UGANDA NATIONAL ACADEMY OF SCIENCES

Ratified Recommendation on the Introduction of Hepatitis B Birth Dose in UNEPI

Updated Recommendation of the 2017 UNITAG recommendation

By

UGANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP (UNITAG)

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EXECUTIVE SUMMARY

Ministry of Health requested Uganda National Immunisation Technical Advisory Group (UNITAG) to analyse updated data on Hepatitis B birth dose for possible revision of UNITAG recommendation reached in 2017 (ADM:80/105/01).

In 2016, member states of the World Health Assembly unanimously adopted a resolution declaring that viral hepatitis should be eliminated by 2030 targeting to reduce prevalence among children less than 5 years of age to less than 1% by 2020 and to less than 0.1% by 2030. However, introduction of the birth dose is still low despite the WHO recommendation that all children globally irrespective of maternal HBV status, should receive a Hepatitis B vaccination ideally within 24 hours to protect infants from mother to child transmission. Consequently, 1.5 million people globally were newly infected with hepatitis B virus in 2019. Moreover, 296 million people were living with chronic hepatitis B virus infection, 6 million being children younger than five. Hepatitis B accounted for 820,000 people deaths.

In 2017, UNITAG decided not to recommend the introduction of HepB BD due to lack of sufficient additional evidence on efficacy of the birth dose in a setting with Hepatitis B given as part of Pentavalent at 6, 10 and 14 weeks in the African context as the recommendation framework excluded vaccine efficacy/efficiency data from Asia citing significant differences in risk of vertical transmission due to significantly different HBsAg prevalence levels. The UNITAG working group on Hepatitis B has thus revisited this recommendation focusing on evidence review of hepatitis B birth dose efficacy/effectiveness and economic considerations, including efficacy and effectiveness data from Asia.

A systematic review of evidence suggests that Hepatitis B is a disease of significant concern in Uganda, affecting mostly children and causing serious illness and death later in life, with no effective cure. Low antenatal attendance and hence low HBV testing rates means low levels of diagnosis and high risk of vertical transmission. Evidence indicates that HepB BD when administered within the first 24 hours significantly reduces vertical HBV transmission especially for infants born to highly viremic mothers and has some value in preventing horizontal transmission when administered before 4 weeks of age. Moreover, addition of HBIG slightly increases vaccine effectiveness though the cost per ml is relatively expensive. In addition, a review of literature on economic evaluations of the birth dose indicates that universal HepB vaccination at birth is not only cost effective against HBV infection and reducing long-term sequelae but is also a more cost-saving primary preventive strategy than the targeted vaccination hence a worthwhile investment of public funds. Likewise, introduction and routinisation of HepB BD is relatively cheaper as compared with many other new vaccines proposed for introduction in Uganda's immunisation program.

The Working Group on HepB concluded that addition of HepB BD to Uganda's EPI will enable Uganda to achieve WHO Elimination much earlier than when using the current HepB3 schedule alone hence made the following recommendations:

i. MOH/UNEPI should introduce Hepatitis B BD into the routine immunisation program using monovalent Hep B vaccine through a universal vaccination strategy targeting all newborn infants regardless of their mother's sero status, as soon as possible after birth, preferably within the first 24 hours. Failing that, the Hep B BD should be administered at the earliest contact between the infant with a health care provider;
    a. Within the first 7 days, although effectiveness declines progressively in the days after birth;

b. After 7 days as a late birth dose can still be effective in preventing horizontal transmission and therefore remains beneficial.

ii. MOH should make efforts to promote mothers delivering within health facilities to facilitate BD administration within the first 24 hours after birth.

iii. Administration of the monovalent HBV vaccine should be followed by HBV vaccination as part of a pentavalent combination vaccine (HBV/DKTP) at 6, 10, and 14 weeks of age.

iv. A single dose of HBIG may be co-administered with Hep B BD to infants of highly viremic mothers only.

v. MoH should make efforts to increase antenatal attendance and screening of Mothers for Hep B. Those having an HBV DNA level higher than 2 × 10^5 IU/mL should be treated immediately with antiretroviral therapy to save the additional cost that comes with administration of the HBIG.

vi. The monovalent hepatitis B vaccine can be given with oral polio vaccine (OPV) and BCG at birth leveraging on the existing vaccination structures and opportunities.

vii. Although the birth dose is acceptable among pregnant women, MoH needs to continuously engage them as key stakeholders during planning to address concerns, in order to raise confidence, maximize uptake and strengthen HBV eradication efforts.

BACKGROUND

Ministry of Health requested Uganda National Immunisation Technical Advisory Group (UNITAG) to analyse updated data on Hepatitis B birth dose for possible revision of UNITAG recommendation reached in 2017.

Hepatitis B virus (HBV) is transmitted by exposure of mucosal membranes or non-intact skin to infected bodily fluids. Most infections are transmitted through perinatal or early childhood exposure. In 2016, member states of the World Health Assembly unanimously adopted a resolution declaring that viral hepatitis should be eliminated by 2030 targeting to reduce prevalence among children less than 5 years of age to less than 1% by 2020 and to less than 0.1% by 2030. According to the updated WHO Hepatitis B vaccine position paper, 2017, hepatitis B vaccination is recommended for all children globally, and all national programs are advised to include a monovalent Hepatitis B vaccine birth dose (HepB BD) to all infants irrespective of maternal HBV status, ideally within 24 hours to protect infants from mother to child transmission. However, WHO recognises that administration within 24 hours may not always be feasible hence also recommends a late birth dose at the first contact of the child with a health care provider at any time up to the time of the next dose of the primary schedule.

In 2017, UNITAG decided not to recommend the introduction of HepB BD due to lack of sufficient additional evidence on the efficacy of the birth dose in a setting with Hepatitis B given as part of Pentavalent at 6, 10 and 14 weeks in the African context. Also, UNITAG recommendation framework excluded vaccine efficacy/efficiency data from Asia citing significant differences in risk of vertical transmission due to significantly different HBsAg prevalence levels. A WHO 2017 Updated Global Hepatitis Report, however showed that although the number of HBsAg-positive individuals was highest in the WHO Western Pacific region (115 million, prevalence estimated as 6·2%; 95% UI 5·1–7·6) the seroprevalence levels were similar with the African region (60 million, prevalence estimate 6·1%; 4·6–8·5).The UNITAG working group on Hepatitis B has thus revisited this recommendation following evidence review on vaccine efficacy/efficiency data from preliminary literature on HepB BD, economic and programmatic considerations. The working group adopted the PICO framework (Annex 1) to review evidence on Hepatitis B birth dose focusing on efficacy/effectiveness and economic considerations, including efficacy and effectiveness data from Asia.

CONTEXT

Burden of Disease

Hepatitis is an inflammation of the liver that is caused by a variety of infectious viruses and noninfectious agents leading to a range of health problems, some of which can be fatal. In particular, types B and C lead to chronic disease in hundreds of millions of people and together are the most common cause of liver cirrhosis, liver cancer and viral hepatitis-related deaths.

In highly endemic areas, hepatitis B is most commonly spread from mother to child at birth (perinatal transmission) or through horizontal transmission (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life. The development of chronic infection is common in infants infected from their mothers or before the age of 5 years.

Transmission of the virus may also occur through the reuse of contaminated needles and syringes or sharp objects. Sexual transmission is more prevalent in unvaccinated persons with multiple sexual partners.

Globally in 2019, 1.5 million people were newly infected with hepatitis B virus. 296 million people were living with chronic hepatitis B virus infection, 6 million being children younger than five. Hepatitis B accounted for 820,000 people deaths.

Table 1: Prevalence of Hepatitis B by WHO regions, 2019

Hepatitis B

WHO region	Prevalence of hepatitis B infection among the general population (%), 2019	People living with hepatitis B infections among the general population, 2019	Prevalence of hepatitis B infection among children younger than five years (%), 2019	Children younger than five living with hepatitis B infections, 2019
African Region	7.5 [5.7–10.5]	82 300 000 [62 100 000–114 700 000]	2.5 [1.7–4.0]	4 300 000 [2 900 000–6 800 000]
Region of the Americas	0.5 [0.3–1.2]	5 400 000 [3 100 000–12 200 000]	0.1 [<0.1–0.2]	51 000 [26 000–130 000]
South-East Asia Region	3.0 [2.3–6.0]	60 500 000 [45 300 000–120 900 000]	0.4 [0.3–1.0]	640 000 [460 000–1 700 000]
European Region	1.5 [1.1–2.4]	13 600 000 [10 200 000–22 100 000]	0.3 [0.1–0.5]	150 000 [74 000–290 000]
Eastern Mediterranean Region	2.5 [2.0–3.3]	18 200 000 [14 400 000–23 800 000]	0.8 [0.5–1.1]	720 000 [420 000–950 000]
Western Pacific Region	5.9 [4.9–7.3]	115 700 000 [95 200 000–141 900 000]	0.3 [0.2–0.5]	360 000 [240 000–560 000]

Ref: WHO 2021. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Web Annex 1. Key data at a glance. http://apps.who.int/iris/bitstream/handle/10665/342808/9789240030985-eng.pdf

WHO Recommendation on Elimination of Hepatitis B

According to the Hepatitis B vaccines WHO Position paper, 2017, WHO recommends that HBV vaccination should be included in national childhood immunisation schedules either in a 3-dose schedule including monovalent birth dose, and second and third doses given with first and third doses of DPT vaccine, or a 4-dose schedule including monovalent birth dose, followed by 3 doses given with DPT at 4, 8 and 12 weeks of age. A first HepB BD is recommended within 24hrs after birth for prevention of vertical transmission. Whilst acknowledging the progressively waning effectiveness of the vaccine within the first 7 days, WHO notes that a late birth dose can still be effective in preventing horizontal transmission, hence recommends administration of a birth dose at first contact with healthcare providers up to the next dose of the primary schedule. WHO further recommends that Hepatitis B Immunoglobulin (HBIG) prophylaxis in conjunction with hepatitis B vaccination may be of additional benefit for new-born infants whose mothers are positive for Hepatitis B encoded Antigen (HBeAg+).

SUMMARY OF THE EVIDENCE

1. Is it possible to achieve the WHO elimination target without the BD?

Elimination of HBV cannot be achieved by 2030 in most geographical regions in the vaccination scenarios analysed in table 2 below. Modelled data on HBV vaccination coverage and estimated median year of elimination of HBV (year that HBsAg prevalence in 5-year-olds falls below 0.1%) on the 3 countries, including Uganda, Senegal and Namibia (the 3 countries were compared because of their similarity in pentavalent coverage rates) from WHO as of March 23, 2021 indicated that if all factors remain constant in terms of vaccination coverage, Namibia and Senegal will be reaching elimination by 2040 and 2050 respectively while Uganda, which has not introduced the birth dose will not reach elimination until after 2100. If the birth dose coverage rates are scaled up to 90%, the period to reach elimination will reduce to 2035 and 2040 respectively, while Uganda would be reaching elimination by 2048 since it has not introduced the birth dose yet. However, if Uganda introduces the birth dose by 2023 before 2030, it may reach elimination by 2049, yet, if introduction is delayed to later (2025 to 2040), the country may reach elimination by 2050.

Disruptions in vaccination efforts in 2020 due to COVID-19 will not delay HBV elimination but will result in an increase in HBV-related deaths in the 2020 birth cohort. Delays in the scale-up of timely HepB-BD coverage will result in both delays in the elimination of HBV and in substantial increases in HBV-related deaths in the following decades.

Table 2: Simulation of HBV vaccination coverage and estimated median year of elimination of HBV in African countries

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Hepatitis B vaccination coverage and estimated median year of elimination of HBV (year that HBsAg prevalence in 5 year olds falls below 0.1%) in Uganda, Senegal and Namibia

World Health Organization

	Hepatitis B infant vaccination (HepB3)		Hepatitis B birth dose vaccination (HepB BD)		Status quo HepB3 & HepB-BD	HepB-BD scale-up (≥90%)	Delayed HepB-BD scale-up (2023 to 2030)	Delayed HepB-BD scale-up (2025 to 2040)
	Year introduced	Coverage	Year introduced	Coverage				
Namibia	2009	87%*	2014	89%*	2040 (2036 to 2043)	2035 (2031 to 2041)	-	-
Senegal	2004	92%**	2016	92%**	2050 (2042 to 2055)	2044 (2038 to 2049)	-	-
Uganda	2002	89%**	-	-	after 2100 (2082 to after 2100)	2048 (2039 to 2053)	2049 (2039 to 2054)	2050 (2044 to 2058)

Sources: - Vaccination coverage: WHO immunization data portal (* 2019 data ** 2020 data)
- Estimated year of elimination: Margaret J et al. The impact of the timely birth-dose vaccine on the global elimination of hepatitis B. Nat Commun. 2021

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Ref: Slide from WHO presentation on Hepatitis B BD vaccination in WHO/ AFRO as of March 16, 2022.

2. Efficacy and Efficiency of Hepatitis B Birth Dose

i) Effectiveness of the birth dose

Evidence from Taiwan where HBV infection was hyperendemic and began a universal hepatitis B virus (HBV) vaccination program for infants in July 1984 showed that the seroprevalence of HBsAg decreased from 9.8% before the vaccination program to less than 1% by 25 years afterward. A study by Ni (2012) assessing HBV seromarkers including HBsAg and antibodies to HBsAg (anti-HBs) and HBcAg (anti-HBc) in 3,332 subjects younger than 30 years of age found that seropositive rates were lower among subjects born after the program in 2009 than for the baseline group in 1984.

Table 3: Comparison of seropositive rates between vaccinated and unvaccinated children younger than 30 years of age in Taiwan

Seromarkers	Seropositive rate (Born after the program in 2009)	Seropositive rate (Baseline group in 1984)
HBsAg	0.9%	10%
anti-HBs	55.9%	24.5%
anti-HBc	7.0%	28%

Following the completion of a 25-year follow-up of the universal infant HBV immunisation program which found a decrease in the seroprevalence of HBsAg among children from 9.8% before the vaccination program in 1984 to less than 1% by 25 years after the launch of universal HepB BD vaccination, another study by Ni (2016) found that only 0.5% of those born afterward were positive for HBsAg, compared with 6.7% of persons born before the universal HBV vaccination program. In this study, most persons positive for HBsAg younger than age 30 were born to mothers positive for HBsAg.

Table 4: Comparison of seropositive rates between vaccinated and unvaccinated children after completion of a 25-year follow-up of the universal infant HBV immunisation program in Taiwan

Seromarkers	Seroprevalence rate (vaccinated)	Seroprevalence rate (unvaccinated)
HBsAg	0.5%	6.7%
anti-HBs	47.4%	69.4%
anti-HBc	4.5%	44.1%

ii) Is there additional efficacy with inclusion of a birth dose compared to using only the current 3 dose schedule as currently practiced in Uganda?

A comparative review by Anderson (2018) of prenatal maternal hepatitis B virus (HBV) screening and different infant vaccination strategies compared rates of HBV infection and found that the strategy that included HBV vaccine at birth plus pentavalent vaccine prevented more cases than the strategy that provided a pentavalent vaccine (DKTP) at age 6 weeks.

Table 5: Comparison of HBV infection rates with among the different birth dose vaccination strategies

Vaccination strategy	HBV infection rate
Universal vaccination with a pentavalent vaccine (DKTP) at age 6 weeks	813/ 10,000 children vaccinated
Universal HBV vaccine at birth plus pentavalent vaccine	429/10,000 children vaccinated
Maternal prenatal HBV screening and targeted HBV vaccine at birth for all exposed infants plus pentavalent vaccine	451/ 10,000 children vaccinated
Neither maternal screening nor infant vaccination	2,360/ 10,000 children

iii) Comparison of efficacy of HepB BD when combined with HBIG vs BD without HBIG

A systematic review of randomised controlled trials (RCTs) by Chen (2017) comparing different measures among newborns and pregnant women with HBV infection found that while the combination of immunoglobulin with vaccine is superior to vaccine alone in newborns starting at birth, prenatal HBIG administration and antiviral therapy offer further advantages over the passive-active immunoprophylaxis for infants of highly viremic (HBV DNA level higher than 2 × 10^5 IU/mL) mothers.

Table 6: Effectiveness of HBVac and HBIG among newborns

Treatment groups	**Relative Risk (95% CI)**
HBVac alone at birth	0.32
HBIG+HBVac	0.37
Prenatal HBIG/HBIG+HBVac	0.31
Prenatal AVT/HBIG+HBVac	0.47

Another systematic review of randomised clinical trials by Lee (2006) evaluating the effects of HBV vaccine alone and HBV vaccine with HBIG in newborn infants of mothers positive for HBsAg found that the vaccine plus HBIG had a better risk reduction compared with vaccine alone.

Table 7: Evaluation of effectiveness of HBIG in high-risk newborn infants

Treatment groups	**Relative Risk (95% CI)**
HBVac alone at birth	0.28
HBIG+HBVac in high-risk newborns	0.54

Lo (1985) in Taiwan found that at 6 months of age, the efficacy of HBV vaccination in preventing HBV infection among high-risk infants was highest among infants who received HBV vaccine plus HBIG at birth and at one month old compared to the other treatments as shown in the table below.

Table 8: Evaluation of HBIG efficacy in high-risk newborn infants in Taiwan

Treatment groups	**Efficacy Rate**
HBVac + HBIG at birth and at one month	94.1%
HBVac + HBIG at birth alone	87.7%
HBVac alone at birth	73.7%

A study by Assateerawatt (1993) evaluating the immunogenicity and the protective efficacy of hepatitis B vaccine, with or without passive immunization with HBIG in high-risk neonates born from HBsAg and HBeAg positive mothers found the protective efficacy rates (PER) in neonates to be 95.5% (in the HBVac + HBIG at birth, 1, 2 and 12 months of age) and 89.8% (in the group that received only the vaccine at one year).

Table 9: Comparison of protective efficacy and prevalence rates among different HBV vaccination groups with or without HBIG

Treatment Groups	Intervention	No. of neonates	PER	Prevalence rate (HBsAg) at one year of age
A	HBVac + HBIG at birth, 1, 2 and 12 months of age	26	95.5%	3.8%
B	HBVac alone at one year	23	89.8%	8.7%
C	No immunization (control group) - high risk infants	40		85%

iv) Comparison of efficacy of administering multiple HBIG injections vs only one HBIG injection at birth

In Asia, a study by IP (1989) found that high risk infants born to HBeAg carrier mothers who received HBV vaccine within 1 hour of birth, and at 1, 2, 6 months with 7 monthly HBIG injections developed a persistent carrier state that was significantly less frequent than in the other treatment groups as shown in the table below. In this study, no serious side-effects were observed from the interventions, even in the babies with intra-uterine infections who had received HBIg and HB-vaccine at birth.

Table 10: Comparison of prevalence of HBV among different treatment groups

Intervention schedules	Persistent carrier state
1. (HBVac within 1hr of birth, and at 1,2,6 months) + 7 monthly HBIG injections	2.9%
2. HBVac within 1hr of birth, and at 1, 2, 6 months) + only 1 HBIG injection at birth	6.8%
3. (HBVac within 1hr of birth, and at 1, 2, 6 months) only without HBIG	21.0%
4. Placebos for both vaccine and HBIG	73.2%

v) Effectiveness of universal vs targeted infant birth dose vaccination programs

A systematic review and meta-analysis by Whitford (2018) of the long-term impact of infant vaccination on the prevalence of hepatitis B virus (HBV) infection at population level of cohorts aged ≥15 years mostly from China who were exposed to universal or targeted infant HBV immunisation programs found that adolescents and adults in birth cohorts who were offered universal infant vaccination had a lower prevalence with a better prevalence and risk reduction compared with targeted vaccination cohorts as shown in the table below.

Table 11: Comparison of relative prevalence and risk reduction rates in universal/ targeted vaccination strategies

Vaccination strategy	Relative prevalence	Prevalence reduction rates	Risk reduction rates
Universal infant vaccination	0.24	76%	77%
Targeted infant vaccination	0.32	68%	67%

3. Cost Effectiveness of the HepB vaccine at birth

i) Is introduction of HepB BD in a routine immunisation program that had 3 dose schedule cost effective?

Evidence from an evaluation of the outcome of immunisation strategies to HBV transmission indicates that vaccination at birth is and routine vaccination of infants in successive birth cohorts to prevent HBV transmission is cost-effective over a wide range of assumptions. Results from a study by Margolis (1995) determining the incremental effects of different hepatitis B immunization strategies in a birth cohort showed that prevention of perinatal infection and routine infant vaccination would lower the 4.8% lifetime risk of HBV infection by at least 68%, compared with a 45% reduction for adolescent vaccination. Although each strategy was found to be cost saving, routine vaccination was not cost saving with respect to direct medical costs as indicated in the table below.

Table 12: Comparison of incremental effects of different HepB immunization strategies in a birth cohort

Vaccination strategy	Estimated cost per year of life saved
HBVac at birth	$164
Routine infant HBVac	$1,522
Routine adolescent HBVac	$3,730

An economic evaluation by Memirie (2020) of the incremental cost-effectiveness of adding HepB-BD vaccine to the three-dose regimen given to infants at 6, 10 and 14 weeks after birth in Ethiopia, where prevalence of HBV among pregnant women is 5%, found that introducing a birth dose of HBV vaccine in Ethiopia would likely be highly cost-effective as the estimated ICER compared very favorably with a willingness-to-pay level of 0.31 times gross domestic product per capita (about USD 240 in 2018) in Ethiopia.

Table 13: Cost, effectiveness and incremental cost effectiveness ratio (ICER) of an additional birth dose of HB vaccine

Strategy	Cost (US$)	Incremental costs	Effects (DALYs averted)	Incremental effects (DALYs averted)	ICER
Without birth dose	4.0243		0.001417		
With birth dose	4.3538	0.3295	0.004117	0.00300	110

In addition, a study by Klingler (2012) analysing the costs and effects associated with avoiding perinatal transmission of HBV through a birth dose vaccination in addition to the existing vaccination schedule in administered at 6-10-14 weeks in Mozambique found an incremental cost-effectiveness ratio (ICER) for the additional birth dose of 250.95 US$ per disability-adjusted life years (DALYs) averted. Assuming a willingness-to-pay threshold of 441 US$, which was the GDP per capita for Mozambique in 2008, the findings show the additional birth dose to be highly cost-effective. However, one-way sensitivity analysis reveals that the outcome changes with parameter variation.

ii) Is it more cost-saving to test and treat infected mothers and vaccinate only children born to infected mothers or to vaccinate all infants irrespective of the mother's status?

Tilson (2007) conducted an economic evaluation of a universal infant HepB vaccination programme, using a six-component vaccine, compared with the selective strategy of vaccinating high-risk infants with a monovalent hepatitis B vaccine. Assuming an incidence of acute HBV infection in Ireland of 8.4 per 100,000 population, the incremental cost effectiveness ratio ranged from €10,992/life years gained (LYG) to €67 200/LYG, at the lowest and highest price estimates for the six-component vaccine, respectively. The cost effectiveness of universal versus selective hepatitis B vaccination was sensitive to the risk of acute HBV infection, the cost of the universal infant vaccination programme and the discount rate. Hence, at a cost of €29.00 per dose of the six-component vaccine, universal infant hepatitis B vaccination was cost effective at €37 018/LYG.

Table 14: Incremental cost effectiveness ratio (ICER) for the base case scenario and one-way sensitivity analysis

Strategy	Cost (€)	Incremental cost (€)	Effect (LYG)	Incremental effect	ICER (€/LYG)
ICER for base case scenario					
Selective	860 000		2 593 413.00		
Universal	3 340 000	2 480 000	2 593 479.99	66.99	37 018

Vimolket (2005) evaluated the cost-effectiveness of four infant different HBV vaccination strategies aimed at protecting the Thai population against HBV infection and concluded that although there is no socially acceptable threshold value for cost per case prevented to guide decisions on funding health care interventions, strategy 3 was the most preferred strategy as shown in the table below.

Table 15: Comparison of Cost effectiveness and incremental cost effectiveness of four strategies for HBV prevention.

No.	Vaccination strategy	Expected cost	Expected case prevented	Cost effectiveness per case prevented (baht)	Incremental cost effectiveness
1	Screening for HBsAg, and vaccination	29,250	99.90	292.79	95,000
2	Screening for HBsAg, then HBeAg, and vaccination	26,400	99.87	264.34	20,000
3	Universal vaccination of all neonates	15,000	99.30	151.05	6,521
4	No vaccination	0	97.00	0	

The same study estimated the annual cost of each strategy for 800,000 newborns and compared the incremental costs and cases prevented for each vaccination strategy.

Table 16: Comparison of incremental costs and estimated annual costs of different vaccination strategies for 800,000 newborns.

No.	Vaccination strategy	Annual cost	Incremental cost	Incremental cases prevented
1	Screening for HBsAg, and vaccination	234,000,000	22,800,000	240
2	Screening for HBsAg, then HBeAg, and vaccination	211,200,000	91,200,000	4,560
3	Universal vaccination of all neonates	120,000	120,000,000	18,400
4	No vaccination	0		

In Vietnam, a study by Tu (2012) aimed at identifying the cost-effectiveness affordability levels for a newborn universal vaccination program against hepatitis B virus (HBV) found that universal newborn HBV vaccination is highly cost-effective. The study simulated a Vietnamese birth cohort using 1,639,000 newborns in 2002 and estimated the ICERs for QALYs gained following universal newborn HBV vaccination and found that newborn universal HBV vaccination reduced the carrier rate by 58% at a cost of US $42 per carrier averted. From the payer's perspective, incremental cost-effectiveness ratio per QALY gained was US $3.77, much lower than the 2002 per-capita gross domestic product of US $440. Vaccination would potentially be affordable starting at a US $2.1 million budget. At the cost-effectiveness threshold of US $3.77 per QALY and an annual budget of US $5.9 million, the probability that vaccination would be both cost-effective and affordable was 21%.

In Africa, a field assessment and economic analysis of the HepB-BD strategy in São Tomé and Príncipe (STP) by Hagan (2019) using a selective HepB-BD vaccination strategy targeting infants born to mothers who test positive for HBsAg found that timely HepB-BD to eligible newborns was a high priority, although timeliness of HepB-BD was not monitored. Compared with the existing selective vaccination strategy, universal HepB-BD would result in a 19% decrease in chronic HBV infections per year at overall cost savings of approximately 44% (savings of USD 5,441 each year). The study estimated an incremental

cost-effectiveness ration (ICER) of USD 5,012 saved per HBV-associated death averted hence concluded that expansion to universal newborn HepB-BD without maternal screening is feasible and could result in cost savings if actual implementation costs and effectiveness fall within the ranges modeled.

ECONOMIC CONSIDERATIONS

1. Availability of global supply of the monovalent HepB vaccine

There are several HBV vaccine products currently available for pediatric populations in sub–Saharan Africa (SSA); all containing 5 to 10 µg of HBsAg in a 0.5-mL standard-volume dose. HBV vaccination has been supported by Gavi, the Vaccine Alliance, since 2000. Gavi recognizes HBV birth dose as a high-impact vaccination that should be included in SSA vaccination platforms hence has listed HepB BD has on the GAVI Vaccine Investment strategy for the 2021-2025 strategic period as one of the six vaccine candidates for endemic disease prevention. This means that subject to availability of funding for the 2021–2025 strategic period and alignment with the final parameters of Gavi's next strategy, from 2021 Gavi would make available support for hepatitis B birth dose in addition to the DKTP-containing booster vaccines to countries through the GAVI vaccine support programmes. (https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy)

i) Current cost of Hepatitis B birth dose in Uganda

Table 17: Awarded price per dose (US$) per product per supplier per calendar year based on a multi-year supply agreement

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Presentation	Supplier Name	Hepatitis B																		
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
HepB vaccine in a single dose presentation	Crucell Switzerland				$0.2700	$0.2700	$0.2700													
	LG Life Sciences (South Korea)				$0.4000	$0.4000	$0.4000	$0.4000	$0.4000	$0.4000	$0.3800	$0.3800	$0.3800	$0.4200	$0.4200	$0.4200	$0.4200	$0.6000	$0.6000	$0.6000
	Serum Institute of India						$0.2300							$0.2000	$0.2000	$0.2000	$0.2900	$0.4900	$0.4900	$0.4900
	Shantha Biotechnics (India)	$0.4100	$0.4100	$0.4100	$0.4100															
HepB vaccine in a two dose presentation	Crucell Switzerland				$0.2400	$0.2400	$0.2400													
	LG Life Sciences (South Korea)	$0.3700	$0.3600	$0.2400	$0.2400															
	Shantha Biotechnics (India)							$0.2900	$0.2900	$0.2900										
HepB vaccine in a six dose presentation	Merck & Co. (USA)	$0.6100	$0.6100-$0.6233	$0.6233																
	Shantha Biotechnics (India)							$0.3400	$0.3400	$0.3400										
HepB vaccine in a ten dose presentation	Crucell Switzerland	$0.3200	$0.3200-$0.3500	$0.3200-$0.3500	$0.2100	$0.2100	$0.2100				$0.1600	$0.1600	$0.1600							
	Heber Biotec (Cuba)	$0.4800	$0.4400	$0.2500-$0.3900	$0.2200-$0.2500	$0.2200	$0.2200													
	LG Life Sciences (South Korea)	$0.2700	$0.2500	$0.1850-$0.2400	$0.1850	$0.1800-$0.1850	$0.1750-$0.1850	$0.1750	$0.1750	$0.1750	$0.1730	$0.1730	$0.1730	$0.1750	$0.1750	$0.1750	$0.2500	$0.2500	$0.2500	$0.2500
	Panacea Biotec (India)				$0.2041	$0.2041	$0.2041													
	Serum Institute of India			$0.2100	$0.2100-$0.2190	$0.2100-$0.2290	$0.2100	$0.2100	$0.2100	$0.2100				$0.2000	$0.2000	$0.2000	$0.2400	$0.2400	$0.2400	$0.2400
	Shantha Biotechnics (India)	$0.2300	$0.2300	$0.2300	$0.2300-$0.2370	$0.2300-$0.2370	$0.2300-$0.2380	$0.2300												
HepB vaccine Adult in a single dose presentation	Serum Institute of India														$0.3000	$0.3000	$0.7000	$0.7000	$0.7000	$0.7000
HepB vaccine Adult in a ten dose presentation	Serum Institute of India														$0.3000	$0.3000	$0.3000	$0.3000	$0.3000	$0.3000

Data shows the awarded price per dose (in US$) per product per supplier per calendar year, based on a multi year supply agreement.
Data shows most prices with CPT incoterms from 2001 - 2003; change to FCA incoterms from 2004-2006 onwards.
Where agreements include a range of prices during a calendar year period or for different countries or groups of countries, prices are shown as a range.
Last updated 27th May 2021.

Ref: Hepatitis B (HepB) vaccine price data: Awarded prices paid per dose of Hepatitis B https://www.unicef.org/supply/documents/hepatitis-b-hepb-vaccine-price-data

ii) Cost Estimates for Introduction and Routinization of Hepatitis B BD in Uganda

According to the WHO costing of immunisation in Uganda as of 2017, vaccine costs (price of the antigen) and the new vaccine introduction costs which included training, injections and supplies, social mobilisation and advocacy, planning and coordination, program management, supervision, surveillance, cold chain (maintenance & equipment), as well as costs pertaining to vaccine distribution and collection were modelled to estimate costs for introducing a new vaccine in Uganda in any given year. While vaccine costs factored in an 8% increment for handling and freight charges, the costs were further inflated at 2% (the usual inflation rate used for vaccine prices) as shown in the table below.

Table 18: Total cost for introduction of Hep at birth in a given year

Hep Birth Dose	2020/21 (US$)	2021/22 (US$)	2022/23 US$	2023/24 US$	2024/25 US$	2025/26 US$
Vaccine Costs	348,179	365,796	384,306	403,752	424,181	445,645
New vaccine introduction costs	2,596,167	3,037,144	3,357,186	3,432,566	3,765,842	4,107,834
Total introduction costs	2,944,345	3,402,941	3,741,492	3,836,318	4,190,023	4,553,479

Moreover, introducing HepB BD was estimated to be cheaper compared to other vaccine introductions such as yellow fever to the whole population which was estimated to attract the highest costs followed by the introduction of MR, then Td to pregnant women and then yellow fever to surviving infants. It is important to note that introduction of Men A, HepB BD and Td to surviving infants appears to attract almost similar costs (Annex 2).

iii) Cost Estimates for Routine Service Delivery of New Vaccines

WHO further estimated the total cost for introducing and sustaining HepB BD considering vaccine costs (price of the antigen) and routine service delivery (RSD) costs including training, injections and safety supplies, social mobilisation and advocacy, planning and coordination, program management, supervision, waste management, surveillance, cold chain (maintenance & equipment), as well as costs pertaining to vaccine distribution and collection over the years as shown in the table below.

Table 19: Total cost for routine service delivery (RSD) of Hep at birth in a given year

Hep Birth	2020/21 (US$)	2021/22 (US$)	2022/23 US$	2023/24 US$	2024/25US$	2025/26 US$
Vaccine Costs	348,179	365,796	384,306	403,752	424,181	445,645
RSD costs	1,916,633	1,654,160	1,688,296	1,722,991	1,774,680	1,827,921
Total RSD Costs for Hep BD	2,264,812	2,019,956	2,072,601	2,126,742	2,198,862	2,273,566

Compared to other vaccines' routine service delivery costs, HepB BD was estimated to be cheaper than the other vaccines such as yellow fever to the whole population which is estimated to attract the highest costs (Annex 3).

Cost of HBIG ranges between $17 and $19 (https://www.paho.org/en/file/64311/download?token=1vIZVflB).

PROGRAMMATIC CONSIDERATIONS

1. Thermostability of the vaccine and cold chain space requirements

According to the Hepatitis B vaccine: WHO Position paper (2017), HBV monovalent vaccine is relatively heat stable. In vivo and in vitro studies provide some indication that HBV vaccine may retain its potency in the absence of continuous cold-chain transport and storage. Although most HBV vaccines have a long shelf life (up to 4 years), current cold-chain requirements for transportation and storage of vaccine are +2°C to +8°C which makes it well suited for Uganda's cold chain capacity. However, specific vaccine-storage details are available in the product package insert.

2. Performance of other Birth Dose vaccines in Uganda

According to programmatic data on coverage of other antigens given at birth from MoH as of March 23, 2022, Polio zero coverage rates had increased steadily from 68% in 2017 to 77% in 2021. In addition, BCG coverage rates had also increased steadily from 85% to 91% in 2020 although 2021 saw a drop-in coverage rate to 83% believed to have been caused by the COVID-19 pandemic and its response which created additional barriers to scaling up timely coverage, both due to disruptions in healthcare facilities which have affected routine immunization and facility-based births and indirectly due to changes in priorities and funding. This trend indicates that introduction and routinisation of HepB BD is feasible and that there are a number of opportunities to leverage the introduction on.

3. Proportion of health facility deliveries in Uganda

According to data from MoH as of March 23, 2022, the proportion of institutional deliveries had increased by 6% from 60.7% (1,186,224/1,954,938) in FY19/20 to 66.0% (1,331,388/2,016,805) in FY20/21. From the same data, over 90% (1,894,874 / 2,079,180) of the estimated pregnant women attended antenantal care (ANC) 1st Visit in FY20/21 while 34.5% (654,054 /1,894,874) of the estimated pregnant women attended ANC during their 1st Trimester in FY20/21. Further to note, in the same financial year, 51.5% (1,070,330/2,079,180) of pregnant women attended the 4th ANC Visit.

4. HBV Testing Strategies in Pregnant Women and Infants in Uganda

All pregnant women that go to a health facility are tested for HBsAg, alongside HIV and syphilis. According to MOH PMTCT data on Hepatitis B, HIV and Syphillis in Uganda as of March 23, 2022, pregnant women found positive after rapid testing are sent to the laboratory for a viral load test which results are picked from the facility within 7 days of testing. While mothers found to have a viral load less than 200,000 IU/ml are treated like the normal HepB positive patients, those found with a viral load greater than 200,000 IU/ml are given antivirals for purposes of PMTCT. Moreover, data showing the percentage of pregnant women tested for HIV, Syphilis and HepB from FY17/18 – FY20/21 indicated that in

FY20/21, 93.3% (1,768,012 1,894,874) were tested for HIV, 88.0% (1,667,662/1,894,874) tested for Syphilis, and only 16.7% (315,928//1,894,874) were tested for Hepatitis B. It was noted that documentation of HepB only started in January 2020, coinciding with change in national health management information system (HMIS). It was also noted that not all women who test positive for Hepatitis B give birth at that same facility hence the possible loss of follow up on high-risk babies.

5. Acceptability of the birth dose to the target population in Uganda

A study by Mutyoba (2021) exploring perceptions, barriers and preferences of pregnant women regarding HBV and the HBV birth dose vaccination in Uganda conducted eight focus groups discussions (FGDs) among 70 pregnant women, stratified by rural-urban residence, age and education level, using a structured focus group discussion guide to explore birth dose awareness, perceptions, barriers and preferences and found that perceptions related to HBV and liver cancer causes and prevention were diverse; most FGD participants did not perceive illnesses as distinctly different. Older women-groups, both urban and rural, had never heard about HBV, but were aware of liver cancer, viewing the disease as fatal. No FGD participants were aware of HBV birth dose. Concerns included vaccine safety, its availability to women who deliver outside the health system and mistrust in health-care worker (HCWs) when handling newborns. Rural-dwelling groups perceived absence of HBV services, while FGDs with young participants believed vaccine side-effects hampered birth dose planning. Most women-groups preferred (i) oral to injectable vaccines; (ii) receiving birth dose education during antenatal, to media-based education; (iii) that newborns receive the birth dose immediately after delivery in the mother's presence.

6. Ministry of Health strategy for introduction of HepB BD in Routine Immunisation (RI)

According to a presentation by the MOH on prevention of mother-to-child transmission (PMTCT) of HepB BD, there are a number of opportunities the expanded program for immunization (EPI) hopes explore to introduce HepB BD in RI. These include but are not limited to; during pregnancy where >90% of pregnant women attend (ANC) hence messages on immunisation would be shared at all ANC visits. In addition, the immediate period following delivery was reported as an opportunity where essential newborn care package (Vit K, eye care and immunisation birth doses-OPV, BCG and HepB) is shared. The period during postnatal care was identified as an opportunity to introduce HepB BD as new mothers contact the health facility within 24hrs of birth to implement post-natal care guidelines and recommendations. Also, the fact that PMTCT interventions provide an opportunity to screen all expectant mothers and provide treatment to those with high viral load can be done was an opportunity identified by the program.

However, the program highlighted a number of common barriers to new vaccine introduction, including limited political will, insufficient funding to facilitate both vaccine procurement and operational costs, births taking place outside health facilities, timely vaccine delivery, access to vaccine deliveries outside facilities, vaccine storage/cold chain limitations, lack/insufficient local disease burden data, and limited UNITAG support for recommendations. Indeed, findings from a study by Hagan (2019) assessing the knowledge, attitudes, and practices surrounding HepB-BD implementation among healthcare workers in five African countries, including Botswana, the Gambia, Namibia, Nigeria, and São Tomé and Príncipe (STP) between August 2015 and November 2016 demonstrated how staff perceptions and lack of outreach programs to reach babies born outside health facilities with essential services are barriers for implementing timely delivery of HepB-BD vaccine. The study noted that addressing these challenges may accelerate HepB-BD implementation in Africa.

CONCLUSION

Based on the preceding evidence, the Hepatitis B Working Group concluded that Hepatitis B Birth Dose should be introduced in Uganda because of the following reasons:

i) Hepatitis B is a disease of significant concern in Uganda, affecting mostly children and causing serious illness and death later in life, with no effective cure. Low ANC attendance and hence low HBV testing rates means low levels of diagnosis and high risk of vertical transmission.
ii) HepB BD when administered within the first 24 hours significantly reduces vertical HBV transmission especially for infants born to highly viremic mothers and has some value in preventing horizontal transmission when administered before 4 weeks of age.
iii) Addition of HBIG slightly increases vaccine effectiveness though the cost/ ml is relatively expensive.
iv) Universal HepB vaccination at birth is not only cost effective against HBV infection and reducing long-term sequelae but is also a more cost-saving primary preventive strategy than the targeted vaccination hence a worthwhile investment of public funds.
v) Introduction and routinisation of HepB BD is relatively cheaper as compared with many other new vaccines proposed for introduction in Uganda's immunisation program.
vi) Addition of HepB BD to UNEPI will enable Uganda to achieve WHO elimination targets much earlier than when using the current 3 dose schedule alone

RECOMMENDATIONS

Following the above conclusions, the Working Group made the following recommendations:

i. MOH/UNEPI should introduce Hepatitis B BD into the routine immunisation program using monovalent Hep B vaccine through a universal vaccination strategy targeting all newborn infants regardless of their mother's sero status, as soon as possible after birth, preferably within the first 24 hours. Failing that, the HepB BD should be administered at the earliest contact between the infant with a health care provider either within the first 7 days (although effectiveness declines progressively in the days after birth) or after 7 days as a late birth dose can still be effective in preventing horizontal transmission and therefore remains beneficial.
ii. MOH should make efforts to promote deliveries within health facilities to facilitate BD administration within the first 24 hours after birth.
iii. Administration of the monovalent HBV vaccine should be followed by HBV vaccination as part of a pentavalent combination vaccine (HBV/DKTP) at 6, 10, and 14 weeks of age.
iv. A single dose of HBIG may be co-administered with Hep B BD to infants of highly viremic mothers only.
v. MoH should make efforts to increase antenatal attendance and screening of Mothers for Hep B. Those having an HBV DNA level higher than 2 × 10^5 IU/mL should be treated immediately with antiretroviral therapy to save the additional cost that comes with administration of the HBIG.
vi. The monovalent hepatitis B vaccine can be given with oral polio vaccine (OPV) and BCG at birth leveraging on the existing vaccination structures and opportunities.

vii. Although the birth dose is acceptable among pregnant women, MoH needs to continuously engage them as key stakeholders during planning to address concerns, in order to raise confidence, maximize uptake and strengthen HBV eradication efforts.

ANNEXES

Annex1: UNITAG PICO framework for evidence review

PICO	Narrative
Population (P)	Infants within 24 hours after birth
	Infants from 24 hours to 7 days after birth for prevention of vertical transmission consideration
	Infants from birth until 6 weeks for prevention of horizontal transmission consideration
Intervention (I)	Hep B birth dose to all infants
	Hep B birth dose to babies born to mothers with a very high (>200,000 IU/ml) viral load/ HBeAg+
	Hep B birth dose with or without HepB immunoglobulin to the baby
Comparator (C)	No Hep B birth dose but Hep B vaccine given with Pentavalent at 6, 10 and 14 weeks
Outcomes (O)	Elimination of Hepatis B equivalent to 0.1% prevalence of HBsAg among children
	Application of Hep B birth dose strategy is cost effective

Annex 2: Summary of total costs for introduction of new vaccines

Antigen	2020/21 (US$)	2021/22 (US$)	2022/23 US$	2023/24 US$	2024/25 US$	2025/26 US$
Yellow Fever (Whole population)	29,773,234	31,691,777	33,516,769	35,086,969	37,074,742	39,152,255
MR (9 and 15 months)	6,964,733	7,903,553	8,618,563	8,875,691	9,627,061	10,401,019
MR (9 months)	3,482,367	3,951,777	4,309,282	4,437,846	4,813,530	5,200,509
Td (pregnant women)	3,948,182	4,586,465	5,054,160	5,176,068	5,664,002	6,165,087
Yellow Fever (12 months)	3,338,448	3,800,575	4,150,430	4,270,956	4,638,196	5,016,303
Men A	3,282,883	3,742,199	4,089,099	4,206,522	4,570,502	4,945,184

Hep Birth	2,944,345	3,402,941	3,741,492	3,836,318	4,190,023	4,553,479
Td (surviving infants)	2,639,919	3,066,701	3,379,421	3,460,934	3,787,187	4,122,233
Td (7-year-olds)	2,540,564	2,951,285	3,252,236	3,330,681	3,644,655	3,967,092
Td (10-year-olds)	2,492,538	2,895,494	3,190,756	3,267,718	3,575,758	3,892,099

Annex 3: Summary of total costs for routine service delivery of new vaccines

Antigen	2020/21 (US$)	2021/22 (US$)	2022/23 US$	2023/24 US$	2024/25US$	2025/26 US$
Yellow Fever (Whole population)	80,115,539	74,505,955	76,871,984	79,324,653	82,333,085	85,463,582
MR (9 and 15 months)	5,677,696	5,284,180	5,457,684	5,637,756	5,855,801	6,082,863
MR (9 months)	2,838,848	2,642,090	2,728,842	2,818,878	2,927,901	3,041,431
Td (pregnant women)	2,985,756	2,627,737	2,690,502	2,754,789	2,843,912	2,936,036
Yellow Fever (12 months)	2,694,929	2,490,889	2,569,990	2,651,988	2,752,566	2,857,225
Men A	2,639,364	2,432,512	2,508,660	2,587,554	2,684,872	2,786,106
Hep Birth	2,264,812	2,019,956	2,072,601	2,126,742	2,198,862	2,273,566
Td (surviving infants)	1,996,400	1,757,014	1,798,982	1,841,966	1,901,557	1,963,155
Td (7 year olds_	1,921,265	1,690,889	1,731,276	1,772,643	1,829,992	1,889,271
Td (10 year olds)	1,884,946	1,658,924	1,698,549	1,739,134	1,795,398	1,853,557

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