RWANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP

(RWANDA-NITAG)

Recommendation on introduction of Hepatitis B birth dose in Rwanda routine immunization

Report of the Technical Working Group

Kigali, 13 October 2023

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Acronyms

ANC:	Antenatal Care
aOR:	Adjusted Odd Ratio~~n~~
BCG:	Bacillus Calmette–Guerin
cART:	combined antiretroviral therapy
CI:	Confidence Interval
DALY:	Disability Adjusted Life Years
DHS:	Demographic Health Survey
DTP:	Diphtheria, Tetanus and Pertussis
EPI:	Expanded Program on Immunization
GSK:	GlaxoSmithKline
GVAP:	Global Vaccination Action Plan
HBeAg:	Hepatitis B e-antigen
HBsAg:	Hepatitis B surface antigen
HBV:	Hepatitis B Virus
HCC:	Hepatocellular carcinoma
HCV:	Hepatitis C Virus
HIV:	Human immunodeficiency virus
HPV:	human papilloma virus vaccine
ICER:	incremental cost-effectiveness rate (ICER)
IPV:	inactivated polio vaccine
MOH:	Ministry of Health
NITAG:	National Immunization Technical Advisory Group
PCV:	Pneumococcal Conjugate Vaccine
PMTCT:	Prevention of Maternal to Child Transmission
SSA:	Sub-Saharan Africa
WHO:	World Health Organization

1. EXECUTIVE SUMMARY

The Rwanda National Immunization Advisory Group (Rwanda-NITAG) was established in December 2017, to guide the Ministry of Health (MOH) for evidence-based policies and decisions for all technical and scientific matters related to vaccines and immunization.

As a strategy to eliminate Hepatitis B, the MOH plans to introduce Hepatitis B birth dose in routine immunization and requested NITAG to provide evidence-based guidance on the vaccine introduction. Upon reception of the request, technical working groups were established and assigned tasks to collect and analyze available information to support the recommendation. The tasks were to:

1. Determine and define the basic elements guiding the recommendation
2. Formulate the questions for different interventions which are part of the recommendation
3. Determine documentation sources and apply literature search strategies
4. Identify publications/articles of interest and pertinent studies
5. Assess the quality of articles retained considering the methods and materials used to conduct the study
6. Develop the technical dossier to support the recommendation based on the findings from published articles and unpublished reports

Seven elements were analyzed, and evidence was sought from published and unpublished studies or reports. These elements served as a basic to develop the recommendation and included:

1. The epidemiological weight of HBV in Rwanda
2. Mode of transmission and risk factors of HBV
3. The impact of Hepatitis B birth dose in countries that have adopted the vaccination strategy
4. Efficacy and Safety of Hepatitis Birth Dose
5. The cost-benefit of the introduction of Hepatitis Birth dose
6. Other alternative interventions to prevent HBV
7. Economic and operational considerations of HBV Introduction

From the literature, available related to the elements cited above, relevant published and unpublished articles and reports were analyzed. The experts noticed the following:

Hepatitis B remains a global public health concern. Globally, the prevalence of HBV infection was estimated at 4.1% equivalent to 316 million people infected. In 2019, about 1.5 million new infections were reported and 820,000 people died from the disease. Africa region recorded a high prevalence of HBV estimated at 7.5% with new infections accounting for 990,000 cases, and HBV-related deaths estimated at 80,000. About 2.5% of infected people were children under five years of age. The HBV prevalence is the highest in the African region and ranges from intermediate (2%-7%) to high (≥8%) in all countries. Co-infection with HIV is very high and increases morbidity and mortality beyond those caused by either infection alone. The global prevalence of HBV–HIV co-infection among HIV-infected individuals is

estimated at 7.4% and ranges from 2% to 30% in Africa. In SSA, the pooled overall prevalence of co-infection among pregnant women was estimated at 3.3%, with a high prevalence observed in West Africa. In Rwanda, the overall prevalence of HBsAg positivity was 3.9% in the screened population aged 15 years and above. The mode of transmission is percutaneous or mucosal contact with infected blood or other body fluids. In high-endemic settings, the commonest route of transmission is from infected mothers to neonates (perinatal transmission), whereas in areas of low endemicity, the infection is mostly acquired during adolescence and early adulthood through high-risk behaviors such as multiple sexual partners, intravenous and percutaneous drug use.

The Hepatitis B vaccine was discovered in 1965 and was registered in 1982 and 1986 for use in adults and neonates respectively. Randomized clinical trials reported high seroprotective response to monovalent recombinant hepatitis B vaccine administered to infants in the first 30 days of life including those born from HBsAg positive. The findings indicated that more than 96% of infants who received 3 or 4 doses of the hepatitis B vaccine, achieved high seroprotective concentrations of anti-HBs with evidence of long-term persistence of antibodies up to 22 years post-vaccination. The evaluation of efficacy in special infant groups such as preterm and low birth rate infants reported low immunogenicity comparatively with full term and normal weight ranging between 77% and 88% when the vaccine is given at birth. The immunogenicity would increase when the vaccine is given at 1 month of age.

The Hep B birth dose is safe and tolerated. Mild adverse events were documented with an approximate frequency of 1–6% for temperature more than 37,7 ^{o}C, and 3% to 29% for pain. Serious adverse reactions in vaccinated children such as chronic fatigue syndrome, hair loss, diabetes, arthritis, multiple sclerosis, and demyelinating disorders, leukemia have been reported, however, the association with the hepatitis vaccine was not clearly elucidated. No evidence of neonatal deaths associated with the hepatitis B vaccine was documented

Hepatitis B birth dose was documented as one of the strategies to reduce the HBV infections acquired through mother-to-child transmission, which would help to achieve HBV elimination. A tremendous decrease in the prevalence of hepatitis B surface antigen (HBsAg) was observed in countries that introduced the hepatitis B birth dose in their immunization schedule. Modeling study findings estimated that scaling up timely HepB-Birth Dose to a consistent WHO target of ≥90% coverage by 2030 could reduce HBV-related deaths amongst the 2020 to 2030 birth cohorts globally by 710,000 (580,000 to 890,000).

Available literature demonstrates the cost-effectiveness of Hepatitis B birth dose in the countries that adopted the strategy to control HBV. Cost-effectiveness studies documented a high incremental cost-effectiveness rate (ICER) per Disability Adjusted Life Years (DALY) averted in several countries. Even though similar studies were not conducted in Rwanda, the evidence from the published results elsewhere clarifies that the introduction of timely Hep B birth dose is a critical and benefit investment for reducing the incidence towards achieving HBV elimination.

The Rwanda Expanded Program on Immunization (EPI) was launched in 1978 but became operational in 1980. Twelve diseases are targeted for these vaccines including tuberculosis, diphtheria, tetanus, whooping cough, viral hepatitis B, Haemophilus influenzae type b, poliomyelitis, measles, rubella, pneumococcal infections, diarrhea, and cervical cancer. High coverage has been achieved for all the antigens in the national schedule.

According to Rwanda DHS 2020, 93% of deliveries happen at health facilities and are assisted by skilled provider. In the event of home delivery, community health workers assist women to report to the nearest health facility within 24 hours for clinical evaluation of the newborn and the mother. The provision of the birth dose within 24 hours would be facilitated by these existing perinatal and postpartum services, and high coverage may be achieved if given in the delivery room and during clinical evaluation of the baby following home delivery.

In comparison with available strategies to prevent the transmission of HBV, the introduction of a Hep B birth dose is the most cost-effective with a high impact on reducing HBV transmission. The high percentage of health facility deliveries and a strong community health system linking the community to the health care system would facilitate the provision of hepatitis B birth dose and the introduction of the vaccine, in routine immunization would be a highly cost-effective strategy to achieve the elimination of chronic hepatitis B.

2. INTRODUCTION

The Rwanda National Immunization Advisory Group Rwanda NITAG was established in 2017 following the recommendations from the World Health Organization (WHO) and in line with the Global vaccination action plan (GVAP) 2011-2020). The Rwanda NITAG is constituted by national experts, whose role is to advise the Ministry of Health on technical and scientific issues related to vaccines and immunization. The function of Rwanda NITAG is to provide evidence-based guidance to health authorities and leaders of national immunization programs on the definition and implementation of national vaccination policies and strategies in accordance with the National Health Strategy and the National EPI Policy and Guidelines.

The implementation of a regional strategy to eliminate Hepatitis B prompted the Ministry of Health to request the Rwanda NITAG to examine the recommendation on the introduction of the Hepatitis B vaccine birth dose in routine immunization.

WHO recommends the introduction of Hepatitis B birth dose as one of the strategic interventions to prevent mother-to-child transmission and therefore contribute to the elimination of viral Hepatitis B by 2030.[1]

Should, Hepatitis B birth dose be introduced in Rwanda routine immunization in newborn within 24 hours?

In the framework to respond to the above question, the present technical report was produced to provide evidence-based recommendations to help the Ministry of Health decide whether they introduce the Hepatitis B birth dose in routine immunization.

2.1. Background

Hepatitis B is caused by the hepatitis B virus, an enveloped virus, classified within the family hepadnavirus. The virus replicates in hepatocytes and interferes with the functions of the liver, causing the activation of the immune system, which produces a specific reaction to fight and possibly eradicate the infectious agent[2]. This results in pathological damage of the liver developing into acute and chronic hepatitis. Most infected people have no symptoms of disease yet may be highly infectious[3]. The HBV infection is transmitted through percutaneous or parenteral contact with infected blood, body fluids, and by sexual intercourse. The transmission from the mother to the infant is very high when the mother is both Hepatitis B antigen surface (HBsAg) and Hepatitis B e-antigen (HBeAg) positive. This transmission is almost inevitable at the time of the delivery[3-5]. People who are positive for Hepatitis B antigen surface (HBsAg) and people who become chronic carriers are constant sources of new infections. Following the acute HBV infection, the risk of developing chronic infection varies inversely with age[6]. Chronic HBV infection develops among 90% of infants infected at birth, 25-50% of children are infected at 1-5 years of age and HBV infection occurs among 1-5% at old children age and adults[7]. Infant HBV immunization has been highly effective in reducing new infections, especially mother-to-child transmission; and WHO has recommended the member states to introduce HBV birth dose in their immunization program as one of the effective strategic interventions to eliminate HBV, however, the vaccination is the most effective if the first dose is given within the 24 hours[8]. Countries that introduced the hepatitis B birth dose, reported a

tremendous decline of seroprevalence rate of HBV infection in the cohort of persons who received a timely hepatitis B birth dose[9-12]

3. METHODS

Technical working groups were assigned tasks to review the details on different aspects of the question, which supports the elaboration of the recommendation note on the introduction of the HB birth dose. The following steps were taken to develop the recommendation:

- Identify and define the basic elements guiding the elaboration of the recommendation
- Frame the questions for interventions that are part of the recommendation
- Determine sources of documentation and apply literature search strategies
- Identify publications, pertinent studies, unpublished reports/articles of interest
- Assess the quality of articles retained considering the methods and materials used to conduct the study

Eight elements were analyzed, and evidence was sought from published and unpublished studies or reports. These elements served as a basis to develop the recommendation and included:

- The epidemiological burden of HBV infection in Rwanda
- Transmission mode and risk factors of HBV infection
- The impact of Hepatitis vaccine birth dose in countries that have adopted the strategy
- Efficacy and safety of Hepatitis B vaccine in neonates
- The cost-benefit of HBV vaccination
- Existing alternative interventions to prevent HBV infection
- Economic and operational considerations of the introduction of Hepatitis B vaccine birth dose
- Provision of calendar in the country's current context in case of introduction of Hepatitis B vaccine birth dose

The formulation of the questions on the introduction of the Hepatitis B birth dose vaccine based on the elements of the recommendation cited above and the PICO method (Population-Intervention-Comparator-Outcomes) was applied to formulate questions.

1. What is the burden of HBV among the Rwandan population?
2. What are the risk factors underlying the transmission of HBV infection and the mode of transmission?
3. What has been the short and long-term impact of the Hepatitis B birth dose vaccine in countries, which implemented the strategy?
4. What are the existing alternative interventions that could be used for the prevention of HBV in Rwanda or elsewhere?
5. What is the cost-benefits of the Hepatitis B birth dose vaccine in comparison with available interventions?

6. What are the economic and operational impacts of the introduction of the Hepatitis B birth dose vaccine?
7. Can the Hepatitis B birth dose vaccine be accommodated in the current vaccination calendar?

3.1 Documentation sources and strategies used for the literature search

A number of databases were consulted including the NITAG resource website, HINARI, Google Scholar, WHO website, university databases as well as government policies and guidelines. The keywords used for the literature search are summarized in the table below:

Questions	Keywords
1	Epidemiology- Burden-incidence- Viral Hepatitis-Hepatitis B-Global-Sub-saharan Africa (SSA)-in Rwanda
2	Global-burden-Viral-hepatitis-Epidemiology
3	Hepatitis-Mortality-Morbidity-economic impact
4	Transmission-Risk Factors-Hepatitis B
5	Hepatitis B birth dose, impact, epidemiology, cost-effectiveness, Africa, Asia, developing countries
6	Cost- benefits-Effectiveness-impact Hepatitis B birth dose in Africa
7	The economic impact of the use of Hepatitis B birth dose in routine immunization
8	Delivering-strategies-Hepatitis B birth dose

1. Identification of potential articles and relevant studies

The relevant published and unpublished articles and reports were selected for inclusion in the final methodological analysis. The team went through and numbered the articles according to the questions listed above, and a summary of the findings of each article was made.

Question	Number of articles
Epidemiological weight of Hepatitis B infection	17
Mode of transmission and risk factors of Hepatitis B infection	15
Efficacy and safety of Hepatitis B Vaccine	13
Impact of the introduction of Hepatitis B birth dose	5
Alternatives interventions for the prevention of Hepatitis B	7
Cost-Effectiveness of HB Birth dose introduction in routine immunization	5
Provision of calendar in the context of Rwanda in case of introduction of Hep Birth dose	1

1. FINDINGS FROM THE ANALYSIS OF EVIDENCE

1.1 Epidemiological weight of Hepatitis B infection

Hepatitis B remains a global public health concern. In 2019, the global prevalence of HBV infection was estimated at 4.1% equivalent to 316 million people infected.[13] In 2019, about 1.5 million new infections were reported and 820,000 people died from the disease and Africa Region recorded a high prevalence of HBV estimated at 7.5% with new infections counting for 990,000 and HBV-related deaths estimated at 80,000. About 2.5% of infected people were under five children.[14] The HBV prevalence is the highest in the African region and ranges from intermediate (2%-7%) to high (≥8%) in all countries.[14-16]

The risk of developing HBV chronic infection increases inversely with the age of infection. Nearly, 80–90% and 30–50% of chronic infections have been infected in the first year and first 5 years of life respectively, compared with only 5% of adults infected later in life.[17] Twenty-five percent of people chronically infected die untimely from cirrhosis or liver cancer.[18] Most of chronic infections are acquired during perinatal and childhood transmission.[19] The risk of horizontal and vertical transmission is also important in endemic areas accounting for 40% to 50% of chronic infections.[20]

The co-infection with HIV is very high and increases the morbidity and mortality beyond those caused by either infection alone. The global prevalence of HBV–HIV co-infection among HIV-infected individuals, is estimated at 7.4% while the mean proportion of HIV patients with HIV-HBV co-infection in SSA is 7.8%, and varies from 0% to 28.4% in different regions of SSA.[21,22] The highest prevalence of co-infection was documented in West and Central Africa, estimated at 16.4% compared to 4.4% and 8.8% from South and East Africa, respectively. In

SSA, the pooled overall prevalence of co-infection among pregnant women was estimated at 3.3%, with the high prevalence observed in West Africa.[23]

In Rwanda, the overall prevalence of HBsAg positivity was estimated at 3.9% in the screened population aged 15 years and above in 2018. The highest prevalence was observed among the population aged 35 to 54 years old with 4.7% of HBsAg positive. Males (4.3%) and those living with HIV (4.2%) were most affected [24,25]. Among children and adolescents living with HIV aged 8 to 17 years and receiving cART, 7% and 9% had evidence of active and past HBV infection respectively[26].
A study conducted among pregnant women attending ANC services evidenced an HBV prevalence estimated at 3.7%. The same study estimated HBV- HIV co-infection at 4.1% while the prevalence of HBV-HIV co-infection was higher among women aged 15-24 years compared and those aged 25–49 years [aOR = 6.9 (95%CI: 1.8–27.0)] and women with more than two pregnancies were more likely to be HBV-HIV co-infected (aOR = 6.9 (95% CI: 1.7–27.8).[27]
The prevalence of HBV was also evaluated among healthcare workers and showed that 2.9% (95% CI 1.9- 4.6) were HBsAg positive and 57.1% reported occupational exposure to blood.[28,29]

1.2 Mode of transmission and risk factors of Hepatitis B infection

Hepatitis B Virus is transmitted through contact with infected body fluids from a natural host which is human. Blood is the most important vehicle for transmission, but other body fluids have also been implicated, including breast milk, semen, and saliva, however perinatal transmission has been recognized as the frequent mode of transmission of HBV with the majority of HBV infections in settings where the virus is highly endemic [30-31] The sexual, parenteral/percutaneous transmission have been reported, in the areas where intermediate endemicity is observed and horizontal transmission through close household contact, medical or traditional scarification procedures has been also documented.[32,33]
Perinatal HBV infection is associated with a 95% risk of chronic hepatitis B, as compared with a risk of less than 5% among adults with intact immunity.[34] It has been demonstrated that the risk of maternal-to-child transmission is significantly associated with a high viral load of maternal HBV viral load.[35,36] The intrauterine infection accounts for an estimate of 10–44% of HBV transmission mainly through placenta leakage.[37-39] Postpartum transmission refers to the infection through intimate and daily contact, however, infection through breastfeeding has not been elucidated[40]. The Factors such as exposure to the blood from the infected persons, history of a family member HBV-infected, multiple sexual partners, perinatal infection, blood, and its derivatives, intravenous and percutaneous drug use, occupational, habitual, and social behavior have been identified as risk factors for hepatitis transmission in various settings.[39-44]

1.3 Efficacy and safety of Hepatitis B Vaccine

The Hepatitis B vaccine was discovered in 1965 and was registered in 1982 and 1986 for use in adults and neonates respectively.[45] Preliminary reports from a randomized clinical trial conducted in China from 1982 to 1984 showed a cumulative seroconversion of 95% at one year of age.[46] Studies reported high seroprotective response to monovalent recombinant hepatitis B

vaccine administered to infants in the first 30 days of life including those born from HBsAg positive. The findings indicated that 98% of infants who received 3 or 4 doses of the hepatitis B vaccine, achieved seroprotective concentrations of anti-HBs, and the high effectiveness of hepatitis B vaccination initiated at birth for the prevention of perinatal and early life acquisition of HBV infection was elucidated.[47] The review of 30 years of efficacy, effectiveness, immunogenicity, and safety data with the use of GSK HepB for primary 3-dose vaccination of healthy infants and children, including infants born to HBsAg positive mothers, using the standard 0, 1, and 6-month schedule documented seroprotection rates of 96.0% or more, with evidence of long-term persistence of antibodies up to 22 years post-vaccination.[48]

Randomized clinical trials comparing different interventions assessing the effects of hepatitis B vaccines and immunoglobulin for newborn infants from HBsAg positive mothers who received hepatitis B vaccine at birth, 1, and 6 months or at birth, 1, 2, and 6 or 12 months to prevent perinatal transmission of HBV reported a significant decrease of the risk of hepatitis B occurrence.[49] The evaluation of efficacy in special infant groups such as preterm and low birth rate infants reported low immunogenicity comparatively with full term and normal weight ranging between 77% and 88% when the vaccine is given at birth. The immunogenicity would increase when the vaccine is given at 1 month of age.[50,51]

Several studies reported minimal reactions such as local pain, myalgia, and transient fever, mostly within 24 hours after vaccination, highlighting the safety and tolerability of the vaccine among newborns.[52,53] The mild adverse events were documented with an approximate frequency of 1–6% for temperature more than 37,7 ºC, and 3% to 29% for pain. Some studies described serious adverse reactions in vaccinated children such as chronic fatigue syndrome, hair loss, diabetes, arthritis, multiple sclerosis and demyelinating disorders, and leukemia, but the associations with the hepatitis vaccine was not clearly elucidated.[54,55] Review of neonatal death cases reported after receiving the hepatitis B vaccine given alone in neonates aged 0-28 days in the United States didn't find evidence of either an increased trend in the overall number of neonatal deaths or in neonatal deaths after hepatitis B vaccination.[56,57]

1.4 Impact of the introduction of Hepatitis B birth dose

Hepatitis B birth dose has been recommended given its efficacy to reduce the HBV infections acquired through mother-to-child transmission and was documented as one of the strategies to eliminate HBV. A tremendous decrease in the prevalence of hepatitis B surface antigen (HBsAg) was observed in countries which introduced the hepatitis B birth dose in their immunization schedule. In China, over 20 years of the provision of the Hepatitis B birth dose, the prevalence of HBsAg sharply reduced by 84.4% from 1995 to 2005.[58] The increase of the coverage of three series of hepatitis vaccination and timely birth dose was associated with the decline in the prevalence of the HBsAg. From 1992 to 2005, the coverage of three series vaccination and timely birth dose increased by more than 211% (from 30% to 93.4%) and 200% (from 22.2% to 82.6%) respectively. This resulted in the HBsAg and anti-HBc prevalence reduction of 83.6% (from 5.5% to 0.9%) and 80% (from 16.5% to 3.3%). The results of these studies evidenced the efficacy of the hepatitis B vaccine for fully and on-time immunized infants, compared with nonimmunized infants which was estimated at 88%.[59] The Hepatitis B vaccination including timely birth dose and three series of Hepatitis B vaccination

in China resulted in reducing HBsAg prevalence among children aged 1–4 years which decreased by 90%. Furthermore, HBsAg prevalence among children aged 5–9 and 10–14 years have decreased by 86% and 72%, respectively. In these cohorts, 16–20 million HBV carriers and 2.8–3.5 million future HBV-related deaths were prevented. [60]

Modeling study findings estimated that scaling up timely HepB-Birth Dose to a consistent WHO target of ≥90% coverage by 2030 could reduce HBV-related deaths amongst the 2020 to 2030 birth cohorts globally by 710,000 (580,000 to 890,000).[61] Two simulation models conducted on scaling up the birth dose coverage from status quo in 2017 to 95% from 2025 onwards in Ethiopia, India, Pakistan, and Nigeria predict reductions in incident chronic HBV cases roughly in line with the WHO goals of a 30% reduction by 2020 and a 90% reduction by 2030 from the baseline in 2015 in the four countries.[62]

1.5 Alternatives interventions for the prevention of Hepatitis B

The HBV infection prevention strategies are informed by HBV transmission modes. These include immunization, routine screening, and treatment of pregnant women, blood, injection and surgical safety, harm reduction for people who inject drugs, and avoidance of risky behaviors.[63]

Immunization has been proven as the primary and most cost-effective intervention to prevent the transmission of HBV infection. Timely birth dose prevents HBV infection at birth and in the first years of life, provides long-term immunity, and minimizes the reservoir of infection.[61,62] Mass neonatal vaccination within the Expanded Programme on Immunization in Sub-Saharan Africa was found to be the most effective strategy to control hepatitis B infection.[64] The other alternative interventions such as the provision of hepatitis B immunoglobulin (HBIG), systematic screening and treatment of pregnant women, blood, injection and surgical safety, harm reduction for people who inject drugs, and avoidance of behavior change, are costly and could not provide alone a long-term and sustained elimination of the risk of transmission.[65,66]

Rwanda introduced the pentavalent vaccine (DPT-HepB-Hib) in routine immunization as a strategy to control the horizontal transmission of hepatitis B infection. The introduction of the hepatitis B birth dose would be a unique affordable and cost-effective intervention to minimize the risk of vertical transmission of HBV.[67]

1.6 Cost-Effectiveness of the Introduction HB Birth Dose in routine immunization

Available literature demonstrates the cost-effectiveness of Hepatitis B birth dose in the countries that adopted the strategy to control HBV. In Italy, after the implementation of immunization strategy against hepatitis B in 1991, the incidence of acute viral hepatitis B reduced by 77.9% from 1980 to 1997 and the saving of the years of the vaccination was evaluated at US$244,308,000.[68]

The investment case for hepatitis B and C in South Africa showed that Hepatitis B birth dose vaccination along with PMTCT, HBV, and HCV treatment could avert more than 670 000 new infections, 200 000 HBV, and 30 000 HCV related deaths in the five years; resulting in the

incremental cost-effectiveness rate (ICER) estimated at $3310 per Disability Adjusted Life Years (DALY[1]) averted.[69] Cost-effectiveness studies conducted in Mozambique and Ethiopia, reported an incremental cost-effectiveness ratio (ICER[2]) of 250.95 US$ and US$ 110 per DALY averted respectively, when adding a birth dose to the three series of Hepatitis B vaccine at 6,10 and 14 weeks would present.[70,71] Adding Hepatitis B birth dose in comparison with RI alone among displaced Somali refugees in Djibouti camps would save 9807 life-years/year, with an ICER of US$ 0.15 per life-year saved while additional Hep B birth dose would save 27,108 life-years/year with an ICER of US$ 0.11 and 18,417 life-years/year with an ICER of US$ 0.16 in Algerian and Mauritania refugees camps respectively.[72]

Although similar studies were not conducted in Rwanda, the evidence from the published results elsewhere clarifies that the introduction of timely Hepatitis B birth dose (within 24 hours) in routine immunization is a critical and benefit investment for reducing the incidence towards eliminating HBV.

1.7 Provision of calendar in the context of Rwanda in case of introduction of Hep Birth dose

The Rwanda Expanded Program on Immunization (EPI) was launched in 1978 but became operational in 1980. The program started with seven antigens including Bacillus Calmette–Guerin (BCG), oral polio, diphtheria, tetanus and pertussis combination (DTP), and measles, as well as tetanus toxoid (TT) given to pregnant women. Later in 2002, six new antigens including HepB and, Hemophilus influenza B vaccine added to the combination of DPT and became the pentavalent vaccine, Pneumococcal Conjugate Vaccine (PCV), Rotavirus, two doses of inactivated polio vaccine (IPV) and human papillomavirus vaccine (HPV). All these vaccines are given at birth, 6, 10, 14 weeks, 9, and 15 months, except for HPV and TT vaccines given to adolescents aged 12 years and women of childbearing age respectively. Eleven diseases are targeted for these vaccines including tuberculosis, diphtheria, tetanus, whooping cough, viral hepatitis B, Haemophilus influenzae type b, poliomyelitis, measles, rubella, pneumococcal infections, diarrhoea and cervical cancer.

In 2002, the pentavalent vaccine which comprises DPT, Hep B, and Hib was introduced in routine immunization. The vaccine is offered at the age of 6, 10, and 14 weeks. The introduction of the birth dose using monovalent hepatitis B vaccine in routine immunization is thought to be effective for the prevention of vertical transmission of HBV.

According to Rwanda DHS 2020, 93% of deliveries happen at health facilities and are assisted by skilled provider.[73] In the event of home delivery, community health workers assist women to report to the nearest health facility within 24 hours for clinical evaluation of the newborn

[1] **Disability Adjusted Life Years**: Is a time-based measure used to assess the overall burden of disease that combines years of life lost due to premature mortality (YLLs) and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (YLDs). One DALY represents the loss of the equivalent of one year of full health. Using DALYs, the burden of diseases that cause premature death but little disability (such as drowning or measles) can be compared to that of diseases that do not cause death but do cause disability (such as cataract causing blindness)

[2] **Incremental cost-effectiveness rate (ICER)** is a summary measure representing the economic value of an intervention, compared with an alternative. It is usually the main output or result of an economic evaluation. An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' – for the more expensive therapy vs the alternative

and the mother. The provision of the birth dose within 24 hours would be facilitated by these existing perinatal and postpartum services, and high coverage may be achieved if given in the delivery room and during clinical evaluation of the baby following home delivery.

2. CONCLUSION

In view of the existing evidence, chronic HBV infection is a public health concern and the endemicity varies from low to high across the countries and regions. In Rwanda, data on the maternal to child transmission is not available. However, prevalence studies have evidenced the intermediate prevalence of the disease in the country. The provision of Hepatitis B birth dose has been cost-effective to reduce the transmission of HBV in the countries that have adopted the strategy and data has evidenced a good safety profile of the vaccine. In comparison with available strategies to prevent the transmission of HBV, the introduction of the birth dose of the Hepatitis B vaccine in routine immunization was the most cost-effective, and a high impact on reducing the prevalence of HBV was evident.

In the context of Rwanda with a high percentage of health facility deliveries and a strong community health system linking the community to the health care system, the introduction of hepatitis B birth dose in routine immunization would be highly cost-effective to achieve the elimination of chronic hepatitis B.

3. RECOMMENDATION

In view of the available evidence, the Rwanda NITAG recommends the introduction of Hep B birth dose in routine immunization with the following considerations:

- Hepatitis B vaccine birth dose should be given to all newborns including preterm and low birth weight within 24 hours of delivery
- Hepatitis B vaccine birth dose delivery services should be established in all health facilities including public and private.
- Maternal and newborns management and EPI guidelines should be revised to include all the information on the Hepatitis B vaccine birth dose
- Screening of HBV for all pregnant women should be reinforced in all health facilities
- The impact of the Hepatitis B vaccine should be evaluated after the introduction of the Hepatitis B vaccine birth dose

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1. APPENDIX

A: Technical working groups on evidence for the introduction of Hepatitis B birth dose, established on 17 September 2019

Points of discussion	Content	Source of information	Team responsible
Epidemiological weight of HBV in Rwanda	1.Worlwide 2. Regional 3. Rwanda	1) WHO epidemiological records 2) Literature/Publications	1) Dr. NAHIMANA Rosette 2) Dr. RUTAGARAMA Florent 3) Dr Raissa Teteli 4) Grace KABANYANA
Weight of the mother-child transmission of the HVB	1) Document risk of maternal to child transmission, estimate the risk of MTCT in Rwanda (Formula and other studies in the region).	Different publications including WHO, NITAG, …	1)Dr. NAHIMANA Rosette 2)Dr. RUTAGARAMA Florent 3)Dr Raissa TETELI
Impact of vaccination against HVB at birth in countries that have Adopted this vaccine strategy	Short- and long-term impact (prevalence before and after introduction of Hepatitis B vaccine at birth, immunity response,	Different publications in Africa and in sub-regions	Dr James HUMUZA Dr Ines BUKI Jean de Dieu HAKIZIMANA
Efficacy and safety of HBV vaccine in new-borns	1) Immunogenicity, seroprevalence studies after introduction of hepatitis B vaccine at birth. 2) Information on AEFIs 3) Contra-indication	1)Different publications/Literature 2) WHO, Global Advisory Committee on Vaccine Safety (GACVS)	Dr Humuza Dr Ines BUKI Jean de Dieu HAKIZIMANA

The cost-benefit of vaccination against HVB at birth	Comparison between vaccinated and non-vaccinated, economic impact in term of cost treating infected non vaccinated children	Different publications/Literature	1) Dr. KATEERA Brenda 2) Prof. Manasse 3) Dr. NAHIMANA Rosette 4) Dr RUGAMBWA Celse 5) TUYISHIME Yvette
Economic and operational considerations of HVB	1) Operational cost 2) incremental cost	1)Different publications 2) Experience from the introduced new vaccines in Rwanda	1) BUKI Ines 2) Dr. KABANO Augustin 3) Dr. HUMUZA James 4) HAKIZIMANA Jean de Dieu

B: Recommendation framework

EVIDENCE TO RECOMMENDATION FRAMEWORK

Question: Should Hepatitis B Birth Dose be introduced into the routine immunization schedule to reduce the risk of Hepatitis B infection

Population: Newborn 24 hours old

Intervention: One dose of Hepatitis vaccine

Comparison: No Vaccine

Outcome: Hepatitis B incidence reduced

Background

Hepatitis B remains a global public health concern. In 2019, WHO estimates Globally, the prevalence of HBV infection was estimated at 4.1% equivalent to 316 million people infected. About 1.5 million new infections were reported and 820,000 people died from the disease. Africa Region recorded a high prevalence of HBV estimated at 7.5% with 990,000 new infections and HBV-related deaths estimated at 80,000. About 2.5% of infected people were under five children. Most chronic infections are acquired during perinatal and childhood transmission. The risk of horizontal and vertical transmission is also important in endemic areas accounting for 40% to 50% of chronic infections. Perinatal HBV infection is associated with a 95% risk of chronic hepatitis B, as compared with a risk of less than 5% among adults with intact immunity. Seroprotection of ≥96% has been documented for the Hepatitis vaccine, using the standard schedule of 0, 1, and 6 months, with evidence of long-term persistence of antibodies up to 22 years post-vaccination. Scaling up timely HepB-Birth Dose to a consistent WHO target of ≥90% coverage by 2030 could reduce HBV-related deaths amongst the 2020 to 2030 birth cohorts globally by 710,000 (580,000 to 890,000). Given its effectiveness in reducing HBV infection and related deaths, WHO recommends the introduction of Hepatitis B birth dose in routine immunization to reduce the incidence and therefore aid to achieve Hepatitis B elimination.

The Rwanda NITAG was requested to provide evidence-based recommendations to guide the decision on the introduction of Hepatitis B birth dose

Issue	Element	Specific data	Evidence	Ranking	Additional information

1. Vaccine and immunization characteristics	Safety	Type, consequences, and frequency of short and long-term adverse events following vaccination	Two types of Hepatitis B recombinant vaccines are used in new-born including RECOMBIVAX HB® and ENGERIX-B. Both are indicated for the prevention of infection caused by all known subtypes of the hepatitis B virus and are approved for use in infants. The Global Advisory Committee on Vaccine Safety (GACVS) has confirmed the excellent safety profile of hepatitis B vaccines. Several clinical trials reported minimal reactions such as local pain, myalgia, and transient fever, mostly within 24 h. No long-term events were documented with HBV recombinant vaccines.	**Very important**	The estimated incidence of anaphylaxis estimated incidence of the severe adverse event of anaphylaxis among vaccine recipients is 1.1 per million vaccine doses. No serious, severe, or fatal anaphylactic reaction has been reported[3]. A comparison of deaths among birth HBV-vaccinated and unvaccinated newborns was carried out with the review of all the causes and circumstances of their deaths. No significant difference in the proportion of HBV-vaccinated and unvaccinated neonates dying of unexpected causes. No plausible causal or temporal association was established between HBV administration and death for vaccinated neonates who died unexpectedly[4] Other events such as chronic fatigue syndrome, hair loss, diabetes, chronic arthritis, leukemia, multiple sclerosis and demyelinating disorders, as well as conditions associated to Hepatitis B vaccine preservatives including Aluminum, thiomersal were claimed to be associated with Hepatitis B vaccination. However, the relationship with Hepatitis B immunization was not demonstrated[5]

[3] World Health Organization. (2017). Hepatitis B vaccines: WHO position paper-July 2017. Weekly epidemiological record, 92(27), 369-392.

[4] Eriksen, E. M., Perlman, J. A., Miller, A., Marcy, S. M., Lee, H., Vadheim, C., ... & Ward, J. I. (2004). Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the vaccine safety datalink project. The Pediatric infectious disease journal, 23(7), 656-662.

[5] Duclos, P. (2003). Safety of immunization and adverse events following vaccination against hepatitis B. *Journal of Hepatology*, *39*, 83-88.

		Risk groups or risk factors for adverse events	No risk factors predisposing to Hepatitis B vaccine adverse events in the newborn were elucidated.	**Important**	A study was conducted to analyze adverse events associated with the immunization of very low birth weight children (<1500 gr), with the hypothesis that adequate vaccination in very low birth weight was associated with an increased risk for apnea and bradycardia with lower gestational age and that cerebral hemorrhage or periventricular leukomalacia did not aggravate side effects. The study concluded that timely vaccination of premature infants with a birth weight under 1500 g is safe. The occurrence of cardiorespiratory events was related to earlier gestational week.[6]
		Contraindications	The Hepatitis B vaccine is contraindicated only for individuals with a history of serious allergic reactions to any of the vaccine components.[7]	**Important**	
	Efficacy and effectiveness	Immunogenicity of Hepatitis B Vaccine	Recombinant Hepatitis B vaccines became available in 1986 and had demonstrated excellent immunogenicity in several groups considered at high risk of acquiring hepatitis B including neonates born to hepatitis B carrier mothers and other high-risk groups. The protective efficacy of Engerix B against HBsAg carriage in healthy infants and children, and in neonates born to hepatitis B carrier mothers was estimated at 95 to 99%	**Very important**	A cross-sectional survey was conducted in Benin to assess the anti-HBs antibody response in Beninese infants following 4 doses of HBV vaccine including birth dose (0, 6, 10, 14 weeks), compared to the standard 3 doses regime (provided at 6, 10, 14 weeks). The study showed that infants who received 4 doses of the HBV vaccine had a significantly higher level of anti-HBs antibodies than those who received 3 doses of the vaccine (557.9 UI/L vs. 386.9 UI/L, respectively, P =

[6] Furck, A. K., Richter, J. W., & Kattner, E. (2010). Very low birth weight infants have only few adverse events after timely immunization. Journal of perinatology, 30(2), 118-121.
[7] Losonsky, G. A., Wasserman, S. S., Stephens, I., Mahoney, F., Armstrong, P., Gumpper, K., ... & Gewolb, I. H. (1999). Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics, 103(2), e14-e14

					0.03). In addition, the findings showed that the scheme of 4 doses was associated with a significantly higher sustained protective response in comparison to the scheme of 3 doses (aOR 2.49, 95% CI 1.03–6.03, P = 0.04)[8] Several studies documented the immunogenicity of recombinant Hepatitis B vaccines. The overall median seroprotection proportion was estimated at 98%, ranging from 52% to 100%. In studies in Taiwanese and Thai neonates born to hepatitis B carrier mothers, seroprotection rates were ≥94% 12 months after immunization with Engerix B. In those studies, the seroprotection rates from Engerix B and Recombivax were not different. [9,10,11] Effectiveness evaluation studies will be necessary to appraise the immune response and immunogenicity of the vaccine in Rwanda.
		Risk of Hepatitis B infection with vaccine worldwide	The risk of Hepatitis B infection was reduced among vaccinated children when compared to unvaccinated. In comparison with children who received birth dose after 24 hours, children who received timely birth dose were less likely to be	**Very important**	The evaluation of the risk of HBV infection among 607 children vaccinated at birth, 6, 10, and 14 weeks in Northern Cameroon, reported an increase of HBV infection among children for whose timing of the first dose was delayed by 48

[8] Accrombessi, M., Adetola, C. V., Bacharou, S., Dossou, Y., Avokpaho, E., Yakoubou, A., ... & Issifou, S. (2020). Assessment of the anti-HBs antibody response in Beninese infants following 4 doses of HBV vaccine, including administration at birth, compared to the standard 3 doses regime; a cross-sectional survey. Vaccine, 38(7), 1787-1793.

[9] Keating, G. M., & Noble, S. (2003). Recombinant Hepatitis B Vaccine (Engerix-B®) A Review of its Immunogenicity and Protective Efficacy Against Hepatitis B. Drugs, 63(10), 1021-1051.

[10] Schillie, S. F., & Murphy, T. V. (2013). Seroprotection after recombinant hepatitis B vaccination among newborn infants: a review. Vaccine, 31(21), 2506-2516

[11] Van Den Ende, C., Marano, C., van Ahee, A., Bunge, E. M., & De Moerlooze, L. (2017). The immunogenicity of GSK's recombinant hepatitis B vaccine in children: a systematic review of 30 years of experience. Expert review of vaccines, 16(8), 789-809.

			infected. The reduction of Hepatitis B infection during perinatal and childhood age results in a diminution of chronic HBV infection and consequently the decline in Hepatocarcinoma. Globally, there has been a decrease in hepatitis-B-related primary liver cancers, attributed to hepatitis B vaccination. Though the impact of universal vaccination programs on HCC prevention may take some time to quantify due to the long latency of HCC development, several longitudinal studies from Asia, The Gambia, and within specific hepatitis B endemic populations have already demonstrated the positive impact of universal hepatitis B vaccination on hepatitis-B-related childhood HCC incidence.		to 96 hours after birth. The risk of HBsAg positivity in children who had a timely HBV birth-dose vaccine (<24 h) was 32·4% from HBeAg-positive mothers with high viraemia, 0% from HBeAg-positive mothers with low viraemia, 0% from HBeAg-negative mothers with high viraemia, and 0·3% from HBeAg-negative mothers with low viraemia.[12] The decline in HCC related mortality was evaluated in China. Two counties were compared including BinYang which did not adopt universal vaccination of infants until 2002, and LongAn where a clinical trials on Hepatiris B birt dose was conducted and all newborn infants between 1986 and 1996 were vaccinated. Childhood mortality within LongAn County was assessed before and after the vaccination clinical trial. It was observed that HCC mortality was significantly higher in the 20–29-year age group in 2004 among individuals who were not vaccinated at birth (7.9/100,000 compared with 1.4/100,000) between 2017 and 2018, highlighting the decline in HCC associated with the universal immunization of newborns. Similarly, a randomized controlled step-wedge trial of

[12] Shimakawa, Y., Veillon, P., Birguel, J., Pivert, A., Sauvage, V., Le Guillou-Guillemette, H., ... & Lunel-Fabiani, F. (2022). Residual risk of mother-to-child transmission of hepatitis B virus infection despite timely birth-dose vaccination in Cameroon (ANRS 12303): a single-centre, longitudinal observational study. The Lancet global health, 10(4), e521-e529.

					infant hepatitis B vaccination in Gambia reported a high degree of protection against primary infection and chronic carriage rate.[13]
2. Disease	Burden of disease	Morbidity and mortality of HBV infection	Hepatitis B remains a public health concern. WHO estimates 316 million the number of people infected. Following the acute HBV infection, the risk of developing chronic infection varies inversely with age. Chronic HBV infection develops among 90% of infants infected at birth, 25-50% of children is infected at 1-5 years of age and HBV infection occurs among 1-5% at old children age and adults. The contribution of HBV in the development of HCC is undisputed and accounts for 55% of cases. According to the GLOBOCAN report, an estimated 66,944 deaths occurred from HCC in Africa in 2020.	**Critical**	HBV prevalence was estimated at 7.5%, in 2019 in Africa Region, with new infections counting for 990,000. About 2.5% of infected people were under five children. HBV-related deaths were estimated at 80,000. The co-infection with HIV is very high and increases the morbidity and mortality beyond those caused by either infection alone. In Sub-Saharan Africa, 7.8% of PLHIV is co-infected with HBV. The highest prevalence of co-infection was documented in West and Central Africa, estimated at 16.4% compared to 4.4% and 8.8% from South and East Africa, respectively.[14,15,16] In Rwanda, the chronic HBV rate was estimated at 3.9% in the screened population aged 15 years and above in 2018, and 3.7% of pregnant women were infected. [17]

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		Hepatitis B disease epidemiology	The number of people developing new chronic infections from hepatitis B has declined, supported by an increase in the coverage of the highly effective hepatitis B vaccine among infants. Globally, 85% of all infants had received the recommended three doses of the hepatitis B vaccine in 2019, up from only 30% in 2000, and the global target of the Sustainable Development Goals and the global health sector strategy to reduce hepatitis B surface antigen prevalence to less than 1% among children younger than five years by 2020 has been met. However, major gaps remain in some regions, including sub-Saharan Africa and South-East Asia. In Rwanda, the first population-based survey estimated the prevalence of hepatitis B estimated at 2.0% among adults aged 15-64 years[18]. The trends of Hepatitis B may not be known yet as the country has recently launched the Hepatitis elimination strategy and impact evaluations will be done in the future.	**Critical**	From 2010 to 2019, the overall incidence of acute HBV declined by 19.3% (95% CI 4.1–32.0, $p < .05$). [19] A systematic review and meta-analysis of epidemiological studies published from 2005 to 2020 reported a prevalence of hepatitis B in East African ranging from 1.05% (95% CI = 0.845 to 1.278%) [54] to 20.9%. The highest prevalence of 8.54% was reported in Kenya, and the lowest in Rwanda, with 4.06% of surveyed population while the population-based survey estimated at 2.0% the prevalence of HBsAg in Rwanda. In 2018, 4.1% of people living with HIV and 3.7% of pregnant women were infected with HBV. Perinatal HBV infection is associated with a 95% risk of chronic hepatitis B. In the African region, the prevalence of HBeAg among HBsAg-positive pregnant women with detectable viral load was 18.9% (95% CI: 14.4–23.9), and the pooled risk of mother-to-child transmission, without any preventive measures, was 38.3% (95% CI: 7.0–74.4%) without prophylaxis. Among HBeAg-negative women, the pooled risk

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					was estimated at 4.8% (95% CI: 0.1–13.3%).[20,21,22]
	Alternative preventive & control measures	Other vaccination strategies	Many strategies to control the MTCT have been evaluated in clinical trials including the provision of antiviral treatment and hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine to the mother with HBV infection, and HBIG and HBV vaccine or vaccine alone to the newborn. All the strategies have shown results in reducing the transmission of mother-to-child transmission. However, the implementation of some strategies including antiretroviral treatment, and provision of HBIG to the mother and the child may be more operationally complex with costly investments for systematic screening of all pregnant women. Universal vaccination was reported as a cost-effective strategy recommended by the WHO to reduce the HBV transmission	**Critical**	Results from a systematic review of Sixteen RCTs showed that compared with the placebo group, HBIG, and HBVac groups had a significant decrease in the number of newborns who were HBsAg positive and had a significant increase in the number of anti-HBs positive newborns. After 1-year follow-up, the number of HBsAg-positive newborns continued to decline and the number of anti-HBs-positive newborns continued to increase in HBIG and HBVac group. Compared with the HBIG group, HBIG, and HBVac groups had no significant difference in the number of HBsAg positive newborns (RR: 1.68, 95% CI [0.66, 4.30], P=.28), and had a significant decrease in the number of HBsAg positive newborns (RR: 0.31, 95% CI [0.12, 0.84], P=.02).[23] Clinical trials evidenced the high effectiveness of tenofovir disoproxil

[20] Bigna, J. J., Kenne, A. M., Hamroun, A., Ndangang, M. S., Foka, A. J., Tounouga, D. N., ... & Nansseu, J. R. (2019). Gender development and hepatitis B and C infections among pregnant women in Africa: a systematic review and meta-analysis. Infectious Diseases of Poverty, 8, 1-12.

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					fumarate, lamivudine, and telbivudine in preventing MTCT.[24] A total of 620 infants born to HBeAg-negative carrier mothers were enrolled in a study to compare the efficacy of the HBV vaccine alone and HBIG and the HBV vaccine. MTCT of HBV was 0% in both groups.[25]
3. Economic and operational considerations	Vaccine-related costs and resource use	Direct and indirect costs to administer the vaccine	Hepatitis B vaccination is the most effective way to prevent HBV infection. Clinical trials have established the effectiveness of the vaccine given within 24 hours after birth, followed by at least two more doses in preventing perinatal HBV infection and inducing immunity to HBV. Current prices of the HepB vaccine are significantly lower, making it highly cost-effective to include in national immunization programs.	**Very important**	According to Rwanda DHS 2020, 93% of deliveries happen at health facilities and are assisted by skilled provider.[26] In the framework of reducing neonatal deaths, Rwanda introduced postpartum care within 24 hours in the event of home delivery. Rwanda has a strong Community Health network and community health workers assist women to report to the nearest health facility within 24 hours for clinical evaluation of the newborn and the mother. The provision of the birth dose within 24 hours would be facilitated by these existing perinatal and postpartum services. Integration of Hepatitis B birth dose delivery with maternal and neonatal care will facilitate the provision of the vaccines within other neonatal services

[24] Song, J., Yang, F., Wang, S., Tikande, S., Deng, Y., Tang, W., & Cao, G. (2019). Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: a meta-analysis. Journal of Viral Hepatitis, 26(3), 397-406.

[25] Zhang, W., Xu, C., Rui, Y., Chen, J., Chen, T., Dai, Y., ... & Zhou, Y. H. (2022). Efficacy of the hepatitis B vaccine alone in the prevention of hepatitis B perinatal transmission in infants born to hepatitis B e antigen-negative carrier mothers. Journal of Virus Eradication, 8(2), 100076.

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					and will be a cornerstone to achieve high coverage. The Ministry of Health will consider the integration of Hep B BD in private clinics which have maternity services but do not deliver immunization services in their package.
	Economic Impact on the immunization program	Cost-benefit, cost-effectiveness, DALY, QALY,	Hepatitis B vaccination is the most cost-effective intervention to control the Hepatitis B infection. No modeling study was done in Rwanda to estimate the cost-effectiveness of the Hepatitis Birth dose. However, a study conducted in other countries found the intervention cost-effective	**Very important**	Cost-effectiveness studies conducted in Mozambique and Ethiopia reported an incremental cost-effectiveness ratio (ICER) of 250.95 US$ and US$ 110 per DALY averted respectively when adding a birth dose to the three series of Hepatitis B vaccine at 6,10 and 14 weeks would present.[27,28] Adding HepB Birth Dose to the series of three doses of Hepatitis vaccines (HepB3) in RI in Burkina Faso yielded a net cost saving of US$18,979 and saved 163 DALYs compared with HepB3 alone. With discounting, HepB-BD + HepB3 compared with HepB3 resulted in an incremental cost of US$554 and 31 DALYs averted, translating into an ICER of US$18/DALY averted.[29]
	Impact on resources	Human, technical, and financial requirements	Given the low price of the vaccine, the target population, and considering the integration of Hep B birth dose delivery	**Critical**	The introduction of Hepatitis B birth dose will require the MOH to engage more with private sectors in health services

[27] Klingler, C., Thoumi, A. I., & Mrithinjayam, V. S. (2012). Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique. Vaccine, 31(1), 252-259.

[28] Memirie, S. T., Desalegn, H., Naizgi, M., Nigus, M., Taddesse, L., Tadesse, Y., ... & Girma, T. (2020). Introduction of birth dose of hepatitis B virus vaccine to the immunization program in Ethiopia: an economic evaluation. Cost Effectiveness and Resource Allocation, 18, 1-10.

[29] Gosset, A., Diallo, M. Y., Betsem, E., Schaeffer, L., Meda, N., Vray, M., ... & Boyer, S. (2021). Cost-effectiveness of adding a birth dose of hepatitis B vaccine in the Dafra district of the Hauts-Bassins Region in Burkina Faso (NéoVac Study). Vaccine, 39(33), 4659-4670.

			with maternal and neonatal services services, the cost of HepB BD would be affordable.		delivery to ensure access to Hepatitis B BD to all neonates
	Ability to evaluate	AEFI monitoring and Availability of information systems to measure coverage and vaccine utilization	Immunization program has the capacity to carry out safety surveillance of vaccines given at birth. The capacity has been strengthened at all levels of the health system to detect, report, investigate and assess the causality of serious AEFIs. The program collaborates closely with the Pharmacovigilance program within Rwanda Food and Drugs Authority to continuously build the capacity of healthcare providers on AEFI surveillance and investigate serious AEFI/AESIs. Expert committee on AEFI has been established to support the investigation, conduct causality assessment, and advise the program on all matters related to vaccine safety. Rwanda is prioritizing the digitalization of the health sector. IT technologies are deployed in all health facilities for data management and use, including Civil Registration and Vital Statistics (CRVS), and immunization registry (e-Tracker) for immunization. These IT infrastructures are supporting data management and use, to monitor health trends including immunization coverage over time.	**Very important**	Training and supportive supervision will be required to strengthen the capacity of nurses and midwives from public and private clinics to deliver HepB BD.