Introduction of Hepatitis B Birth Dose Vaccination in Africa:

A Toolkit for National Immunization Technical Advisory Groups 2022

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Abbreviations

alanine aminotransferase
antibody against hepatitis B core antigen
antibody against hepatitis B e antigen
antibody against hepatitis B surface antigen
aspartate aminotransferase
Coalition for Global Hepatitis Elimination
compact pre-filled auto-disable device
disability-adjusted life year
deoxyribonucleic acid
diphtheria, tetanus, pertussis
Gross Domestic Product
Global Health Sector Strategy
hepatitis B e antigen
hepatitis B immune globulin
hepatitis B surface antigen
hepatitis B virus
hepatitis B virus deoxyribonucleic acid
hepatocellular carcinoma
hepatitis B vaccine
three doses of hepatitis B infant vaccine
hepatitis B birth dose
human immunodeficiency virus
incremental cost-effectiveness ratio
immunoglobulin G
immunoglobulin M
milli-international units per milliliter
mother-to-child transmission
National Immunization Technical Advisory Group
recombinant deoxyribonucleic acid
The Task Force for Global Health
units per liter
upper limit of normal
United Nations
United States Centers for Disease Control and Prevention
World Health Organization
World Health Organization Regional Office for Africa

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Summary

Chronic hepatitis B virus (HBV) infection is a leading cause of liver cancer and liver-related mortality worldwide. With the availability and improved access to safe and effective vaccines, diagnostic testing, and antiviral therapies, the World Health Organization (WHO) has set goals for the elimination of HBV as a public health threat, including elimination of mother-to-child transmission (MTCT) of HBV, by 2030. Most areas of the world are progressing towards HBV elimination by improving coverage of infant hepatitis B vaccination beginning with a timely hepatitis B birth dose (HepB-BD) vaccine in the first 24 hours of life. Achieving ≥90% HepB-BD coverage by 2030 can prevent 41 million chronic infections globally. High coverage with a complete series of infant hepatitis B vaccination, beginning with a birth dose and followed by at least 2 additional doses, can prevent 710,000 HBV-related deaths globally in the 2020 to 2030 birth cohorts; 550,000 (78%) of the prevented deaths would be in WHO African region countries.

In 2019, the WHO African region had the highest prevalence of chronic HBV infection estimated at 2.5% among children <5 years of age—and it is the only region that has yet to meet WHO's global interim goal to reduce chronic HBV prevalence to <1% among children <5 years of age by 2020. Of the 6 million children aged <5 years estimated to have chronic HBV infection globally, 4.3 million were living in countries in the WHO African region.

Children infected with HBV during birth have a 90% risk of developing chronic HBV infection, and they carry into adulthood a one in four risk of premature death from HBV-related liver disease, including liver cancer. However, in 2021, only 14 of 47 African countries had introduced routine HepB-BD vaccination, and only 17% of newborns in Africa received a timely HepB-BD vaccination. Preventing chronic HBV infection and associated deaths in Africa requires improvements in HepB-BD coverage.

To help African countries develop national recommendations for HepB-BD vaccination, the Coalition for Global Hepatitis Elimination, in collaboration with the US Centers for Disease Control and Prevention, the World Health Organization Regional Office for Africa (WHO AFRO), and other partners, prepared this toolkit to bring together essential information that can be used to guide national immunization technical advisory groups (NITAGs) in their decision-making process for HepB-BD introduction.

The information presented in this toolkit covers five key areas. First is a description of hepatitis B disease and its natural history, the risk of developing chronic disease by age at infection, and the modes of HBV transmission in children. Second is a review of the global burden of HBV infection. In the third and fourth areas, the toolkit summarizes data demonstrating the safety of HepB-BD vaccination and its effectiveness in preventing MTCT of HBV and then presents current global HepB-BD vaccination guidelines and hepatitis B elimination goals. In the final section, the toolkit reviews the acceptability, costs, and cost-effectiveness of HepB-BD vaccination and provides additional resources to assist with the development of HepB-BD introduction and implementation plans.

Introduction

Hepatitis B vaccination is the most effective strategy available to prevent transmission of hepatitis B virus (HBV)(1). This bloodborne infection often persists as a chronic illness, leading over time to progressive liver damage, severe scarring (cirrhosis), primary liver cancer, and death (2). Newborns infected with HBV through mother-to-child transmission (MTCT) have the greatest risk of chronic HBV infection, which develops in almost all (90%) children infected through this route (1,3). Of children with chronic infection, one in four are at risk for HBV-related liver disease and premature death (4). The World Health Organization (WHO) recommends routine hepatitis B vaccination for all infants, beginning with a hepatitis B birth dose vaccine (HepB-BD) given within 24 hours of birth, followed by 2 or 3 additional doses within the first year of life (1).

In 2016, WHO set a goal to eliminate hepatitis B as a public health problem and eliminate MTCT of HBV by 2030 (5). To achieve this goal, countries need to attain at least 90% coverage with a timely HepB-BD vaccine and 3 doses of hepatitis B infant vaccine (HepB3) (5). Rates of HepB-BD vaccination have progressively increased in most areas of the world, rising in 2021 to over 90% in high-burden countries, including China, and to 42% globally (6). In 2020, with more children receiving HepB-BD vaccination, the estimated global prevalence of chronic HBV infection among children <5 years of age declined to <1% (7,8). In contrast, HBV prevalence is more than two and a half fold greater among children in Africa than among those living elsewhere, and in 2021 only 17% of newborns in Africa received timely HepB-BD vaccine (6,8). Given an estimated 2.5% prevalence of chronic HBV infection among African children aged <5 years, about 4 million children in this region are living with chronic infection (8). Meeting WHO's target of \geq 90% HepB-BD vaccination coverage by 2030 would prevent an estimated 41 million chronic HBV infections globally and 710,000 deaths, including 554,000 deaths (78%) in African countries among persons born between 2020 and 2030 (9).

The introduction of HepB-BD vaccine into a national immunization program is a country's first step towards protecting newborns from HBV infection and risk of liver cancer in later life. Indeed, one cause of low HepB-BD vaccination in African countries is that relatively few of these countries have introduced this strategy: as of 2021, only 14' of 47 African countries had introduced HepB-BD vaccine into their existing national immunization programs (10). Other barriers unique to this area of the world include the high proportion of births occurring outside of health facilities (e.g., home births); lack of access to skilled birth attendants; and poor awareness of HBV among health workers, parents, and the general public (11).

To help countries in the African region in their decision-making process for HepB-BD vaccination, the Coalition for Global Hepatitis Elimination (CGHE) of The Task Force for Global Health (TFGH), in collaboration with the US Centers for Disease Control and Prevention (US CDC), and the WHO Regional Office for Africa (WHO AFRO) have prepared this toolkit for National Immunization Technical Advisory Groups (NITAGs) and other technical working groups advising Ministries of Health on adding HepB-BD vaccine to existing routine immunization schedules. The toolkit provides information covering at least five key areas: 1) HBV transmission and related disease; 2) the global and regional burden of HBV infection; 3) hepatitis B vaccine safety and effectiveness; 4) elimination targets for hepatitis B and vaccination coverage requirements; and 5) acceptability, cost-effectiveness, and other considerations for implementing HepB-BD vaccination in Africa. While this toolkit is mainly intended for NITAGs in countries in the WHO African region, other countries may wish to use it as appropriate.



Source: US Centers for Disease Control and Prevention Description: Mother holds infant receiving a pentavalent vaccine dose that contains hepatitis B, diphtheria, tetanus, pertussis, and HIB

¹African countries with HepB-BD vaccination and year introduced: Algeria, 2001; Angola, 2015; Benin, 2020; Botswana, 2000; Cabo Verde, 2002; Cote d'Ivoire, 2019; Equatorial Guinea, 2019; Gambia, 1997; Mauritania, 2013; Mauritius (targeted [babies of HBV infected mothers] vaccination), 2000; Namibia, 2014; Nigeria, 2004; Sao Tome Principe, 2003; Senegal, 2016.

Section 1 – Understanding Hepatitis B Disease

Hepatitis B is a serious disease of the liver caused by infection with HBV. HBV is a 42nm double-stranded deoxyribonucleic acid (DNA) virus belonging to the Hepadnaviridae family (1,2,12,13). Humans are the only known reservoir for HBV, and the liver is the primary site of HBV replication (13).

- Hepatitis B is a serious disease of the liver caused by infection with hepatitis B virus (HBV)
- Humans are the only known reservoir for HBV

Ten HBV genotypes, designated A through J, have been described (2). These genotypes differ from each other by more than 8% in viral genome sequence (14). HBV genotypes are further classified into multiple subgenotypes whose genetic sequences differ from each other by 4%–8% (14). The distribution of HBV genotypes varies by geographic region, as shown in Figure 1(15).



Figure 1. Distribution of hepatitis B virus genotypes globally and by country, 2018*

*Pie charts indicate proportional HBV genotype distributions in the respective countries Source: Velkov S, Ott JJ, Protzer U, Michler T. The global hepatitis B virus genotype distribution approximated from available genotyping data. Genes (Basel). 2018;9:495. Genotype A is found predominantly in southern, eastern, and central Africa, genotype D in northern Africa, and genotype E in west Africa and Madagascar (15-17). Most African genotype A strains belong to subgenotype A1, with subgenotype A3 found in western Africa (16,17). Specific HBV genotypes have been reported to be significantly associated with the risk of HBV transmission, liver disease progression, and response to therapeutic treatment (18-20). Genotype A1, for example is associated with a higher risk of liver cancer, especially in younger individuals in Africa. Studies suggest genotype E is associated with high hepatitis B e antigen (HBeAg) positivity, increasing the risk for HBV MTCT (21,22).

Modes of HBV Transmission Among Children

Childhood HBV infection occurs mainly via two routes. First, HBV can be transmitted "vertically" from mother to child (i.e., MTCT) typically during birth. Intrauterine transmission is rare, accounting for approximately 2% of perinatal HBV infections (23-29). Second, HBV can be transmitted "horizontally" through mucosal (i.e., direct contact with mucus membranes) or percutaneous (i.e., skin puncture) exposure to infectious blood or body fluids (23). HBV remains infectious for at least 7 days on environmental surfaces, making newborns and children at risk for horizontal transmission in household settings (30).

Childhood HBV infection occurs mainly via two routes:

- Vertically from mother to child, typically, during birth
- Horizontally from direct contact with infectious blood or body fluids through mucus membranes or skin break exposures

Horizontal HBV transmission can occur from sharing personal care items (e.g., toothbrushes, razors), contact with exudates from dermatologic lesions, contact with saliva through bites or other breaks in the skin, pre-mastication of shared food, sharing of gum or similar items, and contact with surfaces contaminated with hepatitis B surface antigen (HBsAg)(28,31-35).

Infant hepatitis B vaccination, given at 6, 10, and 14 weeks prevents horizontal HBV transmission in Africa, but the prevalence of HBV infection among children attributable to MTCT remains high (36). It is estimated that by 2030, 50% of all new chronic HBV infections globally will be the result of MTCT of HBV (37).

By 2030, 50% of all new chronic HBV infections globally will be the result of MTCT of HBV

Risk for Mother-to-Child Transmission of HBV

The risk for HBV MTCT depends on several factors, one being the amount of virus in the mother's system (38-41). In studies conducted mostly in Asia, the risk of HBV MTCT varies from 10%-40% in mothers with lower levels of viral replication (or those who are HBeAgnegative) to 70%-90% for mothers with high HBV viral load (>10⁶ copies/mL or HBeAgpositive)(42-45). Available data estimating the risk for HBV MTCT in Africa are limited, and there are no African studies with similar design as those completed in Asia. A 2016 meta-analysis that included 15 articles from 11 African countries estimated the risk of HBV MTCT at 38% (95% CI: 7.0%-74.4%) and 4.8% (95% CI: 0.1%-13.3%) for children born to HBeAg-positive and HBeAg-negative mothers, respectively (43). HBV genotype distribution and other epidemiologic factors might explain this contrasting observation between Africa and Asia (43). Asian countries have predominantly HBV genotype C, which is associated with a high risk of vertical transmission (46,47). Compared to individuals with other genotypes, persons infected with genotype C have persistent HBeAg and develop antibodies against hepatitis B e antigen (anti-HBe) at an older age, therefore mothers infected with HBV genotype C have an increased risk for transmitting HBV to their babies at birth (14,46,47). While little is known about genotype E, common in western and central Africa, one study in West Africa reported a higher rate of HBeAg positivity in individuals infected with genotype E (89.8%, 35/39) compared to genotype A (33.3%, 2/6)(22). This also raises the possibility of increased HBV MTCT risk among genotype E infected pregnant women (16,48). A mother-child paired serosurvey in Sierra Leone, where genotype E is the predominant HBV genotype, showed that despite high coverage with 3 doses of pentavalent vaccine, the prevalence of chronic HBV infection in children was 1.3%; the main risk factors for transmission were maternal HBV infection, HBeAg positivity, and high HBV viral load (36). Coinfection with human immunodeficiency virus (HIV) and HBV is known to increase HBV viral load and HBeAg positivity among infected pregnant women, raising the potential for MTCT of HBV in areas with higher HIV prevalence such as Africa (49). The risk of HBV MTCT is also high if the mother acquires HBV infection in the second or third trimester of pregnancy (23,50,51). Among pregnant women who acquire HBV infection at or near delivery, 60% will transmit HBV to their newborns (51). However, breastfeeding by an HBV-infected mother has not been shown to increase the risk for HBV MTCT (1,4).

HBV/HIV coinfection increases HBV viral load and HBeAg positivity among pregnant women, raising the potential for HBV MTCT in Africa

Clinical Features

HBV infection can cause either acute or chronic illness. Its clinical course can be extremely variable, presenting with different clinical manifestations depending on the patient's age at infection, immune status, and the stage at which the disease is diagnosed (1,2,52).

Acute Hepatitis B

Acute HBV infection lasts <6 months, with clinical signs and symptoms resolving within 1–3 months (53). The risk of clinical illness following acute HBV infection increases with age: from 10% in early childhood (1–5 years) to 30% among older children, adolescents, and adults (1). Most neonates with HBV infection are asymptomatic (2). Acute hepatitis B can be self-limited with elimination of the virus from blood and subsequent lasting immunity against reinfection; or, it can progress to chronic infection with continuing viral replication in the liver and persistent viremia (52).

Most neonates with HBV infection are asymptomatic

Resolved primary infection is not a risk factor for subsequent occurrence of chronic liver disease or primary liver cancer (hepatocellular carcinoma [HCC]). However, patients with resolved infection who become immunosuppressed (e.g., from chemotherapy or medication) might, although rarely, experience reactivation of hepatitis B with symptoms of acute illness (52).

Chronic Hepatitis B

Chronic HBV infection is defined as the presence of HBsAg for more than 6 months after initial infection (23). Serologic markers help differentiate acute from chronic HBV infection (Tables 1 and 2).

Serological marker	Description
Hepatitis B surface antigen (HBsAg)	Indicates current HBV infection, either acute or chronic. Chronic HBV infection is defined as presence of HBsAg for >6 months after initial infection. All HBsAg-positive persons are infectious.
Antibody against hepatitis B core antigen (anti-HBc)	Indicates past or current HBV infection. In acute HBV infection, anti-HBc (both immunoglobulin M [IgM] and immunoglobulin g [IgG]) appear 1–2 weeks after the appearance of HBsAg. IgM is a marker of new HBV infection and often becomes undetectable within 6 months following infection. Isolated anti-HBc-positivity can be detected in persons who have recovered but whose antibody against hepatitis B surface antigen (anti-HBs) levels have waned; in populations with a high prevalence of HBV infection, isolated anti-HBc likely indicates previous infection with loss of antibody against hepatitis B surface antigen.
Antibody against hepatitis B surface antigen (anti-HBs)	Indicates immunity to HBV infection either after recovery from HBV infection or in response to hepatitis B vaccination. Persons who recover from HBV infection are typically positive for both anti-HBs and anti-HBc. Persons who respond to hepatitis B vaccination are positive only for anti-HBs. Anti-HBs levels >10 milli-international units per milliliter (mIU/mI) measured 1–2 months after completion of vaccination series indicate adequate immunity to prevent HBV infection.
Hepatitis B virus deoxyribonucleic acid (HBV DNA)	Indicates the presence of replicating HBV. HBV DNA can be detected prior to the detection of HBsAg (e.g., in the "window period" of acute HBV infection). Quantitative tests measure the amount of HBV (i.e., HBV viral load). Measures of HBV viral load are used to guide therapeutic decisions, including antiviral prophylaxis for HBsAg- positive pregnant women.
Hepatitis B e antigen (HBeAg)	Indicates current infection. The presence of HBeAg indicates that the virus is replicating and that the infected person is likely to have high levels of HBV DNA and is highly infectious.
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	ALT and AST are biochemical tests used to diagnose liver inflammation. The standard upper limit of normal (ULN) ALT values are 30 units per liter (U/L) for men and 19 U/L for women (54). Patients with elevated ALT (>2 times ULN) are considered to have liver inflammation; ALT values are used to guide considerations for HBV antiviral therapy (54,55).

Table 1. Description of serological markers of hepatitis B virus (HBV) infection

Source: Centers for Disease Control and Prevention. Viral Hepatitis Surveillance and Case Management: Guidance for State, Territorial, and Local Health Departments. Appendix B: Description of Hepatitis A, Hepatitis B, and Hepatitis C Laboratory Markers.

https://www.cdc.gov/hepatitis/statistics/SurveillanceGuidance/Appendices.htm#Appendix-B. Published August 2021. Accessed 2022 August 15.

HBsAg	Total anti-HBc	lgM anti-HBc	Anti-HBs	HBV DNA	Interpretation	
-	_	_	_	-	Never infected and susceptible to HBV infection	
+	_	_	_	+ or -	Early acute infection; transient (up to 18 days) after vaccination	
+	+	+	-	+	Acute infection	
-	+	+	+ or -	+ or -	Acute resolving infection	
-	+	-	+	-	Recovered from past infection and immune	
+	+	-	-	+	Chronic infection	
_	+	-	-	+ or -	Past infection or passive transfer of anti-HBc to infant born to HBsAg- positive mother. Can be a false positive (i.e., susceptible) in low HBV prevalence populations; past infection with anti-HBs waned; "low level" chronic infection	
_	-	-	+	-	Immune, if anti-HBs concentration is ≥10 mIU/mI after vaccine series completion; passive transfer after hepatitis B immune globulin administration	

Table 2. Interpretation of serological markers of hepatitis B virus (HBV)* infection

Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; IgM, immunoglobulin M; anti-HBs, antibody against hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; -, negative; +, positive; mIU/mI, milli-international units/milliliter

Source: Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(1):1-31.

Persons with chronic HBV infection are at high risk for HBV-related liver disease and mortality, including the development of liver cancer (1,2,12,56,57). For example, in a study conducted in Taiwan, rates of liver cancer were approximately 100 times higher among HBsAg-positive men (495 per 100,000 per year) than among men who were HBsAgnegative (5 per 100,000 per year)(58,59). Risk factors for liver cancer in persons with chronic HBV infection include high levels of virus replication, older age, family history of liver cancer, increased alcohol use, cirrhosis, and the presence of HBV genotype C (58-64). In studies of persons with chronic HBV infection who receive care at clinical centers, the incidence of cirrhosis is as high as 2%–3% (65,66). The annual risk of liver cancer is estimated to be <1% for persons with chronic HBV infection without cirrhosis and 2%–3% for persons with cirrhosis (63).

Clinical Progression of Chronic HBV Infection

The natural history of chronic HBV infection varies among infected persons. Patients can move from having acute HBV infection to having persistent HBV as a chronic infection. Persons with chronic HBV infection can also experience stages of HBV infection that vary by levels of viral replication and liver inflammation and degree of scarring or fibrosis. The levels of viral replication and disease progression can change from active to inactive liver disease, and then revert back to active liver disease years later (67).

Progression to advanced fibrosis can be rapid, slow, or sporadic (67). Studies suggest that persons born in African countries who have chronic HBV infection have a rapid progression of liver disease and an early onset of liver cancer (68). The high prevalence of underlying conditions such as HIV and exposure to aflatoxins likely worsen the clinical course of chronic HBV infection in Africa (69,70). Studies in Africa reveal that genotypes A and E are associated with rapid progression of HBV related liver disease (21,71).

Risk of Chronic HBV Infection by Age at Infection

The risk of developing chronic HBV infection is inversely related to the age at infection. HBV infection acquired during infancy carries a greater risk of premature death later in life from cirrhosis and HCC (72). Of children infected with HBV at birth, 90% develop chronic HBV infection (1). This risk is greater than the risk for children infected at ages 1–5 years (30%) and for older children and adults (5%) (Figure 2). Newborns infected with HBV through MTCT have a 15%–25% risk of premature death from cirrhosis and liver cancer later in life (4). In cohort studies conducted in Taiwan, approximately 25% of persons who became chronically infected with HBV during childhood and 15% of those who became chronically infected at older ages died of HCC or cirrhosis (73,74).

Newborns infected with HBV have a 15%–25% risk of premature death from cirrhosis and HCC later in life

²Aflatoxins, highly prevalent in Africa, are toxic compounds produced by fungi which contaminate improperly stored foods such as maize, wheat, nuts, peanut butter, and dried fruits. They have a synergistic effect with HBV in the development of liver cancer. (*source:* https://www.un.org/esa/ffd/ffd3/wp-content/uploads/sites/2/2015/10/PACA_aflatoxin-impacts-paper1.pdf).



Figure 2. Risk for developing chronic hepatitis B virus (HBV) infection by age at time of infection

Adapted from: World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. Weekly epidemiological record. 2017;92 (27):369–392. http://apps.who.int/iris/bitstream/handle/10665/255841/ WER9227.pdf?sequence=1. Accessed 2022 August 15.



Source: Rise Against Hepatitis Global Initiative Description: Raising hepatitis B awareness with a young mother by sharing flyers at Ibadan Oyo State, Nigeria.

Section 2 – Understanding Hepatitis B Burden

HBV infection acquired during infancy, and especially through MTCT at birth, has the greatest risk of progression to chronic HBV infection (13). Globally in 2019, a total of 6 million children <5 years of age were living with chronic HBV infection (7). Two of every three of these children (4.3 million) were living in Africa. In sub-Saharan Africa, an estimated 370,000 newborns are infected with HBV from their mothers at birth every year (43). The prevalence of chronic HBV infection among children <5 years of age in countries in the WHO African region (2.5%) is more than twofold higher than the prevalence in other WHO regions (7)(Table 3).

Table 3. Prevalence of hepatitis B virus (HBV) infection and number of children <5 years of age with chronic HBV infection, by World Health Organization (WHO) region—2019

WHO Region	Percentage prevalence of HBV infection among children age <5 years (95% Cl*)	Number of children age <5 years living with chronic HBV infection (95% CI)
African Region	2.5(1.7-4.0)	4,300,000 (2,900,000- 6,800,000)
Region of the Americas	0.1(<0.1-0.2)	51,000 (26,000–130,000)
Eastern Mediterranean Region	0.8 (0.5–1.1)	720,000 (420,000-950,000)
European Region	0.3 (0.1–0.5)	150,000 (74,000–290,000)
South-East Asia Region	0.4(0.3-1.0)	640,000 (460,000-1,700,000)
Western Pacific Region	0.3(0.2-0.5)	360,000 (240,000-560,000)

*Confidence interval

Source: Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021. http://apps.who.int/iris/bitstream/hand le/10665/342808/9789240030985-eng.pdf. Accessed 2022 August 15.

In 2019, an estimated 296 million persons were living with chronic HBV infection, representing 3.8% of the world's population (7,12,72). The prevalence of HBV infection varies by WHO region. The WHO African region has the highest HBV prevalence (7.5%), with 82.3 million persons living with chronic HBV infection (7) (Figure 3).

Figure 3. Prevalence and number of persons with chronic hepatitis B virus (HBV) infection in the general population, by World Health Organization (WHO) region—2019



Adapted from: Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; http://apps.who.int/iris/bitstream/hand le/10665/342808/9789240030985-eng.pdf. Accessed 2022 August 15.

In Africa, the prevalence of HBV is higher in countries of western Africa compared with eastern and southern sub-regions (Table 4)(16). The prevalence of HBV in each sub-region of Africa exceeds the global HBV prevalence estimate (Table 4)(75).

- The African region has the highest prevalence rate of chronic HBV infection in the world
- Two of every three children infected with HBV globally are born in Africa

Table 4. Prevalence of chronic hepatitis B virus (HBV) infection in the general population, by African sub-regions—2019

African sub-region	Percentage prevalence of HBV infection among the general population (95% CI*)
Sub-Saharan Africa overall	6.7 (6.0–7.5)
Central sub-Saharan Africa†	6.4 (5.5–7.2)
Eastern sub-Saharan Africa§	4.8 (4.2–5.4)
Southern sub-Saharan Africa [®]	4.5(4.1-4.9)
Western sub-Saharan Africa**	9.0 (8.0–10.0)

*Confidence interval

[†]Includes Angola, Burundi, Central African Republic, Chad, Congo, Democratic Republic of Congo, and Republic of Rwanda

[§]Includes Comoros, Eritrea, Ethiopia, Kenya, Madagascar, Mauritius, Seychelles, Somalia, Southern Sudan, Sudan, Tanzania, and Uganda

[¶]Includes Botswana, Eswatini (Formerly Known as Swaziland), Lesotho, Malawi, Mozambique, Namibia, South Africa, Zambia, and Zimbabwe

**Includes Benin, Burkina Faso, Cabo Verde, Cameroon, Cote d'Ivoire, Equatorial Guinea, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, and Togo

Source: GBD 2019 Hepatitis B Collaborators. Global, regional, and national burden of hepatitis B, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Gastroenterol Hepatol. 2022;7:796-829.

In 2019, an estimated 1.5 million new cases of chronic HBV infection were diagnosed globally (7). Of these cases, 990,000 (or two out of every three) occurred in countries in the WHO African region (Figure 4).



Figure 4. Number of new chronic hepatitis B cases, by World Health Organization (WHO) region—2019

Source: Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021.

http://apps.who.int/iris/bitstream/handle/10665/342808/9789240030985-eng.pdf. Accessed 2022 August 15.

Hepatitis B-Associated Disease and Death

HBV infection is a major cause of disease and death worldwide. In 2019, chronic hepatitis B-related liver disease, including cirrhosis, resulted in 10,772,575 disability-adjusted life-years (DALYs) globally, 1,935,437 of which were in Africa (76). In the same year, HBV caused an estimated 820,000 deaths, 80,000 of which occurred among persons living in countries in the WHO African region (7) (Figure 5). However, these modeled estimates, relative to the high HBV prevalence in Africa, likely underestimate HBV-related deaths. Many African countries have weak or absent surveillance systems, and many deaths due to hepatitis B go unreported (77-79).



Figure 5. Number of hepatitis B virus (HBV)-associated deaths* by World Health Organization (WHO) region—2019

*Global total=820,000.

Source: Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021.

http://apps.who.int/iris/bitstream/handle/10665/342808/9789240030985-eng.pdf. Accessed 2022 August 15.

HBV infection is a major cause of primary liver cancer (80-85). In 2020, primary liver cancer caused an estimated 830,180 deaths globally, making it the sixth most commonly diagnosed cancer and the third leading cause of cancer deaths worldwide (86). In Africa, in 2017, liver cancer ranked first among the leading causes of cancer deaths in several west African countries and in Mozambique in the southeastern sub-region (87) (Figure 6).

In 2020, in sub-Saharan Africa, liver cancer was the second and fourth leading cause of cancer related deaths among men and women, respectively (86).



Figure 6. Rank of liver cancer as a cause of cancer death among total cancer-related deaths in African countries—2017

Source: Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019;5(12):1749-1768.

In sub-Saharan Africa:

- HBV is a major cause of liver cancer
- In 2020, liver cancer was the second leading cause of cancer related deaths among men and fourth among women
- In 2017, liver cancer ranked top among the leading causes of cancer deaths in several African countries

The geographic distribution of liver cancer mirrors that of HBV prevalence (81,83). Countries that are highly endemic for HBV, including those in sub-Saharan Africa, have the highest incidence of liver cancer (age-standardized incidence rate [ASIR]>20 cases per 100,000 persons per year)(86,88,89). In 2019, the proportion of liver cancer caused by HBV infection ranged from 25% in Ethiopia to as high as 60% in Senegal (76)(Figure 7). However, as mentioned previously, given the lack of fully established cancer surveillance in sub-Saharan Africa, those numbers likely underestimate the true burden of liver cancer in Africa.



Source: Hepatitis Aid Organization

Description: Dr. Jamadah Aldine and Lutamaguzi Emmanuel hold a health talk with pregnant women attending antenatal care at Kiira Health Center III in Uganda.



Figure 7. Proportion of primary liver cancer attributable to hepatitis B virus infection in the African Region—2019

Source: Institute for Health Metrics and Evaluation (IHME). GBD Results Tool. Seattle, WA: IHME, University of Washington, 2022; Available from: http://ghdx.healthdata.org/gbd-results-tool. Accessed 2022 August 25.

Section 3 – Understanding Hepatitis B Vaccine

WHO Recommended Schedule for Hepatitis B Vaccination in Children

WHO recommends routine hepatitis B vaccination for all infants beginning with a timely birth dose and 2 or 3 additional doses to complete the infant hepatitis B vaccination series, depending on a country's national immunization schedule.

WHO recommends routine hepatitis B vaccination for all infants beginning with a timely birth dose and 2 or 3 additional doses to complete the infant vaccination series

All infants, regardless of the mother's HBV infection status, should receive the first dose of hepatitis B vaccine (HepB) as soon as possible after birth, preferably within 24 hours (2). This strategy prevents MTCT and other early HBV transmission before the start of the infant HepB series (which begins at 6 weeks in most African countries)(1,11,90). HepB is to be administered by intramuscular injection into the anterolateral aspect of the thigh for infants (1). The primary 3-dose hepatitis B vaccination series for infants consists of 1 monovalent birth dose followed by either 2 doses of monovalent or HepB-containing combination vaccine administered during the same visits as the first and third doses of diphtheria, tetanus, pertussis (DTP)-containing vaccines. Alternatively, 4 doses of HepB can be given (e.g., 1 monovalent birth dose followed by 3 monovalent or HepB-containing combination vaccine doses) and administered during the same visits as the 3 doses of DTP-containing vaccines (1). Most countries in sub-Saharan Africa provide pentavalent vaccine, a combination vaccine consisting of diphtheria, tetanus, pertussis, Haemophilus influenzae type b (Hib), and HepB (pentavalent vaccine) at the ages of 6, 10, and 14 weeks. Hence, in most African countries, addition of the HepB-BD would consist of adding a monovalent dose of HepB at birth for a total of 4 doses of HepB-containing vaccine administered before the age of 1 year.

Vaccine Immunogenicity

The hepatitis B vaccine elicits an immune response to a section of proteins or antigens on the HBsAg (1). This section of antigens known as the "a" determinant is common to all varieties or genotypes of HBV (91). As a result, the same HepB produces equal protection against infection caused by any HBV genotype. After completion of hepatitis B vaccination, a level of anti-HBs ≥10 mlU/ml is a reliable serologic marker of an effective response to vaccination and long-term protection against HBV infection (1) (Table 1). Infants receiving HepB-BD followed by a 2- to 3-dose infant vaccine series attain high concentrations of anti-HBs; the duration of protection from HBV infection extends through adolescence and into adulthood for at least 35 years (1,11). For this reason, WHO does not recommend routine booster doses of HepB (1).

Vaccine Effectiveness

HepB-BD is 75%–95% effective in preventing MTCT of HBV (2,92). The major determinant of the effectiveness of HepB-BD vaccine is how quickly the newborn receives the vaccine after birth. Effectiveness of HepB-BD vaccination declines as the interval between delivery of the newborn and administration of the initial dose of vaccination lengthens (93,94). For this reason, WHO recommends HepB-BD vaccination as soon as possible after birth (1).

- HepB-BD vaccination is 75%-95% effective in preventing MTCT of HBV
- WHO recommends HepB-BD vaccination as soon as possible after birth, ideally within 24 hours of birth
- Effectiveness declines as the interval between the newborn's delivery and initial dose of vaccination lengthens

Studies of the Effectiveness of HepB-BD Vaccination in Africa

To date, two studies on the effectiveness of HepB-BD vaccination have been conducted in Africa. In 2001–2002, Ekra and colleagues conducted a nonrandomized controlled trial in four health centers in Abidian, Cote d'Ivoire (95). Infants of study participants in two centers received HepB at birth, 6, and 14 weeks (HepB-BD cohort), while those in the two other centers received the vaccine at 6, 10, and 14 weeks (6-week cohort). A total of 5,810 mothers were enrolled for the study at their third trimester of pregnancy (3,356 in the HepB-BD cohort and 2,454 in the 6-week cohort). At 6-10 weeks postpartum, 4,385 mothers (2,230 in the HepB-BD cohort and 2,155 in the 6-week cohort) had HBV serological analysis, 337 (7.7%) of whom were HBsAq-positive (171 [7.7%]) in the HepB-BD cohort and 166 [7.7%] in the 6-week cohort). The overall prevalence of HBeAg positivity among the HBsAg positive mothers was 14.5% (49/337), including 14.6% (25/171) in the HepB-BD cohort and 14.5% (24/166) in the 6-week cohort. For the infants, HBsAq results were available at 9 months of age for 1,896 infants in the HepB-BD cohort and 1,900 infants in the 6-week cohort. When tested 9 months after receipt of the last HepB vaccine dose, 9 of the infants in the HepB-BD cohort were HBsAg positive; all 9 infants were born to mothers who tested positive for HBeAg. On the other hand, 10 of the infants in the 6-week cohort were HBsAq positive, all of whom were born to mothers who tested positive for HBeAq. Infection rates for infants at 9 months of age were 0.5% in both groups, but in the subgroup of 41 infants born to HBeAg-positive mothers the infection rate was 38% in the HepB-BD cohort and 59% in the 6-week cohort.

Based on the results of published studies, the authors assumed a 75% transmission rate in the absence of vaccination. With this expected level of HBV transmission, the data suggested a vaccine effectiveness of 50% (95% CI: 16%–70%) among the HepB-BD cohort compared to a vaccine effectiveness of 22% (95% CI: 17%–47%) among the 6-week cohort. These results highlight the benefit of the addition of HepB-BD to the 3-dose HepB vaccination schedule for infants. The authors in this study report several limitations. First, the study was not randomized or blinded. Therefore, the study findings are likely affected by other factors such as maternal HIV status not accounted for in the study. Second, the study groups at the 95% confidence level. Lastly, the overall lost-to-follow up of infants from enrollment to testing at the age of 9 months was very high, especially among the infants in the HepB-BD cohort (44%) compared to the 6-week cohort (23%)(p<0.001). The authors acknowledged that due to the study limitations, the findings should be regarded as preliminary and additional evaluation was needed.

A second effectiveness study was conducted from 2009-2016 in a single center in Tokombéré district, Cameroon. Among the 33,309 targeted pregnant women in this longitudinal observational study, 22,243 (66.8%) were tested for HBsAg and 3,901 (17.5%) were found to be HBsAq-positive (94). Serum and plasma specimens were collected from HBsAg-positive women and tested for levels of HBV DNA, presence of HBeAg, and other markers. Of the 3,901 neonates (all single births) born to the HBsAg-positive mothers, 2,004 (51.4%) received the HepB-BD vaccine-1,800 (89.8%) of whom also completed the 3-dose HepB containing pentavalent vaccine. From 2015-2017, a total of 607 children-30.2% of the original cohort of children receiving a HepB-BD-were identified and enrolled for study participation. Children were tested for HBV infection at a median age of 36 months (interguartile range 20-53 months); 39 (6.4%) of the 607 children were positive for HBsAg. This study revealed greater effectiveness with timely administration of HepB-BD vaccination. Although not statistically significant at <0.05 level, HBsAgpositive prevalence was 5.6% (24 of 426) for recipients vaccinated <24 hours of birth compared to 7.0% (11/157) and 16.7% (4/24) for those vaccinated 24-47 hours and 48-96 hours after birth, respectively. In addition, among infants born to mothers with high viremia (≥5.3 log10 IU/mL), 23 (28.1%) of 82 who received a HepB-BD within 24 hours tested positive for HBsAg compared with 12 (30.8%) of 39 who had a delayed HepB-BD vaccine given from 24-72 hours. In addition, among infants born to low viremic mothers who were HBsAg positive and HBeAg positive, 0% of infants who received timely HepB-BD got infected compared to 22.2% of infants in the delayed HepB-BD group. While this study suggests that HepB-BD vaccination prevented HBV MTCT in this cohort, the study had several limitations. First, of 1,800 infants who received the HepB-BD and completed the 3-dose HepB vaccine series, only 607 (34%) were followed up for HBV serologic testing. This likely introduced selection bias. Second, the study was conducted in a rural

community known to have high HBV prevalence, limiting the generalization of the study findings. Last, HBsAg prevalence was higher (4.0%–10.0%) among infants in the older age groups (>12 months), compared with infants <12 months (1.6%), raising the possibility that horizontal transmission might have occurred in the older age groups.

Studies of the Effectiveness of HepB-BD Vaccination Outside Africa

Studies from multiple countries reveal that HepB-BD vaccine, when accompanied by 2 or 3 additional doses of vaccine in the first year of life protects children from HBV infection. (96,97). A timely HepB-BD followed by 2 or more doses reduces the prevalence of chronic HBV by almost 90% in infants of HBeAg-positive mothers and virtually all HBeAg-negative mothers (98). Vaccination programs that offer HepB vaccines (beginning with a birth dose) have demonstrated large reductions in the prevalence of HBsAg and in the incidence of HBV-related disease and mortality (1,99-102) (Table 5).

Table 5. Prevalence of hepatitis B virus (HBV) infection in pediatric cohorts* before and after implementation of hepatitis B birth dose (HepB-BD) and hepatitis B infant immunization

	Hepatitis B surface an positive (%)	Percentage decrease in		
Country	Before HepB-BD introduction	After HepB-BD introduction	HBSAg prevalence after HepB-BD introduction	
American Samoa	11.0	0.2	98%	
China	9.9	0.3	97%	
Malaysia	2.7	0.4	85%	
French Polynesia	3.0	0.0	99%	
Saudi Arabia	6.7	0.2	96%	
Singapore	4.2	0.4	93%	
Republic of Korea	8.0	0.2	98%	
Taiwan (Taipei)	9.8	0.7	93%	
Marshall Islands	12	0.6	95%	
Oman	2.3	0.5	78%	
Thailand	4.5	0.6	87%	
United States (Alaska)	8.0	0	100%	

* Hepatitis B surface antigen (HBsAg) positive

Source: Ward JW, Wanlapakorn N, Poovorawan Y, Shouval D. Hepatitis B vaccines. In Plotkin SA, Orenstein WA, eds. Vaccines, 8th Edition. London: Elsevier Health Sciences, In Press.

In a prospective study of HBeAg-positive mothers in China, infants who did not receive a timely HepB-BD vaccine had a higher HBsAg positivity rate compared to infants who did [relative risk (RR)=2.87 (95% confidence interval (CI), 1.52–5.40)] (103). A study conducted in Alaska in the early 1980s demonstrated the impact of the introduction of universal newborn HepB vaccine on HBV infection in children (99). By 1988, the study identified 465 HBsAg-positive children and adolescents <20 years of age who were born prior to the start of universal newborn HepB vaccination. By the end of 2008, only 2 persons <20 years of age (born after the start of the universal HepB vaccination) were found to be HBsAg-positive (99). In Italy, after the start of routine HepB vaccination , acute hepatitis B incidence among children and adolescents declined from 1994 to 2001 in the age groups 15–19 years (from 7.3/100,000 to 1.3/100,000) and 20–24 years (from 14.3/100,000 to 3.7/100,000)(104).

Vaccination programs that offer HepB vaccines (beginning with a birth dose) have demonstrated large reductions in the prevalence of HBV infection and related mortality

Moreover, after implementing routine infant HepB vaccination in Hawaii, the incidence of acute hepatitis B (per 100,000 population) fell from 4.5 in 1990 to zero in 2004 (105). In 1984, Taiwan started mass HepB vaccination of infants beginning at birth; the annual average incidence of HCC among children 6-14 years decreased from 0.70 per 100,000 in 1981 through 1986 to 0.36 per 100,000 in 1990 through 1994. After adoption of universal HepB vaccination in Alaska including HepB-BD, the incidence of HCC declined among children, from 3 cases per 100,000 population (1984 through 1988) to no cases since 1999 (99). In Thailand, the incidence of HCC is significantly lower among adults who received HepB vaccination as infants beginning at birth (0.24 per million) compared with other adults (0.97 per million) (106). In 2002, the government of China integrated HepB vaccination into the routine infant immunization schedule, with a priority for administering a HepB-BD vaccine to newborns within 24 hours of birth. From 2002-2013, infant and HepB-BD vaccination coverage increased from 70% to > 95% and from 71% to 94%, respectively (107). In total, the HepB vaccination program in China prevented 28 million chronic HBV infections and 5 million HBV-related deaths. These studies provide assurance that routine infant HepB immunization beginning with HepB-BD vaccination is a highly effective public health strategy that will progressively protect generations to come from HBV-related liver disease, HCC, and premature mortality.

Vaccine Characteristics

HepB are available as monovalent formulations for birth dose vaccination and in combination with other vaccines (e.g., DTP, Haemophilus influenzae type b, and inactivated polio vaccine) for infant vaccination (1). WHO-prequalified monovalent HepB vaccines for infants and children currently include Euvax B[®], Engerix-B[®], Heberbiovac-HB[®], and Hepatitis B Vaccine (rDNA)(108). The HepB monovalent vaccine is available in single- and multiple-dose vials (Table 6). Ideally, HepB should be maintained in cold chain. However, because it is heat-stable, storage of monovalent HepB outside cold chain for limited timeframes and under continuous temperature monitoring has been used to improve birth-dose coverage in areas where cold chain is a barrier (1)(Table 6).

	• Available in single- and multiple-dose vials (109)
	 Multiple-dose vials generally contain 2, 6, or 10 doses (109)
	 Single-dose vials are preferred in facilities with small numbers of births or in settings where most births occur at home
Presentation, formulation, and	 Single-dose, compact pre-filled auto-disable devices (CPADs) are also available (11)
cost per dose	 CPADs are easier to use, require less training for providers, and can be clearly distinguished from other types of injectable medicines (11). These devices are more expensive than single- or multiple-dose vials and might not be available in resource-limited settings (110)
	 The 2022 cost per dose of HepB-BD vaccine ranges from US\$ 0.24-0.25 for a 10-dose presentation to US\$ 0.49-0.60 for a single-dose presentation (111)
	(111)
Co-administration	 Monovalent HepB vaccines can be given at the same time as other vaccines recommended for newborns (e.g., oral polio vaccine and Bacille Calmette- Guérin [BCG])(1), but only if co-administration does not delay the timeliness of the HepB-BD vaccine (i.e., within 24 hours)
	 When co-administered, the HepB-BD and other vaccines should be delivered at different anatomical sites
	 Co-administration does not affect the antibody response to HepB-BD and other vaccines (1)
	HepB vaccine should never be frozen (11)
Heat stability	 HepB vaccine is heat stable (1,112). It can be stored for up to 4 years at temperatures of 2°-8°C (113). Storing HepB vaccine for 1 week at 45°C or for 1 month at 37°C does not alter reactogenicity or the effectiveness of the vaccine to elicit antibody titers considered protective (114)
	 Storage of monovalent HepB vaccine outside cold chain has been used to improve birth-dose coverage in areas where cold chain is a barrier (1)

Table 6. Characteristics of hepatitis B vaccine (HepB)

Vaccine Safety

HepB-BD vaccine is safe. Mild, transient side effects may occur after immunization, including soreness at the injection site, irritability, and fever (1). These transient effects may start within 1 day after vaccine administration and last 1–3 days. Serious allergic reactions are rare (1,11).

Vaccine Administration

There are no contraindications to HepB-BD vaccination. Low birth weight (<2000 grams) is not a contraindication to vaccination. Some infants with low birth weight may not respond to HepB-BD vaccine as well as full-term normal weight infants (1,11). For low-birth-weight infants, the birth dose should not count as part of the primary 3-dose infant immunization series; a full 3 doses as per the infant vaccination schedule should be administered to ensure full protection (1,11).

At the discretion of the health worker, HepB-BD vaccination may be delayed for newborns who are clinically unstable; however, clinical instability is not a medical contraindication to vaccination (11). Co-administration does not affect the antibody response to HepB vaccine or other vaccines (115); therefore, HepB vaccine, including HepB-BD, can be given concurrently with other vaccines administered during infancy as long as they are administered at different anatomic sites (Table 6).

HepB-BD vaccine is safe, and co-administration with other vaccines does not affect the antibody response to HepB vaccine

Section 4 – Elimination Targets for Motherto-Child Transmission of Hepatitis B and Vaccination Coverage Requirements

Targets for the Elimination of Hepatitis B

In 2016, the World Health Assembly adopted the first Global Health Sector Strategy (GHSS) on viral hepatitis aiming to eliminate viral hepatitis as a public health threat by 2030, including elimination of MTCT of HBV (5,116). The GHSS set a 2020 interim impact target of 30% reduction in new HBV infections, equivalent to an HBsAg prevalence of no more than 1% in children <5 years of age, and a 2030 impact target of 95% reduction in new chronic HBV infections, equivalent to an HBsAg prevalence of no more than 0.1% in children <5 years of age (5,116) (Table 7). Countries that provide HepB-BD vaccination only to infants born to HBsAg-positive mothers (selective or targeted vaccination) need to demonstrate achievement of <2% HBV MTCT in addition to the seroprevalence target in children <5 years of age (116).

In addition to achieving the impact targets, countries should achieve programmatic targets to be validated for the elimination of MTCT of HBV and elimination of hepatitis B as a public health threat (5,116). HepB vaccination coverage is the main programmatic target and includes achieving at least 50% coverage of timely HepB-BD vaccination by 2020, 90% coverage of timely HepB-BD by 2030, and 90% coverage with 3 doses of HepB (HepB3) in children by 2020, with levels maintained or surpassed by 2030 (5,116).

Globally, the 2020 impact target of no more than 1% prevalence of chronic HBV infection among children <5 years of age has been achieved. In 2019, 0.94% of children <5 years of age were HBsAg-positive (7). The African region is the only region in the world that has not yet achieved this 2020 target. In 2019, 2.5% of African children <5 years of age were HBsAg-positive, a more than twofold greater prevalence than the global average (Table 3 and Figure 8).

Status of 2020 target for reduction in chronic HBV infections among children <5 years of age (target= <1%):

- Global: 0.9%
- African region: 2.5%

Elimination targets	Elimination of chronic HBV infection as a public health problem
2030 GHSS relative reduction reference targets (compared to 2015)	Incidence 95% reduction
HBV-specific absolute prevalence and incidence targets Heat stability	Elimination of MTCT of HBV ≤0.1% HBsAg prevalence in ≤5 year old population ^{a,b} Additional target: ≤2% MTCT rate (in areas using targeted HepB-BD) ^c
Programmatic targets ^d	Countries with universal HepB-BD vaccination ≥90% HepB3 vaccine coverage ≥90% timely HepB-BD coverage® Countries with targeted HepB-BD ≥90% HepB3 vaccine coverage ≥90% HepB-BD coverage ≥90% coverage of maternal antenatal HBsAg testing ≥90% coverage with antivirals for eligible HBsAg-positive pregnant

Table 7. Impact and programmatic targets related to elimination of MTCT of HBV

Abbreviations: GHSS, Global Health Sector Strategy; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HepB3, three doses of hepatitis B infant vaccine; HepB-BD, hepatitis B birth dose; MTCT, mother-to-child-transmission

^aChildhood prevalence is a proxy for HBV incidence.

^bThe ≤0.1% HBsAg prevalence can be measured among either 5-year-olds, 1-year-olds, or those aged 1–5 years, according to existing country surveillance and data collection activities. For regions and countries that have a long history of high hepatitis B vaccination coverage (e.g., WHO Region of the Americas) and that already conduct school-based serosurveys, there could be flexibility to conduct serosurveys in children >5 years of age.

° The ≤2% MTCT rate is an additional impact target to the ≤0.1% HBsAg prevalence among ≤5-year-old children in countries that provide targeted HepB-BD only to infants of HBsAg positive mothers.

 $^{\rm d}\mbox{All}$ programmatic targets must be achieved and maintained for at least 2 years.

^e Timely HepB-BD is defined as within 24 hours of birth.

^f In accordance with national policies or WHO 2020 guidelines on use of antiviral prophylaxis on preventing MTCT of HBV.

Adapted from: World Health Organization. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus. 2021; Available from: https://www.who.int/publications/i/item/9789240039360. Accessed on 2022 May 5.

Figure 8. Estimated geographic distribution of hepatitis B surface antigen (HBsAg) prevalence among children <5 years of age globally—2019



Source: International Viral Hepatitis Elimination Meeting, 2019. Available from: (https://academicmedicaleducation.com/meeting/international-viral-hepatitis-elimination-meeting-ivhem-2019)

Infant HepB vaccination beginning with a timely birth dose is the cornerstone of HBV elimination. In 2021, coverage with timely HepB-BD was 42% globally and only 17% for infants in the WHO African region (6) (Table 8). In addition, coverage with HepB3 is lowest in the WHO African region. A global push to increase coverage for the infant HepB vaccine series has substantially reduced horizontal HBV transmission among infants (9). In 2021, infant HepB3 vaccine coverage was 80% globally and 71% in Africa (6).

Status of 2020 programmatic target for HepB-BD vaccination coverage (target=≥50%):

- Global: 42%
- WHO African Region: 17%

Table 8. Coverage for timely hepatitis B birth dose and three doses of hepatitis B infant vaccine (HepB3) by WHO region—2021

WHO Region	HepB-BD coverage	HepB3 coverage
African Region	17%	71%
Region of the Americas	59%	80%
Eastern Mediterranean Region	33%	82%
European Region	43%	91%
South-East Asia Region	51%	82%
Western Pacific Region	78%	90%
Global average	42%	80%

Abbreviations: HepB3, three doses of hepatitis B infant vaccine; HepB-BD, hepatitis B birth dose; WHO, World Health Organization

Source: World Health Organization. Hepatitis B vaccination coverage.

Globally, improvements in HepB vaccination coverage reflect changes in national immunization policies: as of 2021, a total of 114 countries worldwide had introduced HepB-BD in their routine immunization schedule (117). Yet, this number includes only 14 (30%) of 47 countries in the WHO African region (10). Despite progress, significant decreases in immunization coverage were noted in 2021 as a result of the impact of the COVID-19 pandemic on access to essential health services (118).



Source: Hepatitis Aid Organization

Description: Pregnant women and new mothers attend a hepatitis B health camp at Kawempe National Referral Hospital in Kampala, Uganda.

As of 2021, only 14 (30%) of 47 countries in WHO African region had introduced HepB-BD vaccination

Strategies to Eliminate Mother to Child Transmission of HBV

Routine HepB-BD vaccination is recommended to ensure all infants receive protection from HBV infection, including those infants born to HBsAg-positive mothers not tested for HBV and when maternal HBsAq-positive test results are not available at the time of delivery. Maternal HBsAg screening and HBV MTCT prevention strategies are needed to achieve the HBV elimination goals by 2030. For children born to HBsAg-positive mothers, the administration of hepatitis B immunoglobulin (HBIG) to newborns immediately following birth (<12 hours) increases protection from MTCT of HBV. The administration of both HepB-BD vaccine and HBIG prevents 94% of vertically transmitted HBV (96,119,120). Despite its effectiveness, HBIG is not readily available in some settings because it requires stringent storage conditions and the cost can be prohibitive, particularly for low- and middle-income countries (40,41). The likelihood for failure of immunoprotection from HepB-BD vaccination increases when maternal HBV viral load before delivery is high (38,39,45,121). Maternal antiviral therapy starting at 28–32 weeks' gestation, together with the timely administration of HepB-BD vaccine and HBIG if available, virtually eliminates the risk of perinatal HBV transmission (54,92). For this reason, WHO recommends antiviral prophylaxis therapy to suppress maternal HBV DNA before delivery for HBsAgpositive mothers with a high viral load (HBV DNA \geq 5.3 log10 IU/mL, \geq 200,000 IU/mL) or if HBV DNA testing is not available, for mothers who are HBeAg positive (90,121-124).

Timely HepB-BD followed by HepB3 remains the foundation for the addition of maternal screening and other interventions to eliminate MTCT of HBV

Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among children aged \leq 5 years through vaccination are urged to focus their efforts on increasing infant HepB vaccination coverage, beginning with timely HepB-BD vaccination. For countries of the WHO African Region with low HepB-BD vaccination coverage, the development and implementation of national plans for HepB-BD vaccination will have the greatest impact on reducing HBV MTCT (90,125). As coverage targets are achieved, maternal HBV screening and, as appropriate, antiviral prophylaxis and HBIG, can be added to the timely administration of the HepB-BD vaccine to eliminate the risk of perinatal HBV transmission.

WHO regions in the Americas and the Western Pacific have achieved the 2020 target of <1% HBsAg prevalence among children aged <5 years (7). To achieve the global target of <0.1% prevalence of HBsAg in this age group by 2030, the regions have set goals for the elimination of MTCT of HBV along with elimination goals for HIV and syphilis (125,126). This "triple elimination" strategy seeks to integrate maternal HBV testing and antiviral prophylaxis with the testing and antiviral treatment interventions for the other infections promoting efficient delivery of maternal- and infant-care services.



Source: US Centers for Disease Control and Prevention

Section 5 – Considerations for Introducing HepB-BD in African Countries

Public Health Impact of HepB-BD Introduction and Scale-up

HepB-BD vaccination and completion of the infant HepB vaccination series has had great public health impact. Vaccination of newborns and infants prevented 210 million new chronic HBV infections by 2015 and will have averted an estimated 1.1 million deaths by 2030 (37). However, without further scale up of elimination strategies, an estimated 63 million new chronic HBV infections and 17 million HBV-related deaths will occur between 2015 and 2030 (37).

Scaling up timely HepB-BD vaccination to \geq 90% coverage, while maintaining status quo coverage for HepB3 in 110 low- and middle-income countries by 2030, can prevent 41 million (36-46 million) new chronic HBV infections (9). Achievement of the WHO target of \geq 90% HepB-BD coverage by 2030 in 110 low- and middle-income countries will prevent an estimated 710,000 deaths (9).

Children in Africa will reap the greatest benefit from this intervention, with 554,318 (78%) of the total expected deaths averted from prevention of progressive liver disease and liver cancer in their adult years (Figure 9)(9).

Among persons born during 2020-2030, scaling up HepB-BD vaccine coverage to ≥90% by 2030 will avert:

- 41 million chronic HBV infections globally
- 710,000 deaths globally, including 554,318 (78%) in African countries

Scaling up HepB-BD coverage to \geq 90% by 2030 in Nigeria alone is projected to prevent 32% (178,909 of 554,318) of the total averted deaths in Africa (Table 9).

Figure 9. Projected number of deaths averted in the 2020–2030 birth cohort by achieving ≥90% coverage of hepatitis B birth dose (HepB-BD) vaccine, by World Health Organization (WHO) Region



Source: de Villiers MJ, Nayagam S, Hallett TB. The impact of the timely birth dose vaccine on the global elimination of hepatitis B. Nat Commun. 2021;12(1):6223.

NOTICE NOTICE NOTICE PLEASE REMEMBER TO GIVE HEPA-()VACCINE IMMEDIATELY AFTER (WITHIN 24 HOURS 0 ECORD IT IN CHILD HEALTH CARD B TALLY IT ON THE TALLY SHEET 4 GET IMMUNIZATION REGISTER AND REGISTER ON THE RIGH TT SETTLEMENT 6 GIVE APPOINTMENT FOR BGG

Source: US Centers for Disease Control and Prevention

Description: Reminder message posted in the labor and delivery room detailing the steps to providing the hepatitis B birth dose vaccine to newborns within 24 hours of birth.

Table 9. Projected number of deaths averted by achieving \geq 90% hepatitis B birth dose coverage in the 2020–2030 birth cohorts, by African country*

African Country	Estimated number of deaths averted in the 2020-2030 birth cohort (95% Cl ⁺)
Algeria [§]	0(0-0)
Angola	23,133 (11,501–40,618)
Benin	9,216 (4,568–15,961)
Burkina Faso	5,807(3,390-9,498)
Burundi	1,810 (1,047–2,944)
Cameroon	14,918 (8,016–25,820)
Cabo Verde§	0(0-0)
Central African Republic	4,201(1,984-7,633)
Chad	29,779 (13,994–57,409)
Comoros	136 (57–272)
Congo	3,312 (1,478-5,920)
Democratic Republic of the Congo	40,138 (17,936–79,794)
Eritrea	494 (239-884)
Eswatini	72 (29–128)
Ethiopia	27,064 (9,979–57,499)
Gambia	629 (252–1,249)
Ghana	16,185 (9,198–25,988)
Guinea	25,843 (12,748-45,476)
Guinea-Bissau	1,362 (695–2,433)
Ivory Coast	15,149 (6,216–28,533)
Kenya	757 (500–1,111)
Lesotho	293 (128–508)
Liberia	7,746 (3,465–15,055)
Madagascar	13,709 (8,447-22,230)
Malawi	1,195 (700–2,005)
Mali	4,613 (2,561-7,672)
Mauritania	2,688 (1,398-4,451)
Mozambique	17,275 (9,529-30,598)
Namibia	21(12–37)
Niger	46,600 (24,135-82,485)
Nigeria	178,909 (81,613–327,990)
Rwanda	1,174 (729–1,884)
Sao Tome and Principe§	0(0-0)
Senegal	830 (411–1,313)
Sierra Leone	6,560 (3,454–11,567)
South Africa	9,362 (3,843–16,351)
South Sudan	5,407(3,881-8,040)
Tanzania	12,473 (5,986–23,635)
Togo	6547 (3,378–11,865)
Uganda	17,511(10,042-29,923)
Zimbabwe	1,399 (781-2,324)

*Data available for 42 of 47 WHO African countries

[†]Confidence Interval

[§]Countries with high hepatitis B birth dose coverage (≥90%) and therefore no change in number of deaths averted by scaling up HepB-BD coverage

Source: de Villiers MJ, Nayagam S, Hallett TB. The impact of the timely birth dose vaccine on the global elimination of hepatitis B. Nat Commun. 2021;12(1):6223

Economic Considerations

Cost of Implementation for HepB-BD Vaccination in Healthcare Settings in Africa

The first study to document the economic and financial costs of introducing HepB-BD vaccination in an African country was recently reported for Senegal (127). Using data collected over a 3-year period from national ministries, health outposts, and health facilities, economic costs were calculated for pre-introduction activities (planning and training), vaccine introduction activities (demand generation and the start of vaccine administration), and activities associated with full implementation of HepB-BD vaccination in health facilities (Table 10).

	Cost by yea	Percentage of total cost per activity				
Activity	Year 1: Preintroduction	Year 2: Introduction	Year 3: Implementation	Year 1	Year 2	Year 3
Pre- introduction	68,555			45.9%		
Training	77,510			54.1%		
Demand generation		60,877	3191		8%	0.4%
Vaccine administration		435,596	556,224		57.4%	63.6%
Storage		45,430	58,913		6.0%	6.7%
Distribution		10,781	13,213		1.4%	1.5%
Supervision		126,648	147,443		16.7%	16.8%
Management		79,841	96,000		10.5%	11.1%
Waste management		226	256		0.0%	0.0%
Economic costs	143,364	759,406	875,240	100%	100%	100%
Actual financial costs*	127,745	81,940	29,915			

Table 10. Economic costs per activity to implement hepatitis B birth dose vaccination, Senegal

*Accounting for use of existing personnel and equipment.

Source: Gosset A, Nishimwe ML, Diallo MY, et al. The costs of introducing the hepatitis B birth dose vaccine into the national immunization programme in Senegal (NeoVac Study). Vaccines (Basel). 2021;9(5):521.

Specifically, economic costs included a valuation of staff time, supplies, and equipment (new or already existing in the infant immunization program). The total economic costs over 3 years to plan, introduce, and implement HepB-BD vaccination in Senegal was US\$1,778,010. However, financial costs (taking into account the use of existing staff and equipment) were US\$239,600, 87% lower than the total economic costs. Over the 3-year period, activities shifted from planning and training (the pre-introduction phase) to demand generation (the introduction phase) to vaccine administration and supervision with the full scale-up of HepB-BD vaccination. In 2016 and 2017, an estimated 314,084 and 391,488 newborns received HepB-BD vaccination within 24 hours of birth, respectively, for total incremental economic and financial costs of US\$130,745 in 2016 and US\$78,720 in 2017. With full implementation of the program, the economic and financial costs per newborn vaccinated within 24 hours of birth were US\$2.40 and US\$0.20, respectively. These data indicate that the cost per dose for HepB-BD vaccination in healthcare settings is similar to that of other vaccines provided by national immunization programs in Africa (127).

In Senegal, economic (all costs) and financial costs (taking into account the savings from the use of existing staff and equipment) of HepB-BD vaccination within 24 hours of birth per newborn were US\$2.40 and US\$0.20, respectively. These costs were similar to that of other vaccines provided by national immunization programs in Africa

Cost-effectiveness of HepB-BD Vaccination

Studies of the cost-effectiveness of HepB-BD vaccination in Africa are relatively few in number and are based in healthcare settings (128-133). It is cost-effective to prevent HBV infection with HepB-BD vaccination, whether analyses include short-term outcomes of infection prevention in children or long-term outcomes of reductions in HBV-associated morbidity and mortality.

South Africa

In a study of the investment case for South Africa's national hepatitis action plan, at an estimated cost of US\$ 15.5 million, scale up of HepB-BD vaccination in that country was shown to be the most cost-effective intervention to prevent HBV infection (132). The US\$329 per DALY averted was well below the benchmark of South Africa's 2015 gross domestic product (GDP) per capita (US\$7,620) (Figure 10). Interventions are considered highly cost-effective when the costs per DALY are less than the national annual GDP per capita (134).

As the most cost-effective of the interventions evaluated and with a low budgetary cost of US\$ 3.3 million over 5 years, HepB-BD vaccination was identified as the "best buy" in South Africa's national hepatitis action plan.

Figure 10. Comparison of gross domestic product (GDP) per capita with cost per disability adjusted life year (DALY) averted with addition of hepatitis B birth dose (HepB-BD) to infant vaccination in four countries in Africa



Sources: Hecht R, Hiebert L, Spearman WC, et al. The investment case for hepatitis B and C in South Africa: adaptation and innovation in policy analysis for disease program scale-up. Health Policy Plan. 2018;33(4):528-38; Gosset A, Diallo MY, Betsem E, et al. Cost-effectiveness of adding a birth dose of hepatitis B vaccine in the Dafra district of the Hauts-Bassins Region in Burkina Faso (NeoVac Study). Vaccine. 2021 Jul 30;39(33):4659-70; Memirie ST, Desalegn H, Naizgi M, et al. Introduction of birth dose of hepatitis B virus vaccine to the immunization program in Ethiopia: an economic evaluation. Cost Eff Resour Alloc. 2020;18:23 and Klingler C, Thoumi Al, Mrithinjayam VS. Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique. Vaccine. 2012;31(1):252-9

Sub-Saharan Africa

In 2018, a study evaluated strategies for preventing HBV infections acquired among children by 10 years of age in sub-Saharan Africa with a focus on Cameroon (133). To model the prevention of vertical transmission and horizontal transmission and the cost per HBV infection prevented, three strategies were evaluated: 1) routine infant immunization; 2) the addition of universal HepB-BD in healthcare settings to the infant HepB vaccination series; and 3) maternal HBsAg testing and targeting HepB-BD vaccination to newborns of HBsAg-positive mothers delivered in healthcare settings (Table 11).

Strategy		HBV infection per 10,000 children	No. of HBV infec- tions prevented per 10,000 children	Cost per HBV infec- tion prevented, US\$		
Reference						
No maternal prenatal HBV screening; no vaccination of the offspring		2,360	NA	Reference		
Intervention						
1.	No maternal prenatal HBV screening; infant HepB vaccine series only	813	1,547	34.90		
2.	No maternal prenatal HBV screening; universal HBV vaccination at birth in healthcare settings + infant HepB vaccine series	430	1,930	53.87		
3.	Maternal prenatal screening for HBsAg; targeted HepB vaccination at birth in healthcare settings + infant HepB vaccine series	451	1,909	52.06		

Table 11. Cost of HBV infections prevented with universal versus targeted HepB-BD vaccination in sub-Saharan Africa

Abbreviations: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HepB-BD, hepatitis B birth dose; NA=not applicable

Source: Anderson S, Harper LM, Dionne-Odom J, Halle-Ekane G, Tita ATN. A decision analytic model for prevention of hepatitis B virus infection in sub-Saharan Africa using birth-dose vaccination. Int J Gynaecol Obstet. 2018;141(1):126-132.

The study revealed HepB-BD vaccination was the most cost-effective intervention for preventing HBV infection in children by age 10 years. The addition of universal HepB-BD vaccination to the country's infant HepB vaccination series would prevent 1,930 HBV infections per 10,000 children vaccinated, at a cost of US\$53.87 per infection prevented (Table 11). Compared with targeted HepB-BD vaccination for newborns of HBsAg-positive mothers, universal HepB-BD vaccination prevented a greater number of infections (1,930 versus 1,909 per 10,000 children). The cost of HepB-BD vaccination falls well below societal-willingness-to-pay threshold of US\$150, estimated by the authors as reasonable for sub-Saharan African countries.

Universal HepB-BD vaccination is a cost-effective intervention for African countries

Burkina Faso

To model the introduction of HepB-BD vaccination in Burkina Faso, the incremental cost-effectiveness ratio (ICER) was calculated for the difference in total costs of HepB-BD plus 3 infant doses of HepB vaccination (pentavalent vaccine) versus 3 infant doses of HepB vaccination alone; cost-effectiveness was compared with the Burkina Faso per-capita GDP of US\$671(128). An ICER smaller than three times the GDP per capita is considered cost-effective and highly cost effective when less than per capita GDP (135). The introduction of HepB-BD plus the 3-dose series resulted in an incremental cost of US\$554 and 31 DALYs averted, for an ICER of US\$18/DALY averted (Figure 10). As this value is far below the national per capita GDP, the addition of HepB-BD is highly cost-effective. This estimated benefit is conservative; the benefits of birth-dose and infant HepB vaccination are lowered or discounted because the reduced costs from prevention of HBV-related liver disease occur several decades after receipt of vaccination.

Ethiopia

In Ethiopia, a 2020 cost-effectiveness analysis of adding HepB-BD to the existing infant HepB vaccination series given at 6, 10, and 14 weeks of age found an incremental costeffectiveness ratio of US\$ 110 per DALY averted (136) (Figure 10). For a 2018 birth cohort of 3.34 million, a total of 10,020 DALYs could be averted at a cost of nearly US\$2.5 million for HepB-BD vaccine introduction. The annual budget for introduction of HepB-BD vaccination would cost an additional US\$0.023 per capita, or about 0.1% of the 2016/2017 annual total health expenditure (US\$3.1 billion) for Ethiopia. The authors of the study conclude that introduction of HepB-BD was cost-effective in Ethiopia.

Mozambique

A 2012 study found the introduction of HepB-BD vaccination in birthing facilities would have an ICER of US\$250.95 per DALY averted (130) (Figure 10). Assuming a willingness-to-pay threshold of US\$441 which was the GDP per capita for Mozambique in 2008, the addition of a HepB-BD was shown to be highly cost-effective when administered in medical settings. Additional data are needed regarding the additional costs required to provide timely HepB-BD vaccination for infants born at home.

Sao Tome and Principe

In the country of Sao Tome and Principe, an economic study revealed that when compared with the existing strategy of selective HepB-BD vaccination of newborns of HBsAg-positive mothers only, adoption of universal HepB-BD vaccination targeting all newborns would be simpler, less expensive, and less likely to miss children at risk for HBV infection (129). Universal HepB-BD vaccination resulted in a 19% decrease in chronic HBV infections per year and a 44% reduction in costs. The estimated ICER of US\$5,012 per HBV-associated death averted was cost-saving for the country. As a result of this study, Sao Tome and Principe updated their recommendations to provide universal HepB-BD to all newborns irrespective of their mother's hepatitis B infection status (137).

Refugee populations

Introducing HepB-BD vaccination among high-risk populations such as refugees has been shown to be particularly cost-effective. In a study involving displaced Somali refugees in Djibouti camps, the addition of HepB-BD to the vaccination series was estimated to save 9,807 life-years/year, with an ICER of US\$0.15 per life-year saved (138). Similarly, administering HepB-BD in Western Saharan refugees in Algerian camps and Malian refugees in Mauritania camps 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), respectively. In this study, the cost per year of life saved by the addition of HepB-BD was much less than the average GDP of the host country.

HepB-BD vaccination is highly cost effective in preventing HBV infection in African countries

Limitations of Cost-Effectiveness Studies

Studies in African countries included sensitivity analysis to identify variations in parameters that might impact the cost-effectiveness of HepB-BD vaccination. These analyses examined at least six parameters: 1) the HBsAg prevalence among pregnant women; 2) the risk of HBV MTCT; 3) the effectiveness of HepB-BD vaccination; 4) the cost of HepB vaccination; 5) the cost of HBV anti-viral therapies; and 6) the transition probabilities of patients moving from chronic hepatitis B to cirrhosis to decompensated cirrhosis to death. In taking possible variations of these parameters into account, HepB-BD vaccination plus completion of infant HepB3 vaccine series remained cost-saving or cost-effective.

Current models examine only the cost-effectiveness of HepB-BD vaccination for infants born in healthcare facilities. Data are needed to model the additional costs for outreach services to provide timely HepB-BD vaccination for infants born at home.

Acceptance and Implementation of HepB-BD Vaccine

High rates of timely HepB-BD vaccination indicate broad acceptance of vaccination by pregnant women and their families and successful implementation of vaccine delivery within health systems. Globally, many countries have already achieved >90% coverage with HepB-BD, indicating high acceptance of the vaccine. In 2021, the highest rates of HepB-BD coverage were achieved among countries in WHO's Western Pacific Region (78%), followed by those in the America Region (59%), South East Asia Region (51%), European region (43%) and African region (17%)(6). In 2020, a total of 114 (58%) WHO Member States had policies in place for routine HepB-BD vaccination (117). In the WHO African region, in 2021, timely HepB-BD coverage was high in Algeria (99%), Cabo Verde (96%), and Namibia (86%), indicating broad acceptance of HepB BD vaccination (139). Compared to 2021, coverage was higher in 2019-2020 in several countries as the COVID-19 pandemic increasingly impacted access to immunization services (118). Despite low rates of HepB-BD coverage in other African countries, vaccine acceptance has not been shown to be a barrier to HepB-BD vaccination. An evaluation of five African countries revealed that HepB-BD vaccination was readily accepted by parents and caregivers; no community refusals were observed (140). Instead, the low rates of coverage in Africa result from other barriers, the first being lack of policies for routine and timely HepB-BD vaccination.

An evaluation of five African countries revealed that HepB-BD vaccination was readily accepted by parents and caregivers; no community refusals were observed

As mentioned previously, only 14 of the 47 countries in the WHO African region have national policies in place for HepB-BD vaccination. It is the goal of this toolkit to assist remaining African countries to overcome this barrier by providing the data that can assist NITAGs and their ministries of health. Another key barrier is poor knowledge of the importance of HepB-BD vaccination among health workers, pregnant women, and other caregivers for infants, limiting the delivery and demand for vaccination. In Nigeria, infants of mothers equipped with accurate information about HBV and the benefits of vaccination were 2.9 times more likely to receive timely HepB-BD vaccination than those whose mothers did not have this knowledge (141). Administration of HepB-BD vaccine at birth has also been associated with an increased likelihood of completion of the HepB vaccination series and other childhood vaccines (142,143).

In Nigeria, infants of mothers equipped with accurate information about HBV and the benefits of vaccination were 2.9 times more likely to receive timely HepB-BD vaccination than those whose mothers who did not have this knowledge

Other Key Programmatic Aspects for NITAGs to Consider

NITAGs can consider issues regarding the feasibility of routine HepB-BD vaccination for in-facility and home births. WHO guidance helps immunization program managers, maternal and child health professionals, and other partners introduce universal HepB-BD vaccination and strengthen the operations of a HepB-BD vaccination programs (11,144,145). Some of WHO's recommendations for operating HepB-BD vaccine programs are outlined in Table 12 below. A full set of these recommendations is available in the WHO document, Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination (11).

The Toolkit as an Information Resource for Key Stakeholders

The primary purpose of this toolkit is to support NITAGs and other technical advisory groups in the decision-making process for HepB-BD introduction into national vaccination programs. However, the toolkit can also be used to raise awareness among community leaders, clinicians, donor agencies and other key stakeholders in a country to introduce HepB-BD vaccination (11).

Appendix 1 highlights selected WHO publications and other documents referenced in this toolkit.

Table 12. Operational considerations for timely hepatitis B birth dose (HepB-BD) vaccination

In-facility births

- □ Increasing access to skilled care at the time of childbirth
- □ Integrating HepB-BD vaccination with maternal and newborn care in health facilities by having
 - Local health facility policy specifying HepB-BD birth dose vaccination
 - Standing orders for HepB-BD vaccination within 24 hours of birth in the delivery room or postnatal ward
 - Reliable vaccine availability in the delivery room or postnatal ward
 - Maternal health workers assigned to deliver HepB-BD vaccination as part of routine newborn care services
 - Coordinated planning by immunization and maternal health staff in health facilities and in districts for delivery of HepB-BD vaccination
 - Availability of free HepB-BD vaccination in the private sector

Births outside health facilities

- **D** Establishing home visits to provide timely vaccination
- □ Integrating HepB-BD with home visits for other postnatal care
- Having vaccine storage outside the standard cold chain in a controlled temperature chain to be delivered by midwives and skilled birth attendants
- Establishing careful pregnancy tracking and notification to deliver timely HepB-BD vaccination (use of community health workers as a link between pregnant women and health workers)
- □ Using single dose vials for home births

Health workforce considerations

- Addressing health workers' lack of knowledge and particular attitudes and perceptions towards newborn vaccination
- Providing training for health workers including education on perinatal transmission of hepatitis B virus (HBV)
 - Reinforcing training with frequent follow-up and supportive supervision
 - Considering task-shifting to reach marginalized populations

Medical technologies relevant to birth dose

- Setting up distribution and storage (utilizing procedures outside the standard cold chain as appropriate), and positioning vaccine close to the birth area
- **Considering use of prefilled syringes for use by community health workers**
- **D** Ensuring supply of monovalent HepB vaccine in single- or multi-dose vials

Health information system practices

- □ Setting up birth registries including tracking home births
- □ Incorporating HepB-BD and its timing within vaccination records
- Defining timely HepB-BD in vaccine coverage reporting
- Conducting serosurveys to track demand and monitor coverage and impact of HepB-BD vaccination

Financial arrangements influencing birth dose coverage

- Adequately funding HepB-BD programs, including for marginalized populations and private Sector
- Minimizing costs to families

Community concerns or lack of knowledge regarding birth dose

- □ Addressing low awareness of the birth dose vaccine and its importance
- **D** Considering traditional practices of sequestering newborns
- Addressing fear of adverse events, including planning for the risk of coincidental newborn death or disease
- **D** Responding to parental refusal of vaccination

Leadership and governance practices: convening the national immunization technical advisory group to review evidence and prepare recommendations for the health ministry regarding HepB-BD vaccination

- **D** Ensuring consideration of a central policy that mandates universal newborn vaccination
- **D** Providing clear national guidance that defines timely birth dose as within 24 hours of birth
- **D** Removing unnecessarily stringent restrictions contraindicating vaccination
- Considering options for vaccine use managed outside the standard cold chain in a controlled temperature chain, and accrediting new vaccinators
- Developing strong central communications to support public confidence in vaccines

General evidence for effective implementation of immunization programs

- D Preparing communication strategies that anticipate and address likely public concerns
- □ Aligning with maternal, newborn, and immunization care guidelines
- Estimating costs of strategies to scale-up birth dose within and beyond health facilities

Adapted from: World Health Organization. Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination. Geneva: WHO, 2015. https://apps.who.int/iris/bitstream/handle/10665/208278/9789241509831_eng.pdf. Accessed 2022 August 17.

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Appendix:

Selected World Health Organization (WHO) and other documents referenced in this toolkit by section topic.

Section topic	Document and hyperlink		
	 Epidemiology and prevention of vaccine-preventable diseases. The Pink Book: course textbook - 14th Edition (2021). https://www.cdc.gov/ vaccines/pubs/pinkbook/index.html. 		
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Section topic	Document and hyperlink		
	 MI4A Market Information for Access to Vaccine: Vaccine Purchase Database. https://www.who.int/teams/immunization-vaccines-and- biologicals/vaccine-access/mi4a/mi4a-vaccine-purchase-data. 		
	 Introduction of hepatitis B vaccine into childhood immunization services: management guidelines, including information for health workers and parents. https://apps.who.int/iris/bitstream/handle/10665/66957/ WH0_V-B_01.31_eng.pdf?sequence=1&isAllowed=y. 		
Hepatitis B vaccine	• Annex C: hepatitis B birth dose investment case: vaccine investment strategy programme and policy committee meeting, 18-19 October 2018. https://www.gavi.org/sites/default/files/document/ppc-meeting-18-19-october-2018—-vis-06a—-annex-c—hepatitis-b-birth-dose-investment-casepdf.pdf.		
	 Improving birth dose coverage of hepatitis B vaccine. Bull World Health Organ. 2006 Jan;84(1):65-71. https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC2626514/. 		
	 Temperature sensitivity of vaccines. https://apps.who.int/ iris/bitstream/handle/10665/69387/WHO_IVB_06.10_eng. pdf?sequence=1&isAllowed=y. 		
	• Appendix B. Immunization management issues. https://www.cdc.gov/ mmwr/preview/mmwrhtml/rr5416a3.htm.		
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Section topic	Document and hyperlink	
	 Practices to improve coverage of the hepatitis B birth dose vaccine https://apps.who.int/iris/bitstream/handle/10665/78616/WHO_ IVB_12.11_eng.pdf. 	
	• Hepatitis B control through immunization: a reference guide. https://apps.who.int/iris/handle/10665/208163.	
Guides for hepatitis B birth dose (HepB-BD) in Africa	• Synthesis brief of the hepatitis B birth dose evidence base, December 2019. https://www.globalhep.org/sites/default/files/content/page/files/2021-08/Hepatitis%20B%20Birth%20Dose%20Evidence%20Base%20Synthesis_14Dec2019.pdf.	
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