ability to evaluate.

Evidence searches and assessment

The PICO approach was used. The PICO question was: In neonates < 1month of age, what is the scientific evidence that a birth dose given within 24 hours, in addition to the currently recommended hepatitis B vaccine series (3 doses at 6, 10 and 14 weeks) is safe and prevents perinatal hepatitis B transmission and long-term complications of chronic hepatitis B?
Population= neonates
Intervention= hepatitis B vaccine
Comparator= no vaccine
Outcomes= perinatal transmission and safety

Technical working groups were formed and looked at the different elements agreed upon in the recommendation framework. Members of each sub-group then developed a search strategy and conducted the literature searches. Databases such as PubMed and Cochrane were searched for specific queries. Identified journal articles were reviewed and evaluated with the appropriate Critical Appraisal Skills Programme (CASP) tools for critical appraisal. The relevant evidence was summarized. Other sources of information were WHO position papers, Ministry of Health reports and the NITAG Resource Centre.

Presentation of the evidence

This section on presentation of the evidence focuses on the burden of disease from HBV in Lesotho, regionally and globally. It also focuses on vaccine and immunization characteristics with regards to safety, efficacy, and effectiveness. Economic, operational, and programmatic considerations as well as health policy and programmatic issues are also presented.

The Disease

Epidemiology of HBV infection globally, regionally and in Lesotho

An estimated 254 million people were living with Chronic Hepatitis B infection globally in 2022 and there are about 1.2 million new infections annually. There are also approximately 1.1 million deaths annually from hepatitis B related issues like acute hepatitis, cirrhosis and hepatocellular carcinoma. In Africa, it is estimated that 64.7 million people are living with Chronic Hepatitis infection [9,10].

The prevalence of acute hepatitis B infection based on HBsAg is estimated at 3.5% and 6.1% Globally and in Africa respectively [1]. In Lesotho, the prevalence of acute hepatitis B infection is estimated at 7%. This is based on a review of HBsAg tests results of 19530 persons reported from public sector laboratories across the country for the period 2019 to 2023[11].

Morbidly and mortality due to acute hepatitis B infection and its complications

A retrospective record review was conducted at Queen 'Mamohato Memorial Hospital (QMMH) from August 2021 to May 2024 to document cases of acute hepatitis and HCC. This facility was selected because it is the country's only referral hospital and the only facility where these cases are likely to be managed.

During this period, there were 18 cases of acute hepatitis B infection requiring inpatient care at QMMH that resulted in 2 deaths (CFR) 11%. During the same period, 7 cases of hepatocellular carcinoma were also admitted that resulted in 5 deaths (CFR) 71.4% [12].

Age specific morbidity and mortality

Infections acquired in infancy through perinatal or childhood exposure account for most of the burden of HBV related disease. This is because infections acquired early on are more likely to become chronic infection as compared to infections acquired at an older age due to host factors. Chronic hepatitis B infection or carrier status can lead to acute hepatitis, cirrhosis, hepatocellular carcinoma and death. Most children infected within the first 12 months of life (80–90%) develop chronic hepatitis while only 5% of infected adults will develop chronic hepatitis B infection [1,13,14].

Alternative preventive and control measures

Primary prevention of hepatitis B infection through immunization has been shown to be the most effective intervention [1]. In settings with suboptimal hepatitis b vaccine coverage, improving hepatitis B knowledge through tailored school-based educational programs has been shown to have a positive impact on in-school adolescents' hepatitis B knowledge and infection prevention practices [15].
Secondary preventative strategies include testing of all adults in settings with a ≥2% or ≥5% HBsAg seroprevalence in the general population with linkages to prevention, care and treatment services. This allows for early intervention and improved treatment outcomes. These strategies should make use of existing community or health facility-based testing opportunities or programs such as at antenatal clinics, HIV or TB clinics [16].

Alternatively, testing can be targeted to pregnant women and their partners, blood donors and at-risk populations that include health care workers, those that are part of a population with a high hepatitis B seroprevalence or those who have a history of exposure and/ or high-risk behaviour for hepatitis B infection [16].

Existence of regional and global recommendations

The Sustainable Development Goal 3 (SDG): Good Health and well-being aims to combat hepatitis. The targets for 2020 and 2030 are to reduce new cases of chronic HBV infection by 30% by 2020, which is equivalent to HBsAg prevalence of 1% among children aged 5 years, and to achieve 0.1% prevalence of HBV infection in children aged 5 years by 2030.

In alignment with the SDG 3, the GHSS aims to reduce the incidence of chronic viral hepatitis B infections by 95% by 2030. The strategy also recommends that countries implementing universal HB-BD achieve a birth dose coverage of ≥90% and a coverage of ≥90% with three doses of the vaccine in infancy. In countries using targeted HB-BD approach, an additional impact target of MTCT rate of ≤2% also applies together with >90% coverage of maternal HBsAg testing and >90% coverage with antivirals for eligible pregnant women [2].

Vaccine and immunization characteristics

Vaccine presentation, formulation, dosage, and route of administration, co-administration with other vaccines and drugs and cold chain and logistic requirements

The hepatitis B vaccine is available in a monovalent formulation or in combination with other antigens. The monovalent vaccine is available in a single or multi-dose vial. The active substance in the hepatitis B vaccine is the viral surface protein HBsAg. Anti- HBs antibody is used as a marker of immunity to HBV. The standard paediatric dose contains 5 µg–10 µg of HBsAg, and is administered by intramuscular injection into the anterolateral aspect of the thigh for infants. Hepatitis B vaccine is safe to co-administer with other vaccines. The HB-BD can also be administered together with BCG and OPV 0. The vaccine is transported and stored at 2–8 °C to maintain potency. Freezing must be avoided as it causes dissociation of the antigen from the alum adjuvant, resulting in loss of potency [1].

Serious adverse events (SAE) following immunization (AEFI) in target populations

Hepatitis B vaccines are reported to have a good safety profile with mostly mild symptoms such as pain, myalgia, and fever within 24 hours reported. Reactions are found to be less in children as compared to adults. No serious adverse events associated with hepatitis B vaccine administration have been reported. Safety for people living with HIV (PLHIV) and pregnant women has also been established [1].

The hepatitis B vaccine contained in the Pentavalent vaccine was introduced in Lesotho in 2008, while the monovalent hepatitis B vaccine formulation has been in use since 2003. In the years since its implementation, there has not been any severe adverse events associated

with its use. Mild reactions to the vaccine such as swelling, pain and abscess at the injection site have been reported [3].

Table 1 Safety of hepatitis B vaccines in preterm infants

Author	Summary of study findings
Wee Tee 2024 [17]	This was a systematic review that looked at adverse events after administration of hepatitis B vaccine in preterm infants. Only three studies in the review looked at adverse events after administration of HB-BD. Gestation at administration ranged from 24 weeks to < 37 weeks. The vaccine was well tolerated with no severe adverse events however one study showed an increased T helper cell polarization that was associated with early vaccination and the occurrence of bronchopulmonary dysplasia (BPD). The conclusion was, for neonates born prematurely who are at risk of BPD and for whom, therefore, hepatitis B vaccination at birth may carry an increased risk there is a paucity of literature regarding the safety of this vaccine .

Immunogenicity and effectiveness of the HB-BD

Table 2 Hepatitis B birth dose effectiveness in Africa

Author	Summary of study findings
Shimakawa 2022 [18]	This was a single centre longitudinal observational study. Children born to HBsAg-positive mothers in 2009–16 who received the HBV birth-dose (Engerix B paediatric) and three subsequent doses of Pentavalent vaccine at 6, 10, and 14 weeks were followed up prospectively in 2015–17. About 17.5% of pregnant women in the study were HBsAg positive. The prevalence of HBsAg was 5·6% in children who received the birth-dose in less than 24 h, 7·0% in

	those who received it 24–47 h after birth, and 16·7% in those who received it 48–96 h after birth (ptrend=0·083).
Ekra 2008 [19]	This was a non-randomized controlled trial comparing hepatitis B vaccination given at age 0, 6, and 14 weeks versus the current Coˆte d'Ivoire schedule of 6, 10, and 14 weeks. Pregnant women were enrolled at four health centres in Abidjan. The birth cohort received Euvax *B* recombinant vaccine, 0.5ml containing 10µg of purified HBsAg. The 6 weeks cohort followed the standard infant immunization schedule. About 7.7% of mothers were HBsAg positive. Among HBsAg-positive mothers, the overall prevalence of HBeAg positivity was 14.5% (49/337), including 14.6% (25/171) in the birth and 14.5% (24/166) in the 6-week cohorts. Among infants of HBeAg positive women, 38% of the birth cohort and 59% of the 6-week cohort became HBsAg carriers despite appropriate vaccination. The calculated vaccine effectiveness during the study was 22% for the 6-week and 50% for the birth cohorts.

Table 3 Hepatitis B birth dose effectiveness outside of Africa

Author	**Summary of study findings**
Bunthen 2023 [20]	This longitudinal study included two parts, study-1 to screen HBsAg among pregnant women and study-2 to follow up babies of all HBsAg-positive and one-fourth of HBsAg-negative mothers at their delivery and six-month post-partum. Hepatitis B immunoglobulin (HBIG) was also administered to 8.6% of exposed infants. HBsAg prevalence was 4.28% (67/1565).

	MTCT rate was 2.86% despite timely HB-BD and immunoglobulin.
Wang 2015 [21]	This was a prospective survey to evaluate the effectiveness of MTCT practices in 3 provinces of Southern China. These practices included universal administration of a HB-BD and HBIG to exposed infants. Infants born to HBsAg positive mothers were evaluated at 7–12 months of age. The study tested hepatitis B virus (HBV) surface antigen (HBsAg) and HBV e antigen (HBeAg) of mothers and tested HBsAg of infants born to HBsAg positive mothers using Enzyme-linked Immunosorbent Assay (ELISA). The HBsAg prevalence among infants born to HBeAg positive mothers (8.4%) was higher than among infants born to HBeAg negative mothers (3.8%) (x2 D 29.11, P < 0.001). HBsAg prevalence among infants without timely birth dose (within 24hrs) (14.1%) was higher than among infants who received a timely birth dose (5.2%) (x2 D 14.35, P < 0.001). HBsAg prevalence among infants with low birth weight (10.40%) was higher than among infants with normal birth weight (5.4%) (x2 D 5.81, P < 0.05). HBsAg prevalence of infants who received 5 ug yeast recombinant vaccine, 10 ug yeast recombinant vaccine, and 20 ug Chinese Hamster Ovary (CHO) recombinant vaccine were 9.9%, 5.3%, and 5.0%, respectively (x2 D 6.54, P < 0.05).
Dhouib 2020 [22]	The study was a cohort study that aimed to compare the efficacy of the first dose of the hepatitis B vaccine: at Birth versus at 3 months and to evaluate the efficacy of the hepatitis B vaccine. The study identified twenty-three cases among the cohort receiving the vaccine at 3 months and 2 cases among the birth dose cohort with an absolute risk (AR) per 100 000 PY of 5.67 (CI 95%: 3.36 – 7.99) and 0.11 (CI 0.001- 0.26) respectively. The HB-BD was 99.4% effective against hepatitis B infection.

Zhang 2022 [23]	This was a retrospective cohort study that compared the efficacy of the hepatitis B vaccine alone and in combination with HBIG in preventing vertical MTCT in infants born to HBeAg-negative carrier mothers in Jiangsu province, China. A total of 620 infants born to HBeAg-negative carrier mothers were enrolled into this study. Group 1 included 195 children who had received the hepatitis B vaccine alone after birth, and Group 2, 425 children who had received both HBIG and the hepatitis B vaccine. Children were followed up to the age of 68 and 42 months, respectively. MTCT of HBV occurred in 0% (0/195) in Group 1 (hepatitis B vaccine alone) and 0% (0/425) in Group 2 (hepatitis B vaccine and HBIG) (p = 1.00). The study demonstrated that hepatitis B vaccine alone given shortly after birth in infants of HBeAg negative mothers was effective against MTCT of Hepatitis B.
van den Ende 2017 [24]	This was a systematic review of the literature summarizing 30 years of immunogenicity and safety data for GSK hepatitis B vaccine in children and adolescents. Estimated protective efficacy against chronic HBV carriage one year after the final vaccination using the 10-µg dose in standard schedules (0, 1, 6 or 0, 1, 2, and 12 months) was at least 94.8% without administration of HBIG at birth, and at least 97.4% when HBIG was administered at birth.

Table 4 Effectiveness of hepatitis B birth dose in preterm or low birth weight infants

Author	**Summary of study findings**
Patel 1997 [25]	The study looked at immune responses to hepatitis B vaccine given to very low birth weight infants at <1000g N=25 and 1000-1500g N=28 vaccinated early (3days) and late (1 month). 2.5µg of Recombivax HB vaccine was administered intramuscularly

	Response rate (antibody to hepatitis B surface antigen titre > 10mIU/ml was 68% in those vaccinated early and 96% in those vaccinated at 1 month P= 0.02.
van den Ende 2017 [24]	This was a systematic review of the literature summarizing 30 years of immunogenicity and safety data for GSK Hepatitis B vaccine in children and adolescents. In some studies, the immune response to GSK hepatitis B appeared to be lower in preterm and low birth weight infants than in term infants, whereas other studies indicated no difference in the response rate. The contribution of gestational age, birth weight and underlying co-morbidities on immunogenicity were unclear.

Table 5 Efficacy of hepatitis B birth dose against infant fulminant hepatitis, hepatocellular carcinoma and end-stage liver disease

Author	**Summary of study findings**
Qu 2014 [26]	This was a population-based, cluster randomized, controlled trial that looked at outcomes in vaccinated and unvaccinated cohorts. The mortality rate of severe end-stage chronic liver diseases, including HCC and chronic liver failure, was significantly lower in the vaccination group than in the control group (HR=0.30, 95% CI 0.11–0.85), and the efficacy of neonatal vaccination against severe end-stage chronic liver diseases was 70% (95% CI 15%–89%). The vaccination group had a significantly lower HCC incidence rate compared with the control group (HR = 0.16, 95% CI 0.03–0.77) with 84% (95% CI 23%-97%) protective efficacy against HBV- related HCC development before age 30.

Flores 2022 [27]	The aim of the review was to outline the global trends in hepatitis B vaccination coverage and the impact of hepatitis vaccination on HCC incidence. The study showed significant reductions in hepatitis b related HCC incidence rates in vaccinated cohorts compared with the unvaccinated cohort in Taiwan, China, the Gambia and Alaska.

Table 6 Risk of hepatitis B infection in infants of HBsAg negative mothers

Author	**Summary of study findings**
Ansari 2023 [28]	This was a systematic review and meta-analysis that looked at studies reporting HBsAg or HBV DNA, or both, in children (aged 0–5 years) of HBsAg-negative mothers. The primary outcome was the risk of HBV infection in children of HBsAg-negative mothers, stratified by vaccination schedule (no vaccination, first dose at 6–8 weeks, or first dose at birth). The pooled risks of infection were 6·16% (95% CI 3·05–12·04; 155/1407) in the no vaccination group, 0·21% (0·04–1·15; 10/3425) in children who received their first dose at 6–8 weeks, and 0·05% (0·00–1·32; 3/2902) in children who received their first dose at birth. The study concluded that in infants of HBsAg negative mothers, there was no clear benefit of the HB-BD.

Economic and operational considerations

Vaccine cost

The table below shows vaccine costs comparison for the different vial doses that are available on the market.

Table 7 Hepatitis B vaccine cost comparison

Hepatitis B vaccine Costs Comparisons								
Vial Sizes	***Target Population (<5)***	***Estimated Coverage (%)***	***No. of doses per person***	***Estimated Wastage (%)***	***Total doses (Including Buffer)***	***Cost $***		***Total cost including all handling fees***
						Vaccines	***Syringes***	
						price/dose	***0.5ml ($0.0468/unit***	
10 doses vial	31,947	95	1	10	37,094	8,903	1,736	**12,176**
6 doses vial	31,947	95	1	5	35,142	11,948	1,645	**15,557**
1 dose vial	31,947	95	1	5	35,142	19,328	1,645	**24,003**

When calculating the total cost, the following assumptions and considerations were made:

- All costs are in USD currency.
- The unit cost per dose used was obtained from latest UNICEF vaccine cost per dose catalogue
- The price per dose (USD):
    - 10 dose vial – 0.24
    - 6 dose vial – 0.34
    - 1 dose vial – 0.55
    - cost per syringe – 0.0468
- The total cost is comprised of freight charges at 5%, handling fees at 4%, contingency fee at 5% and the total cost of vaccines, syringes and safety boxes.
- Buffer stock is calculated at 25% of the total annual vaccine needed.

Table 8 shows the estimated annual cost of HBV testing in pregnancy in Lesotho, while Table 9 shows the estimated cost of treating eligible hepatitis B infected pregnant women.

When calculating the cost, the following assumptions and considerations were made:

- The number of expected pregnant women annually was obtained from the Berea of Statistics of Lesotho.

- The authors assumed a 7% HBsAg seroprevalence in pregnant women like the prevalence in the general population
- The authors also assumed that all hepatitis B infected pregnant women would be eligible for antiviral treatment
- All cost were in USD currency

Table 8 The cost of hepatitis B testing for pregnant women

HBsAg Test for pregnant women In Lesotho		
Expected pregnancy 2024	*Unit cost per pregnant woman test (USD)*	*Annual total cost for HBsAg test (USD)*
52883	0,15	7932,45

Table 9 The cost of antiviral treatment for eligible pregnant women

Tenofovir 300 mg Costing for Hepatitis B pregnant women In Lesotho				
Total expected pregnancy 2024	*7% Hepatitis B prevalence.*	*TDF 300mg Cost per person (USD)*	*Frequency of administration (Months)*	*Annual Total Cost for TDF 300mg (USD)*
52883	3 702	9,62	3	106 834,24

Health policy and programmatic issues

Accessibility of target population

The feasibility of obtaining a high coverage with the HB-BD within 24 hrs of birth is supported by the high facility delivery rate [29]. The vaccine can be given during post-natal examinations that are conducted within 24 hours of delivery and can be co-administered with BCG and OPV 0. No out of expenditure expenses are anticipated. This intervention would however require the engagement of midwives under the leadership of the sexual and reproductive health program.

Availability of resources for vaccine storage, distribution, and administration

The table below summarizes the cold chain capacity requirements for storage of hepatitis B vaccines at national vaccine store and districts vaccine stores in Lesotho. Currently, 4 out of 10 districts do not have adequate cold chain capacity for storage of the hepatitis B vaccines, however a contingency plan is in place to ensure proper storage of hepatitis B vaccine once it reaches to these districts.

Table 10 Cold chain capacity requirements

Location	Total Population (2025)	Target Population (surviving infants)	Total Storage Available	Required Storage		Gap	Remarks (Contingency)
				RI	HB vaccine		
National vaccine Store	**2 127 561**	**196 308**	**14 272**	**8 447**	**98**	**5 727**	Adequate storage
Maseru DVS	604 032	57 794	580	1 066	29	**(516)**	NVS will be contingency
Botha-Bothe DVS	125 529	11 840	356	221	6	**128**	Adequate
Leribe DVS	380 530	35 287	567	671	19	**(123)**	MCH will be contingency
Berea DVS	273 706	25 524	643	483	13	**147**	Adequate
Mafeteng DVS	162 913	14 298	643	287	8	**348**	Adequate
Mohale's Hoek DVS	153 163	12 650	290	270	7	**12**	Adequate
Quthing DVS	106 220	9 590	145	187	5	**(48)**	MCH will be contingency
Qacha's Nek DVS	79 036	7 519	356	139	4	**212**	Adequate
Mokhotlong DVS	102 521	8 464	646	181	5	**460**	Adequate
Thaba-Tseka	139 910	13 342	231	247	7	**(23)**	MCH will be contingency

Dry stock

In addition to the cold chain storage, there is a need to ensure proper storage of ancillary items used during vaccination such as syringes and safety boxes. The table below provides a summary of the current dry stock storage space available and hepatitis B vaccine storage requirements. Based on the analysis, the country has adequate storage for all ancillary items across all levels of the supply chain.

Table 11 Dry stock storage requirements

Location	Total Dry Storage available for HB (m3)	Syringes			GAP (m3)
		0.5ml			
		Qty (unit)	Unit (m3)	Storage Vol Required (m3)	
National	80	35 142	0,00005667	1,99	78,01
Maseru	8	10 478	0,00005667	0,59	7,41
Botha-Bothe	3	2 200	0,00005667	0,12	2,88
Leribe	5	6 633	0,00005667	0,38	4,62
Berea	5	4 740	0,00005667	0,27	4,73
Mafeteng	3	2 852	0,00005667	0,16	2,84
Mohale's Hoek	3	2 674	0,00005667	0,15	2,85
Quthing	3	1 857	0,00005667	0,11	2,89
Qacha's Nek	3	1 474	0,00005667	0,08	2,92
Mokhotlong	3	1 748	0,00005667	0,10	2,90
Thaba-Tseka	3	2 379	0,00005667	0,13	2,87

Universality and accessibility of immunization services for all the inhabitants in the country, including vulnerable and hard to reach populations

The successful implementation of the HB-BD vaccination program requires the administration of the hepatitis b vaccine to newborns within 24 hours of life. This would be enabled by a high coverage of facility deliveries by skilled health care workers. Lesotho still experiences a significant number of home deliveries, and these home deliveries tend to be higher in rural communities [29]. Evidence shows that vaccine administration for home deliveries in African rural areas is often riddled with logistical obstacles [30]. Timely delivery of the HB-BD, which has been shown to be directly associated with the vaccine's effectiveness in preventing mother-to-child transmission of HBV requires better vaccine storage capabilities in these settings [30, 31]. Vaccine storage challenges such as vaccine cold chain maintenance tend to be pronounced in rural health facilities and are worse for community health providers that attend to home deliveries [30, 31].

The HB-BD would also be administered simultaneously with other vaccines given at birth namely BCG and OPV0. The coverage of OPV0 can be used as an indicator of the expected coverage of HB-BD. This is because OPV0 like the HB-BD may only be administered for up to 14 days after birth, unlike BCG that can be administered in infants up to two years of age. The coverage of OPV0 in Lesotho has been shown to be low, with significant differences observed between rural (61%) and urban (68%) areas [32]. The disparity between rural and urban areas in Lesotho was also observed in the number of fully immunized children in rural (60%) compared to urban (68%) communities. Most cited reasons for non-vaccination were lack of awareness for the need for vaccination and unavailability of vaccines [32].

An assessment of the implementation of HB-BD in 5 African countries identified lack of outreach immunization services as a barrier to reaching children delivered at home. Other barriers to timely HB-BD administration included lack of daily immunization services and not including HB-BD into essential newborn packages. Addressing these barriers would lead to an increase in vaccination uptake and reduce inequities in vaccination access [33].

Acceptability: Which option is acceptable to key stakeholders? To the target population?

Health workers with low knowledge about HBV tend to be reluctant to offer the HB-BD to parents with new-borns [31]. Health workers' hesitancy to offer the hepatitis B vaccine tends to be heightened in settings with negative media reports about vaccines [31]. Attitudes of health worker and/or the level of trust and rapport between health providers and parents also affects parents' likelihood of accepting the HB-BD [31, 34].

Knowledge about HBV and HB-BD, sometimes gained through prior interaction with the health facility affects the acceptability of the HB-BD as knowledgeable caregivers are more likely to seek the vaccine than those who are not [31]. Caregivers' acceptance of vaccines including HB-BD are directly linked to their attitudes towards state-run health services [31]. The authors

argue that on the one hand, caregivers are likely to have positive attitudes if health workers provided them with information on the health benefits and safety of vaccines. On the other hand, widespread communication on adverse events following immunisation (AEFIs) results in negative attitudes of caregivers towards the healthcare system and in turn in lack of acceptability of vaccines [31].

Parents perception of the safety of vaccines influences their likelihood of accepting HB-BD with parents who perceive vaccines as unsafe more likely to refuse the vaccine [34]. Parental concerns about administration of multiple vaccines at the same time and the belief by some parents that vaccines may cause the disease that they are supposed to prevent was also shown to contribute to low vaccine uptake [33]. Parents are also unlikely to accept the vaccine if their perception of the risk of their children contracting HBV is low. Interventions focusing on providing parents with information on the safety and benefits of HB-BD have been effective in getting parents to accept the vaccine [31, 33].

A deficiency of data to provide justification for adoption of HB-BD have led to some countries not introducing the vaccine while evidence of high prevalence of hepatitis B and of high rates of paired positivity among mothers with HBsAg and HBeAg and their offspring has led to support for introduction of the HB-BD and HBV related screening during provision of antenatal services [35].

III. Summary of key findings

In this review, the authors attempted to establish the burden of hepatitis B infection in Lesotho and whether it justified the introduction of a HB-BD into the routine immunization schedule. The safety and effectiveness of this intervention in reducing perinatal hepatitis B transmission and its complications in later life was also evaluated. Other elements that were evaluated were the cost-effectiveness of the intervention, the accessibility of the target population and whether the intervention would be acceptable to key stakeholders.

Hepatitis B was found to be highly endemic in Lesotho and this was based on the serological prevalence of HBsAg in the general population [11]. Routine testing in pregnant women is yet to be implemented in Lesotho. In other settings, hepatitis B prevalence in pregnant women ranged from 7% to 17.5% [18,19]. Mortality from acute hepatitis B infection and HCC in Lesotho was also high at 11% and 71.4% respectively [12].

The HB-BD was found to be effective in reducing perinatal transmission, but residual cases remain indicating a need for additional interventions like antivirals and HBIG [18, 20]. HBsAg positivity was higher in infants born to mothers who were HBeAg positive and those with higher viral loads [1, 4, 21]. HBsAg positivity was also higher in late vs early (within 24hrs) HB-BD administration underscoring the need for timely administration of the vaccine.

Immune responses were lower in premature and low birth weight infants in some studies especially where doses lower than 10μg were administered [17, 24]. The role of weight, gestational age and underlying comorbidities on immune response to the hepatitis B vaccine in this population in not well understood [24]. The vaccine was shown to be safe and well tolerated with no major severe adverse events reported [1, 24]. One study however, indicated an increased risk of BPD in sick premature infants. This finding is yet to be reported in other settings but may warrant the deferment of the vaccine in HBV unexposed sick premature infants where there is no clear benefit of vaccinating [17].

The HB-BD intervention was shown to be cost-effective and would leverage on existing delivery platforms. Health care worker engagement and health education for parents were shown to be effective in increasing the acceptability of the intervention and increasing vaccine uptake [31, 33].

Limitations

In this review, the reported HBsAg seroprevalence may not be reflective of the true hepatitis B endemicity in Lesotho. This is because the data was obtained from reporting public health

laboratories and did not include data from private laboratories. Additionally, this data was not segregated by age, sex or geographical location.

The costing analysis only included costing of the vaccine and ancillary items and did not factor in training of health care workers or social mobilization. The analysis also did not include the use and cost of health care (hospitalization and treatment for acute hepatitis B infection and/or its complications) and alternative preventative or control measures.

Furthermore, since pregnant women are not routinely tested for hepatitis B in pregnancy in Lesotho, the authors assumed a HBsAg seroprevalence in pregnant women to be similar to the prevalence in the general population. Additionally, the authors also assumed that all infected pregnant women would be eligible for antiviral treatment while in practice, antiviral eligibility is based on HBeAg positivity and /or high viral loads. The cost of offering HBIG to infants born to HBeAg positive mothers or mothers with high viral loads was also not included in the cost analysis.

IV. Proposed recommendation (s) /options

Based on the findings of this review, it is recommended that:

- A HB-BD should be included in the routine immunization schedule to prevent perinatal transmission of hepatitis B. The HB-BD should be administered to all newborns including those with low birth weight or those born prematurely. The HB-BD may however be deferred in severely ill hepatitis B unexposed newborns, where the benefit of early (within 24hours) vaccination is minimal.
- When administration of the HB-BD within 24 hours is not feasible, the vaccine should still be offered at the first contact with the health care worker, up to 14 days after delivery.
- The HB-BD should be followed by three doses of hepatitis B containing vaccine at 6, 10 and 14 weeks according to the routine immunization schedule.
- All pregnant women should be tested for hepatitis B infection at least once during their pregnancy. This would allow for a better estimation of the prevalence of hepatitis B in this population and the impact of the HB-BD on perinatal transmission.
- Antivirals therapy should be offered to all pregnant women who are HBeAg positive or those with high viral loads.
- HBIG should be offered to infants born to mothers who are HBeAg positive or those with high viral loads within 24 hours of life.
- Strategies to ensure high HB-BD uptake are adopted, including the integration of HB-BD into the essential newborn care package, outreach services for those delivering at home, offering vaccination services daily and ensuring that health care workers are adequately trained on HB-BD administration.
- Robust social mobilization and demand creation to be conducted with the use of messaging that adequately addresses issues of safety and misconceptions and that come from trusted endorsers.
- The strengthening of surveillance systems for monitoring of the disease and adverse events following immunization.

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VI. VI Annexes

Annex 1: Pico specific evidence tables

Annex 2: Evidence to recommendation framework and summary of judgments table

Annex 3: Pico specific evidence search and specific queries

Annex 4: Costing analysis