NNT : 0000AIXM0000

THÈSE DE DOCTORAT

Soutenue à Aix-Marseille Université
le 27 juin 2024 par

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Vers l'élimination de la transmission mère-enfant de l'hépatite B en Afrique de l'Ouest : une analyse combinant modélisation et évaluation économique

Discipline
Biologie santé

Spécialité
Recherche clinique et Santé Publique

École doctorale
ED 62 – SCIENCES DE LA VIE ET DE LA SANTE

Laboratoire/Partenaires de recherche
SESSTIM – Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale
Imperial College London
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Affidavit

I, undersigned, Andréa GOSSET, hereby declare that the work presented in this manuscript is my own work, carried out under the scientific supervision of Patrizia CARRIERI and Timothy HALLETT, in accordance with the principles of honesty, integrity and responsibility inherent to the research mission. The research work and the writing of this manuscript have been carried out in compliance with both the French national charter for Research Integrity and the Aix-Marseille University charter on the fight against plagiarism.

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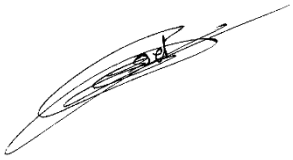

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Publication list and conference participation

1) List of publications produced as part of the thesis project:

    1. **Gosset A**, Nayagam S, Boyer S, Guingané AN, Schmit N, Tiendrebeogo ASE, Carrieri P, Shimakawa Y, Hallett TB. Implementing decentralised hepatitis B screening and antiviral prophylaxis for pregnant women in Burkina Faso - A dynamic modelling study on health impact and cost-effectiveness, (being submitted).
    2. **Gosset A**, Drabo S, Carrieri PM, Tiendrebeogo ASE, Vincent JP, Sombié R, Tall H, Kania D, Shimakawa Y. Costs of integrating hepatitis B screening and antiviral prophylaxis into routine antenatal care in Burkina Faso: Treat All versus targeted strategies. Int J Gynaecol Obstet. 2024 Apr 3. doi: 10.1002/ijgo.15515. PMID: 38567863.
    3. **Gosset A**, Diallo MY, Betsem E, Schaeffer L, Meda N, Vray M, Sombie R, Shimakawa Y, Boyer S. Cost-effectiveness of adding a birth dose of hepatitis B vaccine in the Dafra district of the Hauts-Bassins Region in Burkina Faso (NéoVac Study). Vaccine. 2021 Jul 30;39(33):4659-4670. doi: 10.1016/j.vaccine.2021.06.059. Epub 2021 Jul 5. PMID: 34238606.
    4. **Gosset A**, Nishimwe ML, Diallo MY, Deroo L, Diallo A, Ba EH, Carrieri PM, Sokhna C, Vray M, Shimakawa Y, Boyer S. The Costs of Introducing the Hepatitis B Birth Dose Vaccine into the National Immunization Programme in Senegal (NéoVac Study). Vaccines (Basel). 2021 May 18;9(5):521. doi: 10.3390/vaccines9050521. PMID: 34070184; PMCID: PMC8158493.
    5. Tall H, Adam P, Tiendrebeogo ASE, Vincent JP, Schaeffer L, von Platen C, Fernandes-Pellerin S, Sawadogo F, Bokoum A, Bouda G, Ouattara S, Ouédraogo I, Herrant M, Boucheron P, Sawadogo A, Betsem E, Essoh A, Kabore L, Ouattara A, Méda N, Hien H, **Gosset A**, Giles-Vernick T, Boyer S, Kania D, Vray M, Shimakawa Y. Impact of Introducing Hepatitis B Birth Dose Vaccines into the Infant Immunization Program in Burkina Faso: Study Protocol for a Stepped Wedge Cluster Randomized Trial (NéoVac Study). Vaccines (Basel). 2021 Jun 1;9(6):583. doi: 10.3390/vaccines9060583. PMID: 34206058; PMCID: PMC8227098.

2) Participation in conferences and summer schools during the thesis period:
    1. **Gosset A.**, Nayagam S., Boyer S., Guingané A.N., Schmit N., Tiendrebeogo A.S.E., Kania D., Carrieri P., Shimakawa Y., Hallett T.B., "Optimal strategies for eliminating mother-to-child transmission of hepatitis B in Burkina Faso", EASL Congress 2024, 05 – 08 June 2024, Milan, Italy. Poster.
    2. **Gosset A.**, Shimakawa Y., Guingané A., Tiendrebeogo A., Carrieri P., Hallett T., Nayagam S., Boyer S., "What is the most effective strategy to identify HBV-infected pregnant women eligible for antiviral prophylaxis in Burkina Faso? A

modelling study on different testing strategies", EASL Congress 2023, 21 – 24 June 2023, Vienna, Austria. Poster.

3. **Gosset A.**, Diallo M.-Y., Betsem E., Schaeffer L., Meda N., Vray M., Sombie R., Shimakawa Y., Boyer S., " Analyse coût efficacité de la vaccination à la naissance contre l'hépatite B pour réduire la transmission et la mortalité liées à l'hépatite B au Burkina Faso ", AFRAVIH 2020, 8 - 11 November 2020. Oral communication.
4. ISSPAM Summer School - Health economics in practice - Lecturer - 19 - 30 June 2023, Marseille, France
5. CIVIS Summer School – Health Care Analysis in an International Perspective – Participant – 04 – 08 July 2022, Bucharest, Romania

Résumé

En Afrique de l'Ouest, la prévalence du virus de l'hépatite B (VHB) est particulièrement élevée, l'infection chronique touchant 8-15% de la population et 4% des enfants de moins de cinq ans. La transmission mère-enfant (TME) du VHB est un défi majeur, entraînant une infection chronique chez 90% des nourrissons et un risque accru de cirrhose et cancer. Malgré 20 ans de vaccination, le pentavalent actuel administré à 6-8 semaines de vie, ne prévient pas la TME. L'Organisation mondiale de la santé préconise une dose de vaccin contre le VHB dans les 24 heures suivant la naissance (HepB-BD) pour prévenir la TME, mais sept pays d'Afrique de l'Ouest ne l'ont pas encore adoptée. Le dépistage du VHB chez toutes les femmes enceintes et un traitement par ténofovir chez les femmes fortement virémiques sont aussi recommandés, mais peu accessibles en soins prénataux.

Cette thèse utilise la modélisation et l'analyse économique pour évaluer différentes stratégies de prévention de la TME du VHB en Afrique de l'Ouest, avec un focus sur le Sénégal et le Burkina Faso.

Au Sénégal, l'HepB-BD a été introduit en 2016 avec un coût économique de 759 406$, alors que les dépenses réelles (coût financier) étaient de 82 519$. Au Burkina Faso, l'introduction de l'HepB-BD dans le district sanitaire de Dafra était coût-efficace à un seuil représentant la moitié du PIB par habitant, avec un ratio coût-efficacité incrémental de 18$ par année de vie corrigée de l'incapacité évitée. Pour le dépistage du VHB chez les femmes enceintes et le traitement ténofovir de manière décentralisée au Burkina Faso, l'utilisation d'un test rapide pour détecter l'antigène core de l'hépatite B serait la stratégie la moins coûteuse. Cependant, la stratégie consistant à traiter toutes les femmes enceintes infectées par le VHB serait plus efficiente avec une élimination possible de la TME du VHB au Burkina Faso d'ici 2034.

L'introduction immédiate de mesures préventives contre la TME du VHB en Afrique de l'Ouest est vitale, et ces résultats fournissent des informations pour un plaidoyer en ce sens.

Mots clés : hépatite B, transmission mère-enfant, vaccin à la naissance, dépistage, traitement ténofovir, soins prénataux, modélisation, coût, micro-costing, coût-efficacité, Afrique de l'Ouest

Abstract

In West Africa, prevalence of hepatitis B virus (HBV) is alarmingly high, with chronic infection affecting 8-15% of the general population and 4% of children under five. HBV mother-to-child transmission (MTCT) is a major challenge, leading to chronic infection in 90% of infants and increasing the risk of cirrhosis and cancer. Despite 20 years of vaccination, the current pentavalent vaccine administered at 6-8 weeks of age does not prevent HBV MTCT. The World Health Organization recommends universal hepatitis B birth dose vaccination within 24 hours of birth (HepB-BD) to prevent MTCT. However, seven West African countries have yet to include it in their immunisation programmes. In addition, HBV screening for pregnant women and tenofovir prophylaxis for highly viremic HBV-infected women are recommended, but coverage is low due to their non-availability in antenatal care.

This thesis evaluates different strategies to prevent and eliminate HBV MTCT in West Africa, with a focus on Senegal and Burkina Faso, using modelling techniques and economic analysis.

In Senegal, HepB-BD was introduced in 2016 at an economic cost of US$759,406, while the actual government expenditure (financial cost) was US$82,519. In Burkina Faso's Dafra district, the introduction of HepB-BD was cost-effective at half the Burkina Faso GDP per capita, with an incremental cost-effectiveness ratio of US$18 per disability-adjusted life year averted. For decentralised HBV screening and tenofovir prophylaxis in pregnant women in Burkina Faso, using a rapid diagnostic test to detect hepatitis B core-related antigen in pregnant women emerged as the least costly strategy. However, a 'Prophylaxis for All' strategy, where all HBV-infected pregnant women would be eligible for tenofovir, proved to be more efficient. This strategy could lead to elimination of HBV MTCT in Burkina Faso by 2034.

Immediate implementation of preventive interventions against HBV MTCT in West Africa is vital, and these findings provide crucial insights for advocacy.

Keywords: hepatitis B, mother-to-child transmission, vaccine birth dose, screening, tenofovir prophylaxis, antenatal care, modelling, cost, micro-costing, cost-effectiveness, West Africa

Remerciements

Tout d'abord, je tiens à exprimer ma gratitude à toutes les personnes qui ont participé à l'encadrement de ma thèse. Je remercie chaleureusement Patrizia Carrieri qui a accepté d'être ma directrice de thèse malgré ses réserves au départ concernant le sujet. Ses précieux conseils et son soutien ont été déterminants tout au long de ma thèse. Je lui suis très reconnaissante pour sa disponibilité et tout son accompagnement. Merci également à Sylvie Boyer, avec qui j'ai travaillé depuis mon arrivée au SESSTIM en tant qu'ingénieure d'études il y a quelques années. Je la remercie pour toute l'expérience que j'ai acquise avec elle au fil des années, ce qui m'a également permis d'acquérir plus d'autonomie à la fin de ma thèse. Je lui suis reconnaissante pour tous ses précieux conseils, ainsi que pour son soutien lorsque j'ai dû mettre en place mon projet de thèse et trouver un financement.

Je suis également très reconnaissante envers mon co-superviseur Timothy Hallett. Je considère sa générosité comme un exemple à suivre. Bien qu'il ne me connaissait très peu, il a accepté de co-superviser ma thèse et m'a très bien intégré dans son équipe pendant mes deux séjours à Imperial College London. Je lui suis reconnaissante pour toutes les connaissances que j'ai acquises auprès de lui et des super personnes de son équipe. Merci tout d'abord à Shevanthi Nayagam pour son engagement dans la supervision et sa présence tout au long de ma thèse, ainsi que pour tous ses conseils pertinents. Merci à Nora Schmit, qui a joué un rôle clé lors de mes deux séjours à Imperial. Elle m'a initié à la modélisation des maladies infectieuses, a été si généreuse en m'expliquant et en partageant ses connaissances et son travail de modélisation sur l'hépatite B, et a également facilité mon intégration avec les autres collègues d'Imperial. Je suis également reconnaissant à Margaret de Villiers pour sa disponibilité et toutes les excellentes explications qu'elle m'a données.

Je voudrais également exprimer ma gratitude à Yusuke Shimakawa, un parrain qui m'a guidé non seulement tout au long de mon doctorat, mais aussi avant, lorsque j'ai commencé à travailler sur NeoVac. Il m'a fourni des connaisances approfondies sur l'épidémie du VHB en Afrique subsaharienne et m'a motivé à faire mon doctorat sur la transmission mère-enfant de l'hépatite B. Je lui suis très reconnaissante pour le capital de connaissances qu'il m'a apporté, pour sa grande disponibilité et son aide, et je considère son humilité comme un exemple.

Je souhaite également remercier profondément tous mes collègues du SESSTIM, présents et passés. Je voudrais tout d'abord remercier ceux qui ont directement et significativement contribué à ce travail : Mamadou Diallo, Marie Nishimwe, Lucas Deroo et Seydou Drabo. Au-delà de ces contributions, je suis très reconnaissante pour le soutien indéfectible et les mots bienveillants que j'ai reçus de tous mes collègues, qu'ils fassent actuellement partie du SESSTIM ou qu'ils soient partis vers d'autres horizons. Et à ceux qui continuent à relever les défis de la thèse, ou ceux qui ont finalisé ce parcours avant moi, vos encouragements ont été d'une valeur inestimable. Je suis chanceuse d'avoir été

entourée d'une équipe aussi exceptionnelle. Quelques gestes qui peuvent sembler insignifiants, quelques mots, un sourire, un message, un appel téléphonique, ont eu un profond impact et m'ont beaucoup remonté le moral.

Je suis également reconnaissante pour les mots d'encouragement et le soutien que j'ai reçus de mes ami.e.s, qui font partie intégrante de ma famille élargie.

Je suis naturellement reconnaissante envers ma famille, grande, imparfaite mais que j'aime profondément. Je me souviens des débats passionés que nous avons eus pour savoir si je devais faire ce doctorat ou pas. Il y avait le groupe des enthousiastes, le groupe des sceptiques et le groupe des indifférents complets. Quoi qu'il en soit, vous avez tous contribué à mon développement et je suis très reconnaissante d'avoir cette merveilleuse famille.

Je tiens tout particulièrement à distinguer mon mari, Fabrice, qui faisait partie du groupe des sceptiques, mais il a choisi d'épouser une femme déterminée, ma foi. Il est le meilleur père que nos enfants auraient pu espérer. À Mayel, Gabrielle et Andréas, les trois trésors de ma vie, merci de m'avoir transformé en super-héroïne dont le secret de mes superpouvoirs réside dans tout mon amour pour vous.

A mon père et Edith, ma belle-mère, merci pour tout le soutien que vous m'avez apporté, merci d'être des pilliers de la famille et des grands-parents extraordinaires.

Ma mère, la première personne à m'avoir suggéré de faire un doctorat, mérite une mention spéciale. C'est une visionnaire, bien qu'elle ait été tellement incomprise dans un environnement différent de la culture et de l'éducation dont elle a hérité. Elle était fermement convaincu qu'obtenir le diplôme le plus élevé serait pour moi le meilleur moyen de devenir une femme indépendante et de briser la chaîne de ce qu'on appelle formellement la "reproduction sociale". Je lui suis tellement reconnaissante pour sa détermination, et pour avoir gardé la foi, aussi fragile qu'elle pouvait être, dans les moments où tout espoir semblait perdu. Le chemin a été long, mais voilà nous y sommes. Je lui dédie particulièrement cette thèse.

Enfin je remercie le bon Dieu de donner de la force de manière inconditionnelle, à tous ceux d'entre nous qui se tournent vers lui.

Acknowledgements

First of all, I would like to express my gratitude to everyone who has been involved in the supervision of my thesis. A warm thank you to Patrizia Carrieri who, despite her initial reservations about the topic, agreed to be my supervisor. Her valuable advice and support were crucial throughout my thesis. I appreciate her availability and attentive guidance. I extend my thanks to Sylvie Boyer, with whom I have been working since my arrival at SESSTIM a few years ago as a research assistant. I thank her for all the experience I have gained with her over the years, which has also allowed me to gain more independence at the end of my thesis. I'm grateful for all the valuable advice she shared with me, and for her support when I had to set up my PhD project and find funding for it.

My gratitude also goes to my co-supervisor Timothy Hallett. I consider his generosity an example to be followed. Despite having only a minimal prior acquaintance with me, he accepted the role of co-supervising my thesis and he integrated me very well into his team during my two stays at Imperial. I'm grateful for all the knowledge I gained from him and the great people in his team. Let me start by acknowledging Shevanthi Nayagam for her commitment and presence in supervising me throughout my thesis, and for all her practical advice and insights. Thanks to Nora Schmit, who played a pivotal role during my two stays at Imperial. She introduced me to infectious disease modelling, was so generous in explaining and sharing her knowledge of methods and her modelling work on HBV, and also facilitated my integration with other people at Imperial. I am also grateful to Margaret de Villiers for her availability and all the great explanations I received from her.

I would also like to express my gratitude to Yusuke Shimakawa, a mentor who has guided me not only throughout my PhD but also before when I started working on NeoVac. He provided me with deep insights into the epidemic patterns of hepatitis B in sub-Saharan Africa and motivated me to do my PhD on mother-to-child transmission of hepatitis B. I am very grateful for the knowledge capital I received from him, for his great availability and help, and I took his humility as an inspiring example.

I also wish to express my heartfelt gratitude to all my colleagues at SESSTIM, both present and past. I would like to begin by acknowledging those who directly and significantly contributed to this work: Mamadou Diallo, Marie Nishimwe, Lucas Deroo and Seydou Drabo. Beyond their direct contributions, I am deeply grateful for the unwavering support and kind words I have received from all my colleagues, whether they are currently part of SESSTIM or have moved on to other endeavours. And to those who continue to face the challenges of their doctoral journey, or to those who have walked this path before me, your encouragement has been invaluable. I feel lucky to have been surrounded by such an exceptional team. What may seem like insignificant gestures, a few words, a smile, a message, a phone call, have had a profound impact on me and lifted my spirits.

I am also thankful for the words of encouragement and support I have received from my friends who form an integral part of my extended family.

My gratitude goes naturally to my large, imperfect but loving family. I remember the debates we had about whether this PhD was a good idea, with the team enthusiastic, the team sceptical, and the team indifferent to the whole affair. No matter, you have all contributed to my growth, and I am so grateful to have such a great family.

I would especially like to pay tribute to my husband, Fabrice, who was part of the sceptical team, but he chose to marry an obstinate woman. He is the best father our children could have hoped for. To Mayel, Gabrielle and Andréas, the three treasures of my life, thank you for turning me into a superwoman, with the secret of my superpowers coming from all my love for you.

To my father and Edith, my mother-in-law, thank you for all the support you have given me, for being pillars of the family, and for being such wonderful grandparents.

My mother, the first person to suggest that I do a PhD, deserves special credit. She is a visionary, despite having been so misunderstood in an environment different from her inherited culture and education. She firmly believed that obtaining the highest degree was the best way for me to become an independent woman and break the chain of what is formally called 'social reproduction'. I am so grateful for her determination, and for keeping faith, however fragile it could be, even when there seemed to be no hope. The road has been long, but here we are. I dedicate this thesis to her in particular.

And thank you God for giving strength to all of us who turn to you, unconditionally.

Towards the elimination of mother-to-child transmission of hepatitis B in West Africa: an analysis combining modelling and economic evaluation

By

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For the title of Doctor of Philosophy (PhD)

in

Public Health

Aix-Marseille University

Doctoral School of Life and Health Sciences – ED 62

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List of abbreviations

ALT - alanine transaminase
Anti-HBc - anti-hepatitis B core antibodies
ASBC - community health workers of Burkina Faso
ART - antiretroviral therapy
CHB - chronic hepatitis B
CHE - current health expenditure
CHR - Regional hospital centres of Burkina Faso
CHU - university hospital centres
CMA - medical centres with surgical services of Burkina Faso
CM - medical centres of Burkina Faso
CSPS - primary health centres of Burkina Faso
DALY - disability-adjusted life year
DC - decompensated cirrhosis
ECD - district management team of Burkina Faso
EPI - Expanded programme in immunisation
GAVI - Global Alliance for Vaccines and Immunization
GNI - gross national income
HALY - Health-Adjusted Life Years
HBcrAg - hepatitis B core-related antigen
HBeAg - hepatitis B e antigen
HBsAg - hepatitis B surface antigen
HBV - chronic hepatitis B
HepB3 - three doses of vaccine against HBV
HepB-BD - HBV vaccine birth dose
HCC - hepatocellular carcinoma
HIV - Human Immunodeficiency Virus
HIC - high-income country
ICER - Incremental Cost-Effectiveness Ratio
LMIC - low- and middle-income country
MTCT - mother-to-child transmission
PMTCT - prevention of mother-to-child transmission
PPP - purchasing power parity
RAMU - universal health insurance scheme of Burkina Faso
RDT - rapid diagnostic test
TDF - tenofovir disoproxil fumarate
UHC - universal health coverage
WHO - World Health Organization

1. Introduction

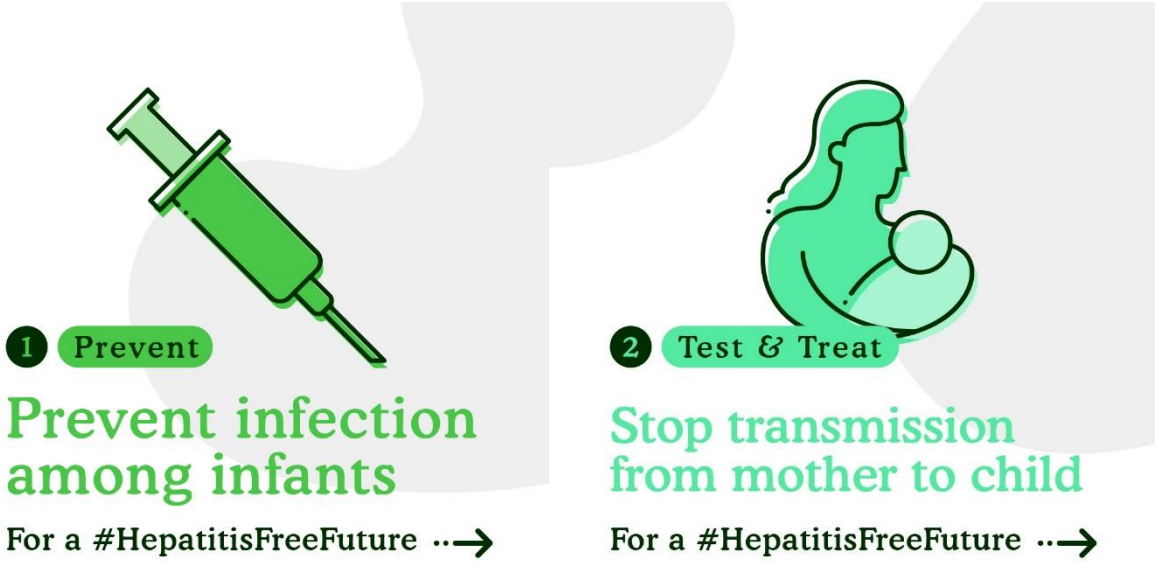


Figure 1.1 - For a hepatitis free future…
Source: World Health Organization, Global Hepatitis Programme, 2023

1.1. Hepatitis B general overview

1.1.1. What is hepatitis B?

Hepatitis B is one of the five primary strains of viral hepatitis infections characterised by their capacity to cause liver inflammation and potentially severe complications, including liver cirrhosis and hepatocellular carcinoma (HCC). Each strain of viral hepatitis has its own global prevalence, geographical distribution, mode of transmission, available treatment options, and associated adverse complications (1). While some strains of viral hepatitis, such as hepatitis C, show widespread prevalence in different regions of the world, with substantial differences both between and within countries, hepatitis B is particularly prevalent in Africa and Asia.

A brief chronological history of hepatitis B

Hepatitis B is one of the oldest viruses known to exist. Research on the hepatitis B virus (HBV) genome has shown that HBV has been transmitted for at least 12,000 years (2). Although epidemics of jaundice, a prominent symptom of HBV infection, have been documented as far back as the time of Hippocrates in 200 BC, the first recorded HBV epidemic was reported by Lurman in 1885 (3). He observed an outbreak of jaundice among German sailors after they had been vaccinated against smallpox. Similar outbreaks were observed in the USA and Great Britain in the early 20th century, and were termed as 'serum hepatitis', although the causative agent remained unidentified. It was not until 1965 that Blumberg et al. identified a novel antigen, termed the 'Australia antigen', in the serum of an Australian Aborigine (4). Three years later, Blumberg et al. conclusively

associated the 'Australia antigen' with 'serum hepatitis'. The Australia antigen became the main seromarker of active hepatitis B, the hepatitis B surface antigen (HBsAg). Blumberg's research led to the development of the first vaccine against HBV in 1976, which was already 95% effective against HBV infection (5). In 1981, the vaccine began to be administered on a large scale around the world. In 1993, Blumberg was awarded the Nobel Prize for his work on HBV.

How hepatitis B is transmitted

HBV is present in a variety of body fluids, including blood, saliva, tears, semen and vaginal secretions, and can be transmitted by a number of routes. Transmission occurs vertically through mother-to-child transmission (MTCT) during the perinatal period from an HBV-infected mother, or horizontally through contact with infected blood (e.g. sharing needles or other injection equipment) or through sexual contact.

The risk of MTCT is significantly increased when pregnant women have high viral loads (HBV DNA ≥ 200,000 IU/mL) or are carriers of the HBe antigen (HBeAg) (6). In endemic areas, horizontal HBV transmission may be common among children under the age of five through the sharing of personal items with infected fluids, such as needles, scissors, toothbrushes or nail clippers. Other groups at risk of horizontal HBV transmission include populations engaging in practices such as scarification, tattooing or body piercing without adhering to proper hygiene measures, people who inject drugs, prisoners, and people who have unprotected sex.

Natural history of hepatitis B

Once being infected, an individual enters the acute phase of hepatitis B. During this phase, there are three possible outcomes: spontaneous clearance of HBV leading to immunity, progression to chronic infection or, in rare cases, death due to fulminant hepatitis (Figure 1.2). The duration of the acute phase typically ranges from one to six months. Most individuals in the acute phase are asymptomatic, although some may experience symptoms such as jaundice, dark urine, fever, fatigue, nausea, vomiting, or abdominal pain for several weeks. Fulminant hepatitis occurs in less than 0.1% of cases, leading to severe health consequences that may necessitate liver transplantation or result in death. If HBV persists for more than six months, the individual progresses to chronic hepatitis B (CHB) infection. The risk of chronicity varies with age. This risk is 90% in infants infected before the age of 1 year, 50% in infants infected between the ages of 1 and 5 years, and 5-10% in adults (7).

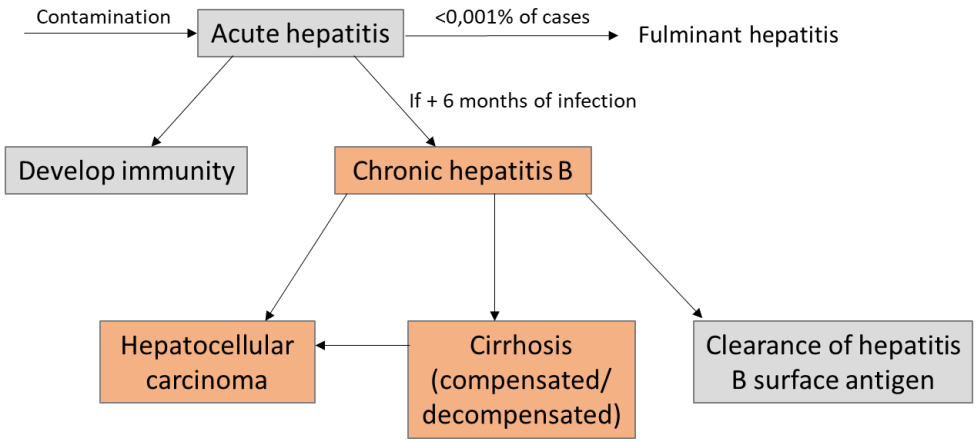


Figure 1.2 - Overview of hepatitis B natural history

The natural history of CHB infection consists of five phases (Figure 1.3). The initial phase, termed HBeAg-positive chronic HBV infection (previously known as the 'immune-tolerant' phase), is characterised by high levels of HBeAg and HBV DNA in the blood, reflecting a high risk of transmission. Liver transaminases (alanine aminotransferases, ALT) typically remain at normal or low levels and may persist for several years, especially if infection occurs at birth or during childhood. This is followed by the HBeAg-positive chronic phase of hepatitis B, when the immune system attempts to attack infected liver cells, causing a sudden rise in ALT levels. During this phase, HBV DNA levels fall, reducing the risk of transmission, and HBeAg becomes negative. At the end of the HBeAg-positive chronic phase, some individuals successfully seroconvert, eliminating HBV DNA and entering the HBeAg-negative phase of chronic HBV infection, others progress to the HBeAg-negative chronic hepatitis B phase, which can last for many years.

In the HBeAg-negative chronic HBV infection phase (previously termed 'inactive carrier'), individuals develop anti-HBe antibodies, have undetectable or very low viral loads (HBV DNA <2,000 IU/mL) and normal ALT levels, thereby halting liver damage and disease progression. Individuals in this phase can then recover from CHB, with the clearance of HBsAg and the presence of anti-HBs antibodies, although this process can be very slow. However, some carriers may maintain normal ALT levels but have detectable HBV DNA (usually between 2,000 and 20,000 IU/ml). Although they are less likely to develop cirrhosis or hepatocellular carcinoma (HCC), they remain at risk of HBV reactivation with or without HBeAg reactivation, accompanied by elevated ALT and HBV DNA levels.

Individuals who progress to the HBeAg-negative chronic hepatitis B phase are HBeAg-negative with high ALT levels. HBV DNA levels can be high or low. Despite the presence of anti-HBe antibodies, severe liver damage typically occurs, generally leading to fibrosis, cirrhosis or HCC.

The final stage, HBsAg-negative, refers to a healing phase in which HBsAg becomes negative, and anti-HBs antibodies appear. Rarely, occult infection occurs, where individuals have detectable low levels of HBV DNA despite being HBsAg-negative and having antibodies.

Most HBV-related deaths result from liver inflammation due to CHB, leading to cirrhosis and/or HCC.

Transition rates through the different phases of CHB vary widely between geographical regions and regardless of local standard of care due to virological, environmental, cultural and socioeconomic differences, including differences in HBV genotypes (8).

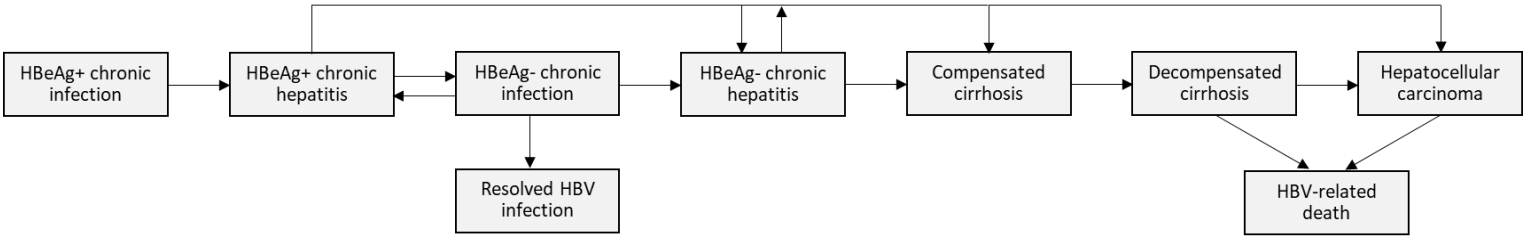


Figure 1.3 - Natural history of chronic hepatitis B infection

1.1.2. Fighting hepatitis B, a top public health priority

The challenge of hepatitis B

The alarming rise in hepatitis-related deaths has made hepatitis control a top public health priority on the global health agenda. From 1990 to 2015, these deaths reached 10 million, surpassing deaths from tuberculosis, HIV or malaria (Figure 1.4). Projections for 2040 indicate that deaths from hepatitis B and C could exceed the total number of deaths due to HIV, malaria and tuberculosis combined (9). In 2022, viral hepatitis was responsible for approximately 1.3 million deaths worldwide, with hepatitis B emerging as the predominant liver infection and a major contributor to liver-related complications. With an estimated 254 million people living with chronic hepatitis B (CHB), it remains a major public health challenge, responsible for 83% of all hepatitis-related deaths and an estimated 1.1 million associated deaths (10). Recognising the urgency of the situation, the fight against hepatitis B has been included in the 2030 Agenda for Sustainable Development. The World Health Assembly adopted the Global Health Sector Strategy for Viral Hepatitis 2016-2021, which outlines the goal of eliminating hepatitis B (11), and was later extended to the Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030 (12).

The global prevalence of CHB infection was estimated to be 4.1% in 2019 (13). However, three levels of prevalence can be distinguished: high endemic areas, which include the World Health Organization (WHO) regions of Africa and the western Pacific, where prevalence was estimated at 6.5% and 7.1%, respectively, in 2019; intermediate endemic areas, which include the Mediterranean, Middle East, Eastern Mediterranean and some Latin American countries, where prevalence ranged from 2% to 6%; and low endemic areas, which mainly include high-income countries (HICs), where prevalence was below 1.5% (13,14).

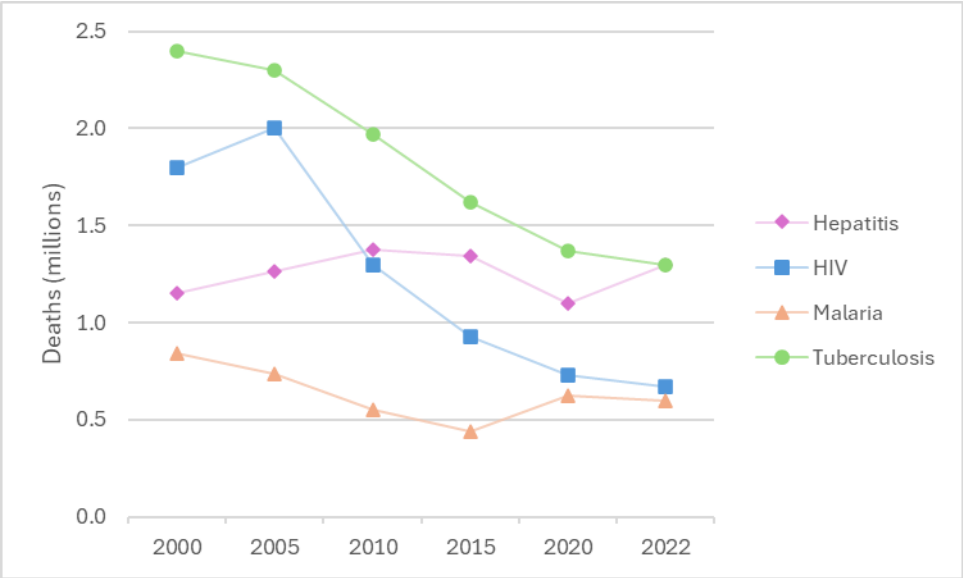


Figure 1.4 - Estimated global number of deaths due to viral hepatitis, HIV, malaria and TB, 2000–2022

Source of data: Hepatitis, Malaria, Tuberculosis: WHO; HIV: UNAIDS

Hepatitis B has often been described as a 'silent epidemic', particularly in low- and middle-income countries (LMICs) where universal health coverage (UHC) is compromised (15,16). Individuals can carry chronic infection for decades without showing any symptoms. Symptoms often emerge when cirrhosis or HCC is already well established, at which point life expectancy becomes very short, a few months without any intervention. An individual infected by MTCT or in early childhood may present with cirrhosis or HCC at 20-30 years of age, but the link with HBV infection may be difficult to establish due to the long delay between infection and symptoms. Although an antiviral treatment can slow the progression of the disease, there is currently no treatment that can cure hepatitis B, making prevention the primary strategy against HBV transmission.

HBV screening recommendation

Worldwide, only 14% of HBV-infected individuals were estimated to be aware of their status in 2022 (17). The screening process for HBV primarily involves the identification of HBsAg using serological diagnostic tests, either a laboratory-based immunoassay or a rapid diagnostic test (RDT), depending on the availability of and access to laboratory testing. The WHO recommends a population-based testing approach in areas where prevalence of CHB infection is greater than 2%. This recommendation implies that all adults should have access to and be offered testing, and that all pregnant women should be systematically screened for HBV in antenatal care and their partners offered HBV screening (10,18). In all settings, regardless of HBV prevalence, targeted screening is recommended for populations known to be most affected by HBV (mobile/migrant populations from high/intermediate endemic countries, people who inject drugs, prisoners, etc.), people with clinical symptoms of CHB infection, family members of HBV-infected persons, and healthcare workers (18). Screening of blood donors is mandatory in all settings (18).

In settings where prevalence of CHB infection exceeds 0.4%, a single HBsAg test is recommended, and in case of positivity, an evaluation of HBV DNA levels and liver disease staging is recommended. Conversely, in settings where prevalence of CHB infection is below 0.4%, a second confirmatory test is recommended following an HBsAg-positive result, before assessment of HBV DNA levels and liver disease staging, with the option of repeating the test after six months (18).

Treatment for people infected with HBV

Worldwide, only 8% of people eligible to receive a treatment to stop HBV progression were estimated to be effectively treated in 2022 (17).

Antiviral treatment is recommended to suppress HBV replication, prevent progression to advanced stages of the disease, and improve survival. Treatment should be initiated for all adults and adolescents (aged ≥12 years) who meet any of the following criteria: evidence of significant fibrosis (≥F2) or cirrhosis; HBV DNA levels >2000 IU/mL with abnormal ALT levels; coinfections with HIV, hepatitis D, or hepatitis C; a family history of liver cancer or cirrhosis; conditions causing immune suppression; comorbidities such as diabetes or metabolic dysfunction; or extrahepatic manifestations. Additionally, in the absence of access to an HBV DNA assay, individuals with persistently abnormal ALT levels should also be treated, regardless of APRI score, HBV DNA levels, or ALT levels (19).

It is estimated that between 12% and 25% of people with CHB should receive antiviral treatment (1). As this treatment is not curative, it may require lifelong administration. In HICs, people with HCC may have access to surgery, chemotherapy, or liver transplantation, which could also improve their survival (1).

Vaccination the main strategy for preventing HBV

The main way of preventing HBV infection is to vaccinate infants against hepatitis B. Achieving complete immunisation requires receiving at least three doses of hepatitis B vaccine (HepB3). In 2022, HepB3 was included in the immunisation programme of 190 countries. Globally, HepB3 immunisation coverage was estimated to be 84% among 1-year-olds (17). However, there are substantial regional disparities in HepB3 coverage, with West Africa and South-East Asia having the lowest coverage at 73%, while East Asia leads with the highest coverage at 98% (17).

The WHO has set a target of 90% coverage by the year 2030 (12). Despite the need for a substantially high vaccination coverage to limit HBV transmission, determining the minimum vaccination coverage in the general population or in infants required for the complete eradication of HBV transmission is complex. This difficulty of finding a minimum vaccination coverage arises from the complexity of HBV behaviour, which varies both within and between populations, influenced by multiple factors such as age structure, variations in contact rate patterns, or considerations of behaviour and environment (20).

Other preventive measures include HBV vaccination of healthcare workers and high-risk groups, HBV screening of blood and organ donations, improved safety of medical injections and procedures, and harm reduction services for people who inject drugs.

Specific prevention of MTCT of HBV

Given the higher risk of chronicity in early life, the WHO recommends that all infants receive a timely birth dose of hepatitis B vaccine within 24 hours of birth (HepB-BD), followed by 2 or 3 additional doses to complete the HepB3 series. The WHO aims to achieve 90% HepB-BD coverage by 2030 (12). However, global HepB-BD coverage in newborns was estimated at 46% in 2022, with Central Asia having the highest coverage (97%), while many other countries, particularly in sub-Saharan Africa, have no coverage because they have not yet included HepB-BD in their immunisation programme (17).

While HepB-BD is a primary intervention to reduce the risk of HBV-MTCT, it does not achieve full efficacy, particularly among pregnant women at higher risk (6,21). The effectiveness of HepB-BD varies across geographical regions, reflecting specific natural history and transmission patterns of HBV. In Asia, HepB-BD can significantly reduce the risk of HBV MTCT in HBeAg-positive mothers from 70%-90% to 20%. In sub-Saharan Africa, where the risk of MTCT in HBeAg-positive mothers without intervention ranges from 35% to 59%, HepB-BD can reduce this risk to 32%-38% (6,21). To achieve complete eradication of HBV MTCT, HepB-BD needs to be complemented by interventions such as hepatitis B immunoglobulin (HBIG) and peripartum prophylaxis with antivirals.

HBIG is derived from plasma donors with high levels of anti-HBs antibodies and is recommended in addition to HepB-BD within 12 to 24 hours after birth to reduce the risk of MTCT. However, debates remain regarding the efficacy of HBIG against MTCT, with some studies supporting its reduction when administered with HepB-BD (22), while others arguing that HBIG in combination with HepB-BD is no more effective than HepB-BD alone, especially for infants born to HBeAg-negative mothers (23). HBIG is a blood product that needs to be screened for infectious diseases and its effective implementation is associated with many challenges due to its high cost and the need for a rigorous cold chain (24). In the 2020 guidelines, the WHO recommended the use of HBIG in settings where it is available, particularly for infants born to mothers with HBeAg or high HBV DNA. However, the WHO also recognised the residual risk of MTCT despite the use of HBIG alongside HepB-BD, as well as the limited evidence supporting the benefit of HBIG in LMICs (24). In the updated 2024 guidelines, the WHO suggests the administration of HBIG only in high-income settings where it is available, but no longer includes it as an official recommendation (19).

Because of the residual risk of MTCT despite HepB-BD administration with or without HBIG, the WHO recommended, prior to the 2024 updates, additional antiviral prophylaxis for pregnant women with HBV DNA higher than 200,000 IU/ml or 5.3 $\log_{10}$ IU /ml, or for HBeAg-positive pregnant women when viral load quantification was not accessible, starting from 28 weeks of pregnancy until at least birth (24). In the 2024 updates, the WHO extended antiviral prophylaxis to all HBsAg-positive pregnant women where neither HBV DNA nor HBeAg testing is available (19). Tenofovir disoproxil fumarate (TDF) is the antiviral prophylaxis of choice due to its high barrier to drug resistance compared to lamivudine and telbivudine (19,24).

Table 1.1 provides a comparison of the 2020 and 2024 WHO guidelines for preventing MTCT of HBV.

Table 1.1: Comparison of 2020 and 2024 WHO guidelines for prevention of mother-to-child transmission, and assessment of eligibility of mother for treatment for her own health

	Common to 2020 and 2024 guidelines	2020 guidelines	New in 2024 guidelines
1. Serological testing	HBsAg testing in all pregnant women (laboratory-based immunoassay or RDT)		
2. Assessment for maternal antiviral prophylaxis	Prophylaxis if HBV DNA ≥200,000 IU/mL or HBeAg positive		Prophylaxis for all HBsAg-positive pregnant women if HBV DNA or HBeAg testing is not available
3. Assessment for long-term antiviral treatment in pregnant women for their own health		Long-term treatment if: presence of cirrhosis; or HBV DNA >20,000 IU/mL + persistently abnormal ALT	Long-term treatment if: significant fibrosis (≥F2) or cirrhosis; or, HBV DNA >2,000 IU/mL with abnormal ALT; or Presence of coinfections, family history of liver cancer/cirrhosis, immune suppression, comorbidities, or extrahepatic manifestations; or persistently abnormal ALT (when HBV DNA testing is unavailable)
5. Infant interventions	HepB-BD followed by 3 doses of hepatitis B vaccine		
		+ HBIG (if available) for infants born to HBsAg-positive mothers	Addition of HBIG is mentioned only as a suggestion where it is already available

In Asia, few studies have assessed the efficacy of antiviral prophylaxis, often in combination with HBIG, with mixed results regarding the efficacy of TDF in reducing HBV MTCT. Some, including randomised controlled trials, have found significant reductions in HBV MTCT when TDF is provided in combination with HepB-BD and HBIG, compared with the provision of HepB-BD and HBIG alone (25–29). But another multicentre, double-blind

clinical trial conducted in Thailand found no reduction in HBV MTCT between these two comparative strategies (30).

Very few studies have evaluated antiviral prophylaxis in combination with HepB-BD but without HBIG. A single-arm, multicentre, phase 4 trial, in Cambodia found that none of the babies born to the 36 HBV-infected mothers who received TDF for more than 4 weeks prior to delivery were HBV-infected, despite non-receiving HBIG (31). Another feasibility study in the Democratic Republic of Congo found similar results, where none of the babies born to the 10 pregnant women with high-risk HBV infection who received TDF were HBV-infected. Despite the small sample sizes of these two studies, their encouraging results suggest that TDF prophylaxis is effective against HBV MTCT even without HBIG, providing potential alternatives in LMICs (32).

The implementation of antiviral prophylaxis in HBV-infected pregnant women requires systematic screening of pregnant women in antenatal care, as recommended by WHO when prevalence of CHB infection exceeds 2% (10,18). Routine HBV screening of all pregnant women is recommended along with screening for syphilis and HIV in antenatal clinics (10). Screening involves HBsAg testing by RDT or laboratory-based immunoassay, performed at least once and as early in pregnancy as possible. Prior to the 2024 updated guidelines, pregnant women who tested positive for HBsAg required further testing for HBV DNA viral load or HBeAg, and assessment for cirrhosis using clinical criteria and non-invasive tests such as APRI score or Fibroscan. If HBV DNA ≥200,000 IU/mL or HBeAg positive, pregnant women without cirrhosis were eligible for TDF prophylaxis. They should have been reassessed for long-term TDF treatment after delivery (Table 1.1).

Current RDTs for the detection of HBsAg have excellent performance, with sensitivity and specificity approaching 100%, are relatively inexpensive (between US$1.25 and US$4.00), and results can be obtained within 15-20 minutes (33,34).

HBV DNA quantification is performed by PCR, but one of the major barriers to its uptake, particularly in LMICs, is its high cost (US$20 to US$130 per test) and the need for sophisticated laboratories and highly trained staff (35). HBeAg screening, either by RDT using capillary blood or by laboratory-based immunoassays using plasma, is much more affordable (US$0.50 to US$1.3 per RDT, and between US$7.5 and US$15.0 per laboratory-based immunoassay test) (35). However, the performance of RDTs to detect HBeAg is very poor, with sensitivity ranging from 28% to 72% depending on the RDT (36–38). The use of RDTs to detect HBeAg is not recommended as it can result in missing pregnant women at high risk of MTCT. In addition, although laboratory-based immunoassays for HBeAg testing require laboratories that can be equipped at a more affordable cost, it still requires a nearby laboratory (35). Another constraint of laboratory-based immunoassays for both HBV DNA quantification and HBeAg testing is that results can take several days, which may be an additional burden in settings where laboratories are not close by.

To ensure full coverage of the packages of prevention to combat MTCT particularly in LMICs, alternative strategies to HBV DNA quantification and HBeAg screening test are being explored. One is the use of newer markers, such as a rapid diagnostic test to detect

hepatitis B core-related antigen (HBcrAg-RDT), a novel new assay that does not yet have regulatory approval (39). HBcrAg-RDT presents the advantages of rapid on-site testing directly in antenatal services with results available within 30 minutes, and improved sensitivity compared to HBeAg-RDT to detect pregnant women with viral load ≥200,000 IU/mL (91.4% compared to 70.1% for HBeAg RDT) (35,39). Another alternative strategy is to offer TDF prophylaxis to all HBsAg-positive pregnant women without additional testing, which might be relevant in settings with limited access to HBV DNA and HBeAg testing. However, this strategy has not yet been evaluated in a real-world setting, whereas a global model study found that this strategy may be more efficient than HBV DNA and HBeAg testing in most countries (40).

1.2. Background: Hepatitis B specific situation in West Africa

1.2.1. HBV infection in West Africa

HBV epidemiology

Sub-Saharan Africa stands out as one of the regions most affected by prevalence of CHB infection. But the situation is particularly alarming in West Africa where most of the countries have some of the highest prevalence rates in the world, ranging from 6% to 17% in 2022 (17) (Figure 1.5a). Prevalence of CHB infection in children under 5 years of age is also alarmingly high in West Africa with an average rate of 2.7% (17) (Figure 1.5b). West Africa is not only burdened by a substantial HBV prevalence, but is also estimated to bear a significant proportion of advanced liver disease and HBV-related deaths (Figure 1.5c). However, estimates on HBV burden and HBV-related deaths may be conservative due to under-reporting hepatitis B notifications and HCC-related deaths in registries (16). Also there is almost no registry for collecting data related to deaths attributable to decompensated cirrhosis which contributes to the challenge of accurately assessing the full HBV burden (41).

HCC is one of the most common cancers in West Africa, being the second most common cancer in men and the third most common in women (42).

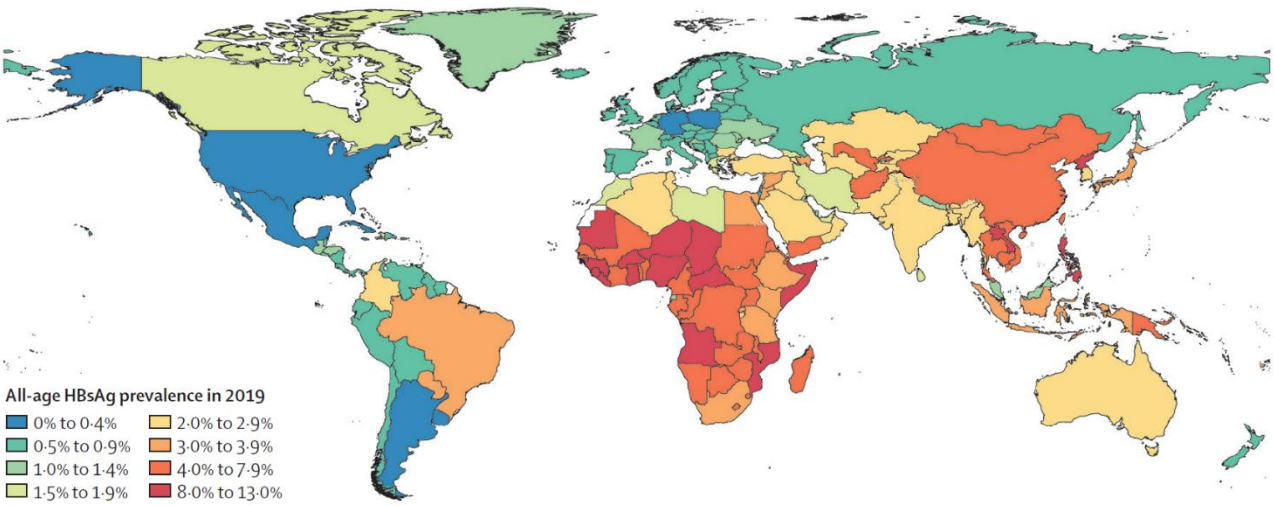


Figure 1.5a - Geographical distribution of all-age HBsAg prevalence in 2019

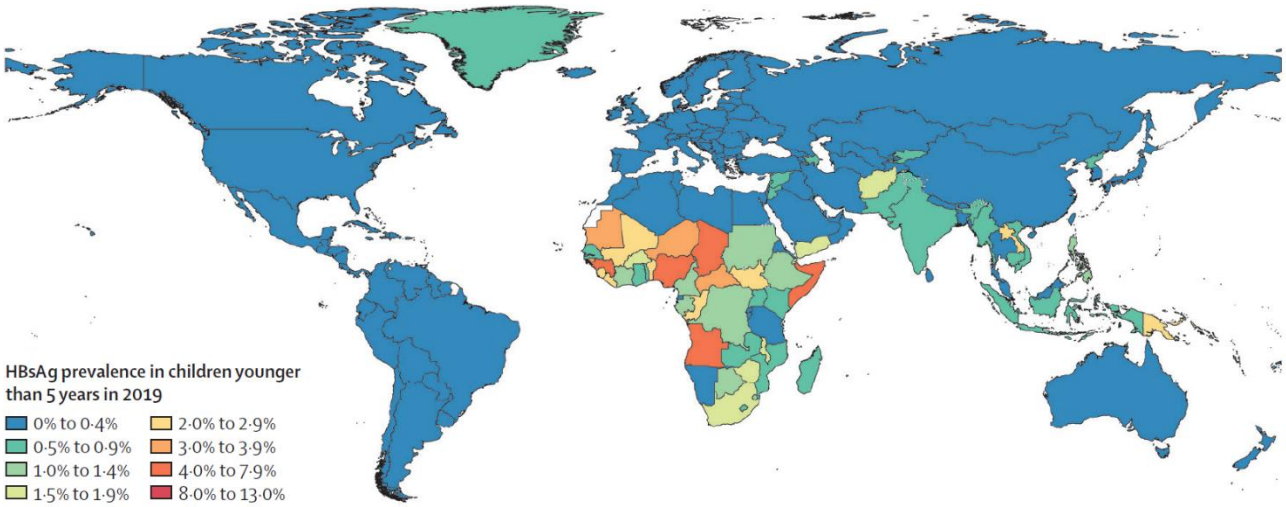


Figure 1.5b - Geographical distribution of HBsAg prevalence in children younger than 5 years in 2019

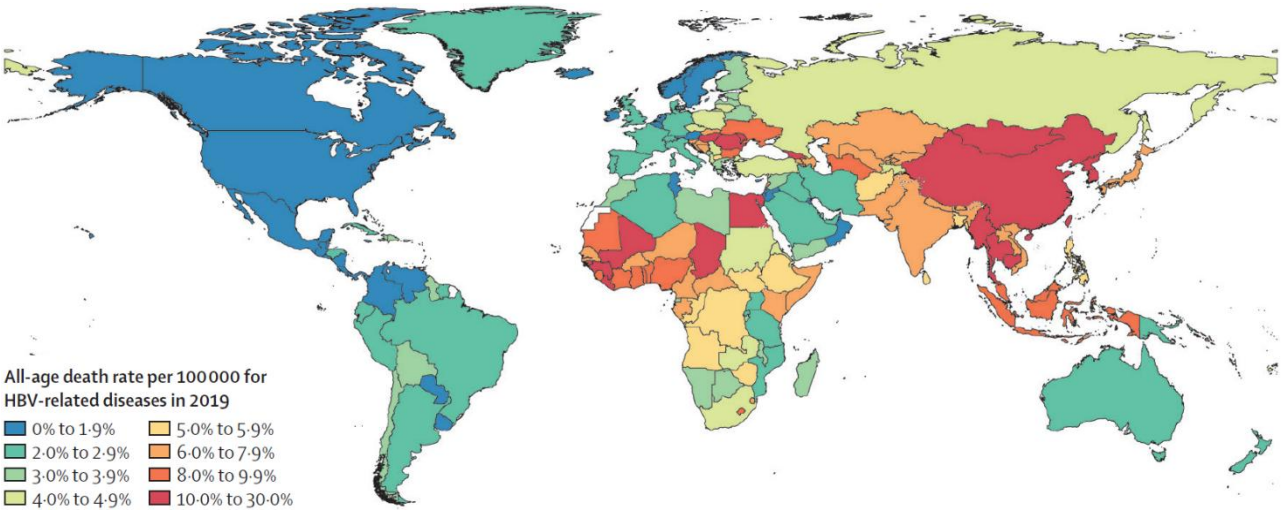


Figure 1.5c - Geographical distribution of all-age death rate per 100 000 for HBV-related diseases in 2019

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

Specific patterns of HBV transmission and natural history in West Africa

There are a limited number of studies that have examined patterns of HBV transmission in the specific context of West Africa. Regarding MTCT, a longitudinal study in The Gambia found that 16% of chronic HBV infections between 1974 and 2008 were due to MTCT (43). However, no other estimates of this proportion have been made in the specific context of West Africa. A global model estimated that the proportion of new chronic cases attributable to MTCT is likely to increase rapidly from 16% worldwide in 1990 to 50% in 2030, because the introduction and uptake of childhood vaccination is increasing faster than the introduction and expansion of MTCT interventions (44). The risk of HBV MTCT is estimated to be lower in sub-Saharan Africa than in Asia, with a risk of 38% in HBeAg-positive and 5% in HBeAg-negative mothers, compared with 70-90% in HBeAg-positive and 5-30% in HBeAg-negative mothers in Asia (6). This pattern appears to be consistent in West Africa, as observed in studies specific to the region. Risk factors for HBV MTCT include younger maternal age and lower birth order, as lower age is associated with a higher risk of being HBeAg positive and children of lower birth order are more likely to be born to young mothers (45). In West Africa, the mean age at childbearing (29.4 years) is slightly higher than the global and Asian averages (28.3 years), potentially exerting a positive impact on decreasing MTCT risk (46).

In the absence of MTCT, birth order plays a contrasting role in horizontal transmission. Children of high birth order, in the absence of MTCT, could be infected earlier by their HBV-infected older siblings, compared with children of low birth order, who encounter HBV infection later, typically when they start school (45). Having a higher number of older siblings was associated with a higher risk of HBV transmission in children (47) and with a higher risk of developing HCC later (45). Pre-vaccination studies in The Gambia, Ghana and Liberia found that the proportion of children with active and passive markers of HBV infection increased significantly with age (47–49). Before the age of 5, about 50% of

children presented these markers, rising to about 80% in those under the age of 20 (47,48). In addition, pre-vaccination studies in The Gambia showed that HBV transmission was often clustered within families, particularly between siblings (47). Larger family size was associated with an increased risk of HBV transmission, a finding supported by phylogenetic analyses indicating intrafamilial transmission in at least two-thirds of the families studied (50).

HBV co-infection with HIV significantly increases the risk of HBV disease progression, with co-infected individuals having five times the rate of progression of HBV mono-infected individuals. This increased risk leads to a further increase in the likelihood of developing cirrhosis and HCC (51).

1.2.2. The fight against HBV in West Africa

The fight against HBV in West Africa is part of a global effort to eliminate viral hepatitis. However, despite the long-identified and well-documented high endemic status of HBV in West Africa, the implementation of key strategies for prevention, diagnosis, and treatment has been a lengthy process and is still ongoing.

Vaccination against HBV in West Africa: a long story

West Africa played a pioneering role in the early trials of the first hepatitis B vaccine in the late 1970s and 1980s. The Niakhar site in Senegal hosted one of the first experimental studies on hepatitis B vaccine led by French virologist Philippe Maupas, in collaboration with doctors from French and Senegalese universities. The vaccine tested was a home-made, unconventional HBV vaccine developed by Maupas' team in France in 1974. This vaccine was based on a new concept called "plasma" and consisted of virus envelopes, known to be non-infectious but immunising, derived from the sera of blood of donors who were healthy carriers of anti-HBsAg. This experimental study took place in a context where ethics committees did not exist in Senegal or in France, there was no clear idea of the doses to be administered and little was known about the reliability of the antibody response to the vaccine and its potential adverse effects (52). HBV infection was already known to occur through MTCT and to be highly transmitted among children, therefore, all children aged between 6 months and 2 years, and pregnant women had to be immunised even if they were already known to be HBsAg-positive. The sample included between 3,000 and 3,500 vaccinated children and 746 pregnant women, but 50% of the children were lost to follow-up, partly due to infant mortality, which was around 20% at the time, and confusion about the children's names. Early results from the study demonstrated high efficacy of the vaccine, reducing CHB infection by 85% in susceptible children after one year of follow-up, and 94.5% of children had an immune response after three injections (53). The conclusions of the study clearly supported the critical role of immunisation in the elimination of HBV in this specific context and emphasised the urgent need to ensure the affordability of the vaccine (53). At the time, the cost of the HBV vaccine was about US$50 per unit dose, which represented 10 times the health budget per capita in Senegal (52). Maupas' untimely death in a car accident in 1981 marked the end of this pioneering study in Niakhar. Despite attempts to manufacture the plasma vaccine locally at the

Institut Pasteur in Dakar to decrease the unit cost of the vaccine, the production cost alone could not be reduced below $2 per dose, which would make the vaccine unaffordable compared to the per capita health budget (52). A genetically modified HBV vaccine developed in South Korea in 1987, and widely administered in Asia achieved a cost of only $0.9 per dose by 1990 (54,55). Yet, it was not until 2004, 30 years after the Maupas study, that hepatitis B vaccine was included in the Expanded Programme on Immunisation (EPI) in Senegal. This delay in making the vaccine available in Senegal, despite its proven efficacy and urgent need, raised ethical concerns. In addition, the Maupas study left a lingering sense of mistrust in the population, despite its important findings. Controversial practices, such as contentious collection of blood samples from children, high infant mortality without investigating possible links between the vaccine and infant deaths, and the exclusive use of French by researchers without adequate explanations in local languages, left families confused about the ongoing interventions. These practices contributed to lasting mistrust and traumatic memories that persist to this day (52). An important dialogue led by local people and village chiefs, with translation into the local languages of Wolof and Serer, played a crucial role in allaying concerns, rebuilding trust, and fostering a more transparent and collaborative environment with research teams (52).

Other pioneering studies were conducted in West Africa, in addition to the research conducted in Senegal. A study conducted in Nigeria between 1982 and 1984 evaluated the efficacy, effectiveness and safety of a hepatitis B vaccine produced by the Institut Pasteur. The study showed positive results with no infections among participants who received two or three doses of the vaccine (56). The largest known hepatitis B vaccine study conducted in West Africa is the Gambia Hepatitis Intervention Study, initiated in 1986. This study underscored the robust protection offered by hepatitis B vaccination against HBV infection, which led to the successful integration of hepatitis B vaccine into the EPI in 1989, making The Gambia the first country in West Africa to include hepatitis B vaccine in its national immunisation programme (57).

Despite the proven efficacy and critical need for the hepatitis B vaccine in West Africa, its implementation has faced significant delays. In 1991, the WHO recommended universal inclusion of hepatitis B vaccination in national immunisation programmes by 1997, and in 1994 the World Health Assembly called for an 80% reduction in the incidence of HBV carrier in children by 2001. The Gambia led the way, but other West African countries introduced the vaccine at a very slow pace. Although localised programmes offered infant vaccination from the 1990s, their coverage remained very limited, mainly targeting specific facilities in urban areas (58). After Gambia, the inclusion of HepB3 into EPIs was delayed until 2001/2002 in Ivory Coast, Cabo Verde, Ghana, and Benin. Subsequently, West African countries progressively introduced HepB3 into their EPIs, achieving universal implementation by 2009 (59). The main reason contributing to the delayed adoption of HepB3 in the EPI was the higher cost of HepB3 compared with other EPI vaccines, coupled with a lack of financial resources from governments to finance it. The important increase in HepB3 uptake was made possible by financial support

initiated in 2000. This support, provided by the Global Alliance for Vaccines and Immunisation (GAVI) and the Vaccine Fund, facilitated the inclusion of HepB3, initially as part of a tetravalent vaccine, which was later replaced by a pentavalent vaccine. This support was intended to address inequities in the availability of vaccines in developing countries. The effective implementation of HepB3 into the EPI in West African countries resulted in a significant reduction in prevalence of CHB infection among children aged 5 or below, from 11.3% in 1990 to 4.4% in 2019 (13). According to the latest data in 2022, the coverage of HepB3 in West Africa was lowest in Guinea (47%) and Nigeria (62%), while four countries (Burkina Faso, Cabo Verde, Ghana and Sierra Leone) had coverage rates above 90% (59).

HepB3 in its pentavalent form is administered from 6-8 weeks of age, which does not provide protection against the risks of MTCT and horizontal transmission of HBV in the first weeks of life, implying the need for specific administration of HepB-BD at birth. Early studies on hepatitis B vaccination in West Africa were already recommending vaccination at birth to prevent HBV MTCT (53,57). The Gambia is the only country in West Africa to have introduced HepB-BD very early in its EPI, alongside HepB3, since 1989. In Senegal, the National hepatitis control programme (PNLH) provided HepB-BD at birth from 1999 but it was only for newborns in some specific health facilities (58). With the implementation of pentavalent vaccines, efforts were focused on the administration of HepB3 from 6-8 weeks of age, as control of horizontal transmission was considered a higher priority. In this context, HepB-BD has taken longer to introduce in West Africa than HepB3. After The Gambia, Cabo Verde and Nigeria were the next countries to introduce HepB-BD in 2002 and 2004, respectively, followed by Mauritania in 2013, Senegal in 2016, Ivory Coast in 2019, Benin in 2020, Guinea in 2021, and Burkina Faso in 2022. Seven of the 16 West African countries have not yet implemented HepB-BD in their EPI.

Among the countries that have implemented HepB-BD, the latest data on coverage show that only one country, Cabo Verde, has HepB-BD coverage above 90%. Benin and Senegal have coverage of around 75%, Ivory Coast 67%, Burkina Faso 53% for its first year of implementation, and the other countries have lower or no reported coverage.

Preventive measures for the control of HBV MTCT

Current other preventive interventions mainly focus on MTCT prevention. To ensure the effective implementation of all strategies available to control HBV, the development of a national strategic plan for viral hepatitis is essential. The importance of such national plan lies in defining specific targets to eliminate viral hepatitis as a public health threat, in guiding, implementing and monitoring effective responses to viral hepatitis, in supporting the efficient allocation of domestic resources and mobilising external funding (60). In 2021, nine of the 16 West African had a national strategic plan for viral hepatitis (61). However, Cabo Verde stands out as the only country to report guidelines for routine HBsAg screening of pregnant women and provision of antiviral prophylaxis to eligible women, in addition to HepB-BD (62). In settings without formal recommendations, health workers may still encourage pregnant women to undergo HBV screening. Despite this,

HBV screening of pregnant women in West Africa is not universally and routinely offered as part of antenatal care, and the cost remains the responsibility of the woman. Furthermore, due to the serological nature of HBeAg or HBV DNA testing, its availability is concentrated in areas with laboratories, which are typically located in urban areas, neglecting rural areas. This is a challenge, as the identification of pregnant women with high HBV DNA or HBeAg levels was a prerequisite for the administration of antiviral prophylaxis in the guidelines prior to the 2024 updates. In addition, antiviral prophylaxis is not routinely provided in antenatal care. Paradoxically, TDF can be freely available in antenatal care, but only for pregnant women living with human immunodeficiency virus (HIV), thanks to funding from the Global Fund, PEPFAR or UNITAID, but despite the availability of the drug, it cannot be freely provided to mono-infected HBV-infected pregnant women (63).

Besides there is also a lack of recommendations for counselling and medical management of HBV-positive pregnant women, as well as for possible additional screening of partners, siblings or children (64).

With regard to hepatitis B immunoglobulin (HBIG), its availability in West Africa is almost non-existent and limited to a few private sector facilities where the cost is borne by the patient. Given the high unit price of HBIG, which ranges from US$150 to US$200, and the associated logistical constraints, its use is not universally recommended (24).

HBV treatment and care

Effective prevention of advanced, life-threatening HBV-related disease requires comprehensive screening to identify chronically infected individuals, followed by appropriate follow-up and treatment. In West Africa, similar to pregnant women, the cost burden of HBV screening, treatment eligibility assessment and treatment falls on the patients themselves. In the WHO African region as a whole, it is estimated that by the end of 2022, only 4.2% of people living with HBV were diagnosed, and just 0.2% had access to treatment (10). Access to HBV screening is already a complex task, and prior to the simplified treatment guidelines in 2024 (19), treatment recommendations were equally complex, depending on viral replication and the degree of fibrosis inflammation. Previous guidelines for clinical assessment before initiating treatment required a detailed clinical history, physical examination, complete blood count, prothrombin time, creatinine, liver profile, alpha-fetoprotein and ultrasound imaging, placing an additional resource burden on patients (64,65).

A multicentre PROLIFICA project assessed the feasibility and cost-effectiveness of a large-scale test-and-treat programme in The Gambia during community-based testing activities, and among blood donors (66). Among communities, 69% accepted HBsAg screening, while the acceptance rate among blood donors was 81%. Among HBV-infected individuals, 81% were linked to care in the community, while only 42% were linked to care among blood donors. Among those attending a clinic, 4.4% were eligible for treatment, compared with 9.7% among blood donors. This study showed good feasibility and acceptability of such intervention strategy in The Gambia. Based on these acceptability and feasibility results, the cost-effectiveness analysis showed that such a

strategy would be cost-effective at a threshold of one times GDP per capita, but the probability of such a strategy being cost-effective at this threshold was only 20%, and it was no longer cost-effective at a threshold of 0.5 times GDP per capita (67). The cost-effectiveness results were more sensitive to tenofovir and screening costs and to the rate of transition to compensated cirrhosis.

Regular follow-up is imperative for HBV-infected patients, regardless of treatment eligibility. In Sierra Leone, a study evaluated retention in care among HBV-infected patients attending a rural HBV clinic providing free care and treatment (68). The findings showed that 65.5% of eligible individuals initiated treatment. Of those who initiated treatment at baseline, 51.3% remained in care at one year. In contrast, only 32.3% of patients who were ineligible for treatment at baseline but eligible for one-year follow-up remained in care at one year.

Prevalence of HCC is particularly high in West Africa, posing a significant challenge in a region where UHC has yet to be achieved and public health infrastructure and human resources are inadequate. This situation results in a high demand for care from traditional healers who offer a wide range of remedies such as herbs, healing prayers and massage at low-cost to treat all types of diseases, including advanced liver disease and cancer (69,70). But, poorly managed and untreated cancers can have a profound impact on the physical and mental health, functional capacity and quality of life of cancer patients, potentially leading to reluctance to take medication and a desire for death (71,72).

1.2.3. Main challenges hindering expansion of HBV interventions in West Africa

The elimination of HBV relies on prioritising the implementation of multiple prevention and treatment interventions. However, progress is being delayed due to several barriers identified at different levels of the health system.

Barriers at the policy level

At the policy level, policy inertia characterised by a lack of political interest and willingness to optimally implement intervention strategies against HBV is an important barrier (73,74). This is partly due to insufficient awareness and advocacy to draw political attention to the burden of HBV. Advocacy can be effective when there is sufficient evidence on the epidemiology of HBV and sufficient data on the effectiveness of new intervention strategies. Affordability and cost-effectiveness assessments are essential for policymakers to consider new intervention strategies, particularly in LMICs with limited health budgets and significant health investment needs. However, the accuracy of these assessments also depends on the availability of data on the feasibility, acceptability, effectiveness and costs of implementing these intervention strategies. Furthermore, because the evolution of HBV is complex, long-term and varies between geographical areas, modelling could be used to assess the long-term impact of interventions, but this also requires sufficient data on the natural history of HBV in the context of interest. Even if certain innovations are found to be successful in improving health at the local level, the

delay in translating these innovations into routine practice by national programmes can also be a barrier (75). Some innovations have been shown to increase immunisation coverage, such as mHealth technology, community-based services, reminder systems, or mobile outreach services, but their implementation at national level can take time. Prolonged political and social unrest and instability also have a negative impact on the smooth functioning of health programmes (76).

Another critical barrier is the lack of alignment between the priorities of international funding agencies and local health needs, including HBV (73,77). This misalignment in funding allocation has led to controversy and inconsistencies. Funds are not only allocated based on organisations' priorities, which are biased towards specific diseases, but they can also influence policies regarding local disease priorities in LMICs (78,79). For instance, in the early 2000s, an important mobilisation against HIV resulted in major funding for LMICs to specifically address HIV and provide access to antiretroviral therapy (ART). However, this funding failed to account for the diverse health priorities across African countries. In settings with high HIV prevalence, ART was crucially lacking, whereas in countries with low HIV prevalence (below 1%) such as Senegal, HIV-infected people could benefit from sophisticated and expensive antiretroviral treatments, while these countries faced more pressing problems such as hepatitis B, cholera or high infant and child mortality (80–83). In addition, the implementation of such programmes required the mobilisation of additional local resources, including capital and human resources, representing an opportunity cost to local health systems. A more recent example occurred in the context of COVID-19, where global mobilisation constrained many countries in Africa to prioritise the prevention and containment of the virus, while facing disruptions to medical supply chains, transportation challenges, facility closures, and other impacts on the population (84). In the end, the impact of COVID-19 in Africa was less than expected. Unfortunately, COVID-19 also disrupted GAVI's plans to support the introduction of HepB-BD. Until 2018, GAVI was reluctant to fund HepB-BD introduction in LMICs that had not yet implemented it, as the unit cost of HepB-BD fell below its minimum vaccine unit cost criteria for providing funding. But in 2018, the GAVI Alliance's vaccine investment strategy changed their policy to prioritise support for the implementation of HepB-BD from 2021. With the emergence of COVID-19, GAVI shifted its priority to scale-up COVID-19 vaccination instead of HepB-BD (85). Finally, in 2023, GAVI announced that it would again prioritise the implementation of HepB-BD (86). In addition to the misalignment of international funding with local needs, another inconsistency is the imposition of 'conditionalities' on recipient countries. These conditionalities are requirements or policies that funding organisations expect recipients to follow in exchange for funding. They can range from the production of statistics to the adoption of mass privatisation, cuts in health or education budgets, or the removal of price and trade regulations. The term 'conditionalities' originated from the International Monetary Fund (IMF) loans in the mid-1980s, with several studies showing evidence of adverse impacts on health (87). Although the issue has been debated since the Paris Declaration in 2005, the problem still persists (88,89). Moreover, private donors, often referred to as 'philanthropic capitalists', have a growing influence in health policy

decisions (90,91). One of the most influential private donors is the Bill and Melinda Gates Foundation, which is the fourth largest investor in the GAVI Alliance, as well as a major donor to the Global Fund or UNITAID. The number of donors multiplies with the number of commitments, and critics argue that these commitments prioritise short-term goals over more effective long-term investments (89,92). Furthermore, these short-term goals are closely linked to conflicting interests, and no agency exist to regulate these funding programmes (93,94).

Barriers at the facility level

Cost is an important barrier to access to HBV screening, to HepB-BD in settings where it is not freely provided, or to antiviral as prophylaxis for pregnant women at risk of MTCT or as treatment for eligible HBV-infected people (63,73). Even in settings where HepB-BD is provided free of charge, some private facilities may charge an additional fee for providing a vaccination card (73). The availability of antiviral drugs can also be limited in healthcare facility pharmacies, except at some central level (63). Beyond the cost of screening and drugs, HBV-positive patients must face the financial burden of numerous medical examinations that are an integral part of their follow-up and treatment. HBV screening tests and medical examinations are often centralised at a regional level, requiring patients to travel long distances and endure long waiting times, with significant opportunity costs (95).

Effective administration of HepB-BD include challenges in maintaining the vaccine cold chain, with some facilities lacking refrigerators that meet safety standards or monitoring tools for temperature control (73,96). However, the WHO Strategic Advisory Group of Experts has urged hepatitis B vaccine manufacturers to relabel monovalent hepatitis B vaccines for use outside the cold chain, as they have been shown to be safe and effective when stored at temperatures up to 37°C for one month (97). Another barrier is the lack of awareness and/or training of health workers responsible for administering HepB-BD on topics such as HBV, the benefits of vaccination, and the proper administration of HepB-BD (96). Insufficient pre- and post-test counselling of pregnant women and lack of awareness of the importance of HepB-BD are additional challenges (98). The unavailability of HepB-BD directly in health facilities in settings where it has not yet been implemented can be a barrier if the mother wishes to afford the vaccine (98).

Depending on the facilities, health workers responsible for administering HepB-BD may be those working specifically in maternity wards, while in other facilities they may be those responsible for administering the EPI. During weekends and public holidays, health workers specifically dedicated to HepB-BD may be off duty, causing potential delays in administering HepB-BD (96). Additionally, some facilities may lack adequate recording tools to accurately capture timely HepB-BD coverage at the facility level, leading to incomplete or inconsistent coverage (96).

An important barrier to the treatment and care of people living with HBV is the lack of knowledge and training of health care workers. This limitation hinders their ability to provide comprehensive advice to patients screened as HBV-positive, compelling them to refer these patients to specialists (63).

Barriers at the individual level

Several individual factors can affect the uptake and timeliness of HepB-BD, with home births being a common barrier to optimal administration. The lack of formal outreach programmes to vaccinate newborns at home or to refer mother-child pairs to nearby facilities amplifies this barrier (73,96,99). Even when mothers do attend health facilities with their babies, this is often after the 24-hour period recommended for HepB-BD. Burkina Faso and Cabo Verde stand out as the only two West African countries where more than 90% of births take place in health facilities, thanks to strong policy initiatives to promote such births. In Niger, Nigeria, Guinea and Guinea-Bissau, by contrast, more than half of births take place outside health facilities (100). While some pregnant women may prefer to give birth at home and wait to bring their babies to a health facility because of cultural norms or traditions (96), others may face barriers such as distance and transport that limit their access to a health facility and may prevent them from giving birth in a facility or seeking postnatal care (99).

Home delivery and increasing distance to a vaccination site are also important risk factors for non-completion of HepB3 in infants (101,102). Other risk factors for non-completion of HepB3 include adolescent motherhood, lower wealth index, fewer than four antenatal visits, religious beliefs, ethnicity, lower education, season of birth (dry/wet) due to seasonal migration of mothers or high birth order (101,102).

The high cost and limited accessibility of HBV treatment and care often lead people with HBV to prefer traditional remedies as first-line treatment, believing them to be more effective and less costly (63,95,103). The use of traditional medicine may also be related to cultural beliefs about HBV infection, which may be perceived as punishment from the gods, an act of witchcraft, or the result of spiritual poisoning (95). Dissatisfaction with formal care, particularly when doctors do not prescribe medication at the first visit or when patients perceive a lack of expertise, may motivate individuals to seek traditional remedies (95). These barriers, combined with fear of stigma, limited infrastructure, lack of resources, lack of knowledge about HBV treatment, long waiting times in hospitals, and the absence of chronic HBV signs and symptoms, can discourage people with HBV from seeking formal care or adhering to treatment and can worsen their condition (95,103). People with HBV often seek hospital care too late when their condition becomes critical and irreversible (63).

Barriers hindering the expansion of HBV interventions in West Africa exist at various levels of the health system and are composed of multiple factors. These factors are often intertwined and not isolated entities. To ensure effective future expansion efforts, a comprehensive understanding of this complex interplay is necessary. However, some factors, such as those linked to financial resources, are known to serve as underlying causes for many other barriers.

2. Rationale and research objectives

2.1. Rationale

Although West Africa is an area of high HBV endemicity, HBV has long been neglected as a pressing public health issue. Despite this, progress have been made, driven by a growing awareness of the imperative to control and eliminate HBV. The gradual inclusion of HBV on political agendas, the increased availability of epidemiological data, the positive results of the implementation of HepB3 in the EPI and a growing body of evidence on effective interventions have all contributed to a better recognition of the urgency of eliminating HBV. However, HBV infection has been described as a poverty disease because cost is a fundamental barrier that encompasses many other underlying barriers to the implementation and scale-up of effective interventions against HBV transmission (101). Cost is at the forefront of challenges, discussions and solutions at various levels of implementation strategies, whether for advocacy, policy considerations or expanding access to HBV interventions, training and awareness programmes.

The first step in controlling HBV is to stop its transmission through preventive measures, especially in settings where diagnostic tests, medical examinations, monitoring services and treatment for HBV-infected individuals are not only costly, but also rarely available or accessible in many health facilities in West Africa. While there is an urgent need to implement preventive interventions, the prevention of mother-to-child transmission (MTCT) has been left behind. This is particularly alarming given that infants infected through the MTCT route are at significantly higher risk of developing chronic disease and related complications. Although the WHO recommends HepB-BD for all newborns, only half of the countries in West Africa have integrated HepB-BD into their EPI programmes. Quantifying the budget needed to implement HepB-BD is a critical step for countries that have yet to integrate it. Drawing on the experience of West African countries that have successfully integrated HepB-BD into their EPIs provides an opportunity to identify the resources needed and the associated costs.

Besides, while studies in highly HBV-endemic areas of Asia have shown that HepB-BD has a significant impact on reducing HBV MTCT, its efficacy is much more limited in West Africa. There remains a significant residual risk of HBV MTCT, particularly in HBeAg-positive pregnant women, despite the administration of HepB-BD. Uncertainties extend not only to the costs of implementing HepB-BD, but also to its cost-effectiveness, given the much more limited impact on HBV MTCT reduction. This is even more important in West Africa, which faces multiple health challenges with limited human, logistical and financial resources. Governments need to invest in the most optimal strategies to maximise health benefits for their populations.

HepB-BD alone is not sufficient to prevent MTCT, and additional interventions such as HBV screening in pregnant women and antiviral prophylaxis are needed. However, access

to HBV screening and antiviral prophylaxis in West Africa is even more limited than for HepB-BD and remains the responsibility of women. Despite the WHO recommendation to conduct systematic screening for HBV in antenatal clinics when the prevalence surpasses 2%, and the availability of reliable RDTs for HBV diagnosis, HBV screening tests are still not available in antenatal facilities. There is also a lack of knowledge, awareness and training among health workers, which hinders their ability to systematically prescribe HBV screening for pregnant women. In addition, pregnant women identified as HBV-positive are supposed to undertake HBV DNA quantification or HBeAg test to assess their eligibility to antiviral prophylaxis. However, HBV DNA is very expensive, and HBeAg testing, although less expensive, requires laboratory equipment available at some central level, which would require pregnant women to travel long distances, representing an additional opportunity cost. Moreover, once pregnant women have been identified as eligible for antiviral prophylaxis, even in case they can afford paying their treatment, there is still the need to access TDF drugs, which are mostly not directly available at the health facility, except in regional or national hospitals.

Evaluation of the costs and cost-effectiveness of implementing screening tests and antiviral prophylaxis within antenatal care in the context of West Africa remains unexplored and is essential for advocating the implementation of these interventions. Standard criteria for determining eligibility for antiviral prophylaxis, such as high HBV DNA and the presence of HBeAg, could be compared with newer strategies that may be more optimal for eliminating HBV MTCT in West Africa. Examples include offering antiviral prophylaxis to HBcrAg-positive pregnant women, requiring only RDT testing for identification, or adopting a "prophylaxis for all" strategy.

2.2. Research objectives

The overall objective of this thesis was to evaluate different intervention strategies for the prevention and elimination of HBV MTCT in West Africa, using modelling techniques and economic analysis to identify efficient approaches.

This overall objective could be subdivided into four specific objectives:

1. Assessing resources and costs for HepB-BD introduction in the EPI

Building on Senegal's experience in introducing HepB-BD into the EPI in 2016, this objective was to identify the resources mobilised at different levels of the health system and to assess the financial cost (actual government expenditure) and economic cost (financial cost plus opportunity cost of existing resources) of introducing HepB-BD in the EPI through a micro-costing study. No previous study had assessed the financial and economic costs of implementing HepB-BD in a West African country, and the results provided a clearer overview of the resources and budget needed to implement HepB-BD.

2. Analysing the cost-effectiveness of introducing HepB-BD in the EPI

Recognising the unique patterns of HBV transmission in sub-Saharan Africa, where the effectiveness of HepB-BD is more limited than in other highly endemic areas such as in

Asia, this objective aimed to assess the cost-effectiveness of implementing universal HepB-BD. This study was conducted in the Dafra health district in the Hauts Bassins region in Burkina Faso, using comprehensive data on HBV epidemiology and HepB-BD effectiveness in the context of West Africa. The results shed light on the feasibility and cost-effectiveness of universal HepB-BD and identified influencing factors.

3. Identifying resources and costs of implementing HBV screening and antiviral prophylaxis in antenatal care

To achieve systematic HBV screening and high coverage of TDF prophylaxis among pregnant women at risk of MTCT, these interventions must be readily available within routine antenatal care services. Specifically, this objective focuses on evaluating the total costs associated with implementing HBV screening, performing additional HBV testing to assess eligibility for TDF prophylaxis in HBV-infected pregnant women, and administering TDF prophylaxis directly during antenatal care visits. The analysis compared the two pre-2024 WHO recommendations (based on high HBV DNA levels and the presence of HBeAg) with two alternative strategies, including HBcrAg positivity and inclusion of all HBV-positive pregnant women. This analysis was conducted at the national level in Burkina Faso and provided an overview of the resources and costs required for successful implementation.

4. Modelling the impact and assessing the cost-effectiveness of HBV screening strategies and antiviral prophylaxis in antenatal care

Given the variable performance of tests used to assess TDF eligibility, different strategies yield different levels of effectiveness. This objective involved modelling the impact and cost-effectiveness of HBV screening strategies and antiviral prophylaxis in antenatal care. The study aimed to estimate the effectiveness of introducing TDF prophylaxis, to project the expected year of MTCT elimination compared to introducing HepB-BD alone, and to identify optimal cost-effective strategies. The analysis was conducted at the national level in Burkina Faso, providing valuable insights into the most efficient approach.

3. Methods

3.1. Study setting

3.1.1. Senegal

Overview

With an area of 196,722 km^2, Senegal is administratively divided into 14 regions, 46 departments, 133 districts and 557 communes. The population of 16.88 million in 2023 is particularly young, with 52.1% under the age of 20 (104). The population density is 85 inhabitants per km^2 (105). Most of the population lives in urban areas (53.3%) (106).

In 2023, the fertility rate was 4.5 births per woman and life expectancy at birth was 68 years. The maternal mortality rate was 315 per 100,000 live births and the infant mortality rate was 29 per 1,000 live births (105).

Senegal is classified as a lower-middle-income country with a gross national income (GNI) per capita of US$1,570 in 2021 (105). With economic growth of 6% per year between 2014 and 2018, and 4.6% in 2023, Senegal is one of the most dynamic economies in Africa. Senegal's economy is mainly driven by investment in mining, tourism, construction, fishing and agriculture (105,106).



Figure 3.1 - Map of Senegal

Health care system

Senegal's health system reflects its administrative structure and comprises: a central level (Ministry of Health and Social Affairs), an intermediate level (14 regions) and a peripheral level (77 health districts). Public health facilities, including health posts, health centres and various levels of hospitals, are complemented by the private sector, which accounts for 45% of all health facilities (107). Senegal is particularly affected by brain drain, which affects the number of health workers available in the country. In 2019, the density of physicians was only 0.088 per 1,000 people and the density of nurses and midwives was 0.5 per 1,000 people (105), both well below the threshold of 2.3 health workers per 1,000 people required to achieve the Millennium Development Goals (108).

In 2013, the Senegalese government launched a strategic plan for the development of UHC, which aims to provide the population with full or partial coverage of healthcare costs. This plan has several components: the promotion and development of mutual health insurance, the implementation of a reform for compulsory health insurance, the strengthening of free access to health care for specific groups such as the elderly (Plan Sésame), women who have undergone caesarean sections or children aged 0 to 5 years. The Agency for Universal Health Coverage (ACMU) was created in 2015 to coordinate actions to achieve UHC (109). Despite these efforts, out-of-pocket expenditure remains very high and represented 47% of total current health expenditure (CHE) in 2021, while the share of social health insurance represented 8% of CHE (110). Furthermore, domestic general government health expenditure represented only 4% of general government expenditure in 2019, far below the Abuja Declaration target of 15%. With external health expenditure representing 18% of CHE, Senegal is also highly dependent on external sources of funding.

In terms of maternal health, in 2019, 98% of pregnant women received antenatal care from a skilled health worker, 56% attended the recommended four antenatal visits, and 64% attended their first visit during the first trimester of pregnancy (111,112). The proportion of pregnant women who were screened for HIV was 81%, but only 70% of HIV-positive pregnant women received antiretroviral therapy (113). Deliveries and caesarean sections are free in Senegal. In 2019, the percentage of births that took place in a health facility was 80%, and the percentage of women who received postnatal care within two days of delivery was also 80% (111).

3.1.2. Burkina Faso

Overview

Burkina Faso covers an area of 274,200 km^2, divided into 13 regions, 45 provinces, 350 departments, 359 communes and over 8,000 villages. With a population of 20.5 million in 2019, and a density of about 75 inhabitants per km^2, Burkina Faso is predominantly rural, with 73.9% of the population living in rural areas and engaged in agriculture and livestock farming. The demographic landscape is characterised by a young population, with 45% in the 0-15 age group (114).

In 2023, the fertility rate was 4.9 births per woman, and life expectancy at birth was 60 years (105). Maternal mortality was 320 per 100,000 live births and infant mortality was 53 deaths per 1000 live births.

With a GNI per capita of US$830 in 2021, Burkina Faso is classified as a low-income country. Economic growth was 6.9% in 2021, then 3.0% in 2023, driven mainly by steady progress in gold exports and the retail sector (115,116). A large majority of the population (63%) works in the agricultural and livestock sector, especially women, who make up seven out of ten people working in this sector (114).

Since the first jihadist attack in the Sahel region of Burkina Faso in 2015, terrorist networks have expanded their presence across the territory, making the fight against terrorism one of Burkina Faso's biggest challenges. In the midst of these heightened tensions, the country plunged into political instability, experiencing two coups d'état in 2022.

Burkina Faso is also facing environmental challenges, with increasingly prolonged droughts threatening the food security of households that depend on agriculture for their livelihoods.



Figure 3.2 - Map of Burkina Faso

Health care system

Burkina Faso's national health system comprises central, intermediate and peripheral levels (117). The central level includes structures organised around the cabinet of the Minister of Health and Public Hygiene and oversees policy development, resource mobilisation and performance evaluation. The intermediate level, consisting of 13 regional health directorates, coordinates and monitors activities carried out at the district level in accordance with the strategic orientations set out in the national health policy.

The peripheral level comprises 70 health districts, each managed by a district management team (ECD), which is responsible for the clinic, planning, management and organisation of health facilities. Public health facilities are also organised into three levels, which form the health pyramid. The first level is made up of two sublevels: a first one that includes 2057 primary health centres (CSPS), 110 isolated dispensaries, 10 isolated maternity hospitals and 70 medical centres (CM), and a second one that includes 48 medical centres with surgical services (CMA), which act as reference centres for the public health facilities of the first sublevel. The second level of public health facilities includes nine regional hospital centres (CHR), which serve as a reference for CMAs. The third level includes six university hospital centres (CHU), which represent the highest level of reference. Public health facilities are complemented by private health facilities, mainly concentrated around Ouagadougou and Bobo-Dioulasso, which represent 28% of all health facilities (118). A majority of the population (59.8%) lives less than 5 km from a health facility.

In 2019, the density of physicians was only 0.094 per 1,000 people and the density of nurses and midwives was 0.9 per 1,000 people (105). Health services are substantially complemented by 17,648 community health workers (ASBC), who are mainly deployed in rural areas to provide basic prevention, health promotion and care services at the local level.

Domestic government spending on health accounted for 10% of general government expenditure in 2019, making Burkina Faso the country that spends the highest proportion of its budget on health in West Africa (105). Despite these efforts, out-of-pocket expenditure remains important, representing 35% of total CHE, and external health expenditure represents 18% of CHE.

In 2015, Burkina Faso adopted a law to create a universal health insurance scheme (RAMU) that would be compulsory for all. RAMU is intended to build on existing insurance mechanisms, in particular community and professional health insurance. The plan provides for the gradual introduction of compulsory health insurance for workers in the formal sector (civil servants and private sector employees) and a voluntary health insurance scheme for workers in the informal and agricultural sectors, with a gradual transition to compulsory status. The operationalisation of the RAMU began in 2018 with the creation of the National Fund for Universal Health Insurance (CNAMU). The Burkinabe government is also committed to provide full and free health care to indigent people who are unable to contribute to health insurance. To this end, a pilot phase is being carried out in four regions (Boucle du Mouhoun, Centre, Hauts-Bassins, North), in which cards are being distributed to the indigent, giving them access to free medical care, with the exception of certain medicines and treatments for chronic diseases. As part of the RAMU initiative, Burkina Faso introduced free healthcare for pregnant women and children under five throughout the country in 2016, leading to significant improvements in child and maternal health. In 2021, 98% of pregnant women received prenatal care from skilled health personnel, with 72% attended the recommended four prenatal visits (119). Furthermore, 88% of pregnant women were screened for HIV in 2019, and 100% of HIV-positive pregnant women received antiretroviral therapy (120). In 2021, the proportion

of births that took place in a health facility was 92.4%, and the proportion of women who received postnatal care within two days of delivery was 78% (119).

3.2. Main methods of analysis

This section provides a comprehensive overview and description of the main analytical methods used in this thesis.

3.2.1. Economic evaluation

The adoption of optimal interventions that maximise health benefits in a world of limited resources is a public health concern. Economic evaluation serves as a critical decision-making tool that aims to compare alternative options (products, services, health programmes, interventions, etc.) and determine the most resource-efficient allocation. It focuses on the benefits to the collective, rather than to individuals, and involves identifying, measuring, valuing and comparing the costs and consequences associated with the alternatives under consideration (121). There are four types of economic evaluation:

- **Cost-minimisation analysis (CMA)**: Appropriate when the options considered produce equivalent outcomes, focusing only on costs.
- **Cost-effectiveness analysis (CEA)**: Compares costs and outcomes in terms of a specific assessed outcome such as number of life years gained, number of cases detected, or a clinical criterion expressed in physical units (blood pressure, cholesterol levels, etc.).
- **Cost-utility analysis (CUA)**: Extends cost-effectiveness analysis by considering the quality of life (Health-Adjusted Life Years, HALYs) associated with the survival gained.
- **Cost-benefit analysis (CBA)**: Evaluates costs and outcomes in monetary terms and determines the option that maximises net benefits.

In this thesis, economic evaluation has used both CEA and CUA approaches. While both are often combined under the term CEA, the same convention is followed here.

Several methodological considerations are crucial in economic evaluation to avoid misleading results or misinterpretations. These include the perspective retained (societal, government, patient, health facility), time horizon (short- or long-term), discounting to reflect the fact that costs and consequences do not have the same weight in the present as they do in the future, and the credible valuation of costs and outcomes.

The **Incremental Cost-Effectiveness Ratio (ICER)** is the traditional summary result in a CEA. Calculated as the difference in cost between two interventions divided by the difference in their effect, the ICER represents the average incremental cost associated with one additional unit of the measure of effect:

$$ICER = \frac{Cost_{intervention} - Cost_{control}}{Effect_{intervention} - Effect_{control}}$$

Interpreting the ICER alone can sometimes be ambiguous. To complement the interpretation, results can be presented on a **cost-effectiveness plane** (Figure 3.3).

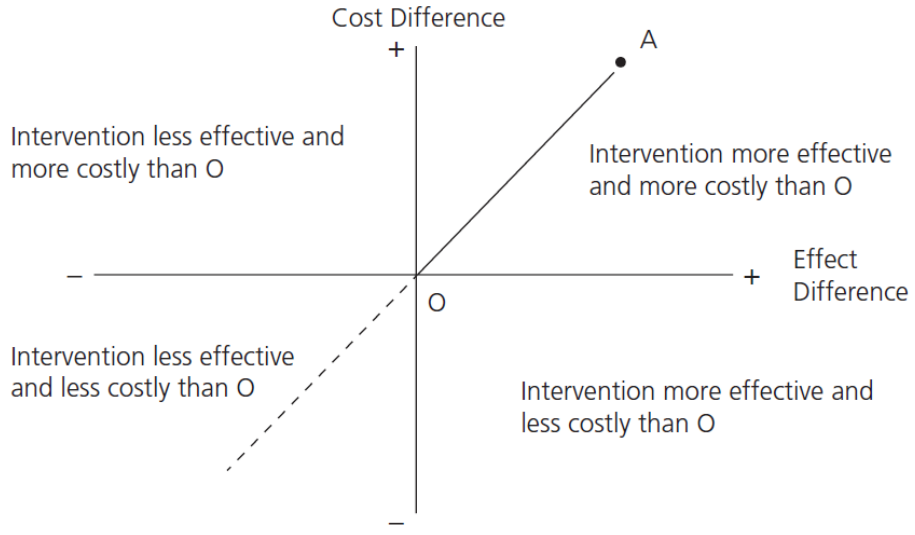


Figure 3.3 - The cost-effectiveness plane
Source: M.F. Drummond et al., Methods for the economic evaluation of health care programmes, Fourth edition. 2015

In scenarios with multiple alternative strategies, it is important to identify dominant and non-cost-effective options. **Dominated strategies** either demonstrate inferior incremental health benefits than another option at the same cost or incur higher incremental costs compared to another option for the same benefit. Strongly dominated strategies result in higher costs and worse outcomes than any other strategy, while extendedly dominated strategies may yield better outcomes than some alternatives but at a higher incremental cost than a more effective strategy. The **cost-effectiveness frontier** connects **dominant strategies** on a cost-effectiveness plane.

If a strategy is more effective but more expensive than the compared strategy, it is considered cost-effective if the ICER falls below the **cost-effectiveness threshold**. This threshold represents the maximum value of a unit of health gain and is based on either an estimate of the health that would be foregone as a result of substituting existing services to pay for the new strategy, or an estimate of society's willingness to forgo consumption in exchange for health improvement. Using an incorrect cost-effectiveness threshold can lead to a net health loss in the population (122). The **cost-effectiveness acceptability curve** plots the probability that a strategy is cost-effective against a range of possible threshold values.

3.2.2. Micro-costing study

Economic evaluations depend on accurate estimates of the costs of interventions or programmes. Reliable cost estimates are essential to avoid misleading results in economic evaluations (123,124). Assessing costs is also informative for planning and efficiently scaling up interventions or programmes. Costing methods range from gross costing, which uses highly aggregated costs, reimbursement amounts, or charges, to micro-

costing, which is considered the 'gold standard' for detailed analysis but is infrequently used due to its labour-intensive nature (123). Conversely, relying solely on fees, prices or payments as a proxy for costs can lead to inaccurate estimates (125). Where feasibility is limited, hybrid approaches can be employed, where, for example, a micro-costing approach is used to estimate the costs of an intervention or programme, while gross costing is used to estimate the cost consequences (126).

Micro-costing studies offer the most precise method for cost analysis, in which all resources used in the implementation of an intervention or programme are enumerated, their values are established, and these values are aggregated to derive total costs. Micro-costing studies are particularly useful for estimating the costs of implementing new technologies, interventions or non-market goods, for which standardised cost estimates are less likely to exist (127). Data collection through a micro-costing study can use a variety of tools and methods, including surveys, forms or interviews, expert panels, activity logs, direct observation, administrative databases, routine records, literature reviews, or reviews of patient records (126,127). Information gathered in a micro-costing study depends on the perspective retained for the analysis (societal, government, patient, health facility).

For a better understanding of micro-costing analysis, some terms need to be defined:

- ***Recurrent costs*** *vs.* ***Capital costs***: Recurrent costs refer to ongoing expenses within a short-term period, usually one year. Recurrent costs are repetitive and include items such as salaries, utilities, maintenance, consumables, and other regular expenditures. Capital costs involve expenditures associated with long-term assets (usually beyond one year), such as buildings, equipment, or initial training programmes.
- ***Financial costs*** *vs.* ***Economic costs***: Financial costs are the actual monetary expenses incurred in implementing an intervention or programme. Economic costs include not only financial costs, but also opportunity costs associated with resource allocation. Economic costs often do not reflect market prices, as resources have alternative uses. Resource units may include a percentage of a health worker's total time, a square metre of facility space, or a share of a vehicle used for transportation. Even if new health workers are not hired, buildings are not constructed, or vehicles are not purchased, including these resource units as opportunity costs involves trade-offs due to these resources not being available for other programmes or interventions. The use of economic costs in economic evaluations ensures that the efficient allocation of resources is considered.

3.2.3. Modelling

When comparing alternative interventions or programmes, measuring their effect in terms of life-years or HALYs is preferable (128,129). This allows all effects to be considered, allows comparisons to be made between different options beyond a single pathology, and allows the results of the economic evaluation to be expressed as a ratio of cost per life-year gained, which may be more meaningful, especially to non-specialists.

Trials often measure only intermediate efficacy using specific disease criteria (e.g. HBV DNA level). However, evaluating the long-term impact of an intervention over a lifetime proves challenging in trials, especially when outcomes manifest long after the intervention. To address this limitation, the use of modelling involves synthesising available evidence from a variety of sources and goes beyond experimental studies to fully evaluate the effect of alternative options. In modelling, patients progress through different health states that represent the evolution of a disease until the final outcome. In the economic evaluation, each state has an associated cost and a health-related quality of life weight to estimate HALYs, allowing the calculation of expected costs and outcomes.

The choice of the appropriate modelling approach is crucial for the accurate measurement of effects. Common models in economic evaluation include decision trees, Markov models and dynamic transmission models (121,130).

Decision trees

A decision tree is one of the simplest and most widely used techniques for evaluating the outcomes of different options. Visually, it represents a sequence of pathways illustrating choices and their consequences. Typically, decision trees consist of three types of nodes: decision nodes, chance nodes and terminal nodes. The process begins with a decision node, which reflects the initial policy decision (e.g. choosing between treatment A or treatment B). Chance nodes represent uncertain events with associated probabilities, such as positive or negative test results, while terminal nodes represent endpoints and final outcomes. Expected values (costs and effectiveness) are calculated by averaging the associated outcomes and costs for each branch and rolling back the tree from the terminal node to the decision node.

While decision trees are straightforward for simple questions (e.g., determining the effectiveness of a treatment for an acute infection), they present challenges for complex diseases with long-term evolution. In such cases, decision trees can become dense, difficult to interpret and more time-consuming than other modelling approaches. In addition, decision trees are limited in that they do not define events within a specific time frame. Progression through different events occurs instantaneously in discrete periods, making them less suitable for considering time-dependent factors, and particularly for discounting costs and effects.

Markov model

A Markov model is a stochastic model, where transitions to the next health state depend solely on the current health state, without consideration of preceding events. In this model, individuals move between states based on the probability of transition—a conditional probability that an individual will be in the next state at the end of a time cycle, given their state at the start of the cycle. The time cycle is the time interval at which transitions between states are assumed to occur. Individuals within a Markov model are independent of each other with respect to their health status. The Markov model uses a cohort-based approach that traces the evolution of disease among individuals with common characteristics at the beginning of the process (e.g. individuals born in a

particular year) and analyses their outcomes. Unlike decision trees, which aggregate costs and effects along pathways and weight them by associated probabilities, the costs and outcomes associated with each state in a Markov model are weighted by the time an individual spends in that state.

Despite its utility, the memoryless nature of the Markov model poses challenges in dealing with time-dependent transition probabilities. Attempts to incorporate such time-dependent probabilities can quickly become unwieldy. In addition, the assumption of independence between individuals in Markov models makes it difficult to incorporate time-varying parameters, particularly the risk of infection, which may increase or decrease over time depending on the number of infected individuals in a given population. As a result, Markov models are often used as static models.

Dynamic transmission models

When simulating infectious diseases over time, the incidence of the disease depends on the current number of susceptible and infected individuals, shaping the epidemic's dynamics. Dynamic transmission models allow the dynamics of an epidemic to be captured. In addition, interventions such as vaccination, which reduce the number of susceptible individuals, induce a herd immunity effect that indirectly affects the dynamics of the epidemic. Dynamic transmission models can thus capture the effect of externalities induced by the intervention.

Various dynamic transmission models exist, ranging from stochastic to deterministic and from population-based to individual-agent-based approaches (131).

Stochastic models incorporate the effect of chance into epidemic dynamics, assuming individuals transition between health states at a random rate. These models often present outcomes as a range (minimum and maximum number of cases that is likely to occur) or probability of an outbreak. Stochastic models are suitable for scenarios where events are random, as may be the case with small or isolated populations. Stochastic models can follow an individual-based approach, simulating disease dynamics for each person in the population, or a population-based approach, where chance determines the number of cases in different health states.

On the other hand, deterministic models always use a population-based approach as they can only be applied to large populations and describe the outcomes of an epidemic as what happens on average in the population. These models are often called **deterministic compartmental models**, as health states are often represented as compartments, with the population divided into different subgroups. They can be constructed using either difference equations when events are considered to occur at discrete time steps, or differential equations when events are considered to occur continuously.

3.3. The Neovac study

The Neonatal Vaccination against Hepatitis B in Africa (NeoVac) study is a multidisciplinary project comprising three research components: epidemiology,

anthropology and economic evaluation. It is coordinated by the Institut Pasteur. All data on costs collected during this thesis were gathered within the framework of the NeoVac project.

The overall objective of the NeoVac study was to promote and develop an effective strategy for the implementation of timely HepB-BD in Senegal, Burkina Faso and Madagascar. The study consisted of two phases. The first phase was the pilot study.

3.3.1. Phase 1: the pilot study

The pilot study, which started in 2015 and ended in 2017, aimed to develop a sustainable strategy, adapted to the local context, to provide timely HepB-BD within 24 hours of birth, and to improve neonatal care practices for babies born in a health facility and those born at home in Senegal, Burkina Faso and Madagascar.

Secondary objectives of the pilot study were:

- Epidemiology work package: Estimate the proportion of births in health facilities or at home, determine the percentage of infants vaccinated against hepatitis B within the first 24 hours, assess neonatal mortality rates, identify the main causes of death and explore associated factors.
- Anthropology work package: Generate socio-cultural knowledge on pregnancy, childbirth, hepatitis B transmission and vaccine prevention, to help formulate a strategy for timely HepB-BD and improve neonatal care practices.
- Economic evaluation work package: Assess the economic feasibility of different options for providing timely HepB-BD and other postnatal care to infants born in health facilities and at home in the three study countries.

Data collection methods varied by country. In Senegal and Madagascar, data were collected through the Demographic and Health Surveillance System (SSDS) at sites where the SSDS had been in place for several years. In the SSDS, households are visited every 6-12 months to record housing occupation status, demographic events (births, deaths, migrations, pregnancies), household availability of insecticide-treated nets, immunisation status, or level of education. In Burkina Faso, there was no SSDS at the study site, and the pilot study generated the idea of establishing a new SSDS site. For the epidemiology work package, the study population target was to include all women of childbearing age (between 12 and 54 years) and all children between 0 and 59 months (< 5 years) residing in the study area who consented to participate.

In Senegal, the study area covered the health districts of Niakhar, Bambey and Fatick, which have been part of the SSDS since 1962, with an estimated population of approximately 140,000 in 2015.

In Burkina Faso, the study focused on the Dafra health district in the Hauts Bassins region, with a resident population of approximately 337,112 in 2016. The population was followed through repeated and regular household visits every 6-12 months to collect information on pregnancies, births, deaths, migrations and vaccinations.

In Madagascar, the study area covered the Moramanga district in the Alaotra Mangoro region, with an estimated resident population of 71,601 in 2014.

3.3.2. Phase 2

Following the pilot phase, phase 2 of NeoVac had different objectives according to the three study countries.

In Senegal

In Senegal, the government introduced timely HepB-BD in 2016. The primary objective of phase 2 was to evaluate the impact of timely HepB-BD introduction on HBV MTCT in Senegal and to assess the performance of the HBV LAMP test - an alternative test to identify women with high HBV viral load (≥200,000 IU/mL). Secondary objectives included estimating the HBV prevalence in children aged 9-12 months and their mothers, assessing the acceptability of the HBV LAMP test among the community and health care workers, and evaluating the cost and cost-effectiveness of the HBV LAMP test.

In Madagascar

In Madagascar, the pilot study revealed challenges related to the potential implementation of HepB-BD, including negative perceptions of the vaccine. Phase 2 involved an anthropological study examining the perception of symptoms following HBV infection in two study sites: Antananarivo and Moramanga. The aim was to understand local perceptions of liver disease associated with hepatitis B and to identify the types of care provided for liver disease. A secondary objective was to develop awareness messages for public health actors at all levels, based on local concepts.

In Burkina Faso

In Burkina Faso, phase 2 started in 2019 and consisted of a stepped-wedge cluster randomised controlled trial in rural areas of the districts of Dafra and Do in the Hauts-Bassins region.

The trial protocol was published in *Vaccines* (132). The primary objective was to evaluate the effectiveness of adding HepB-BD to the current hepatitis B vaccination schedule at 8-12-16 weeks of age on the risk of MTCT, and to assess its acceptability among healthcare workers and community members, and its cost-effectiveness.

Secondary objectives included exploring the dose-response relationship between the number of hepatitis B vaccine doses administered (0-4) and the risk of HBsAg positivity in infants, examining the association between the timeliness of the first dose of hepatitis B vaccine and the risk of HBsAg positivity in infants, and evaluating the public health benefits and costs of introducing HepB-BD in the EPI of Burkina Faso.

The population was estimated to be around 548,000 in Dô and 348,000 in Dafra in 2017. The trial aimed to enrol 8,500 mother-child pairs in order to achieve 84% power to demonstrate that the intervention can reduce the risk of MTCT from 60% to 20% in HBeAg-positive pregnant women and from 5% to 0% in HBeAg-negative pregnant women, with a significance level of 5%. The intervention consisted of the sequential

introduction of HepB-BD in the 24 CSPS enrolled in the trial. After an initial period without HepB-BD, one CSPS was randomly selected every three weeks to cross over from the control group to the intervention group until all 24 CSPS entered the intervention period.

The flow of participants was organised into three visits, in line with routine visits in current practice (Figure 3.4). The first visit took place during antenatal care visits to the CSPS, where pregnant women were assessed for eligibility and invited to participate in the study. Women who went directly to a CSPS for delivery without a previous antenatal care visit were invited to participate immediately after delivery. The second visit took place at the time of delivery for women who gave birth in a CSPS or at the first postnatal care visit for women who gave birth outside a CSPS. If the CSPS was in the intervention period, HepB-BD was administered to the infants. The third visit was the routine visit at nine months of age. At this visit, mother-child pairs were screened for HBsAg using capillary blood collected via finger prick for an RDT (DETERMINE™ HBsAg 2, Abbott, Abbott Park, IL, USA). Participants received immediate HBsAg test results. An additional blood sample was collected from HBV-positive participants and sent to the Centre Muraz in Bobo-Dioulasso. Sera from HBV-positive mothers underwent a battery of tests at Centre Muraz, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), HBV DNA PCR (RealTime HBV Viral Load Assay, Abbott), qHBsAg and qHBeAg (ARCHITECT, Abbott), HBeAg RDT (SD Bioline, Abbott), HBcrAg (Lumipulse, Fujirebio Europe, Ghent, Belgium) and HBV-LAMP (Eiken Chemicals, Tokyo, Japan). Sera from HBV-positive children were analysed for ALT, AST and HBV DNA. HBV-positive participants were scheduled for another appointment to receive the results of the laboratory tests (Figure 3.5).

If ALT levels were elevated (>40 IU/L), women were referred to the CHU. Those with both ALT >40 IU/L and HBV DNA >2000 IU/mL started anti-HBV therapy (generic TDF) and followed up at the CHU every three months. HBV-positive women not receiving treatment were followed up at the CMA of the district every six months. HBV-positive children were followed every 12 months at the CMA if their ALT was ≤40 IU/L and at the CHU if their ALT was >40 IU/L.

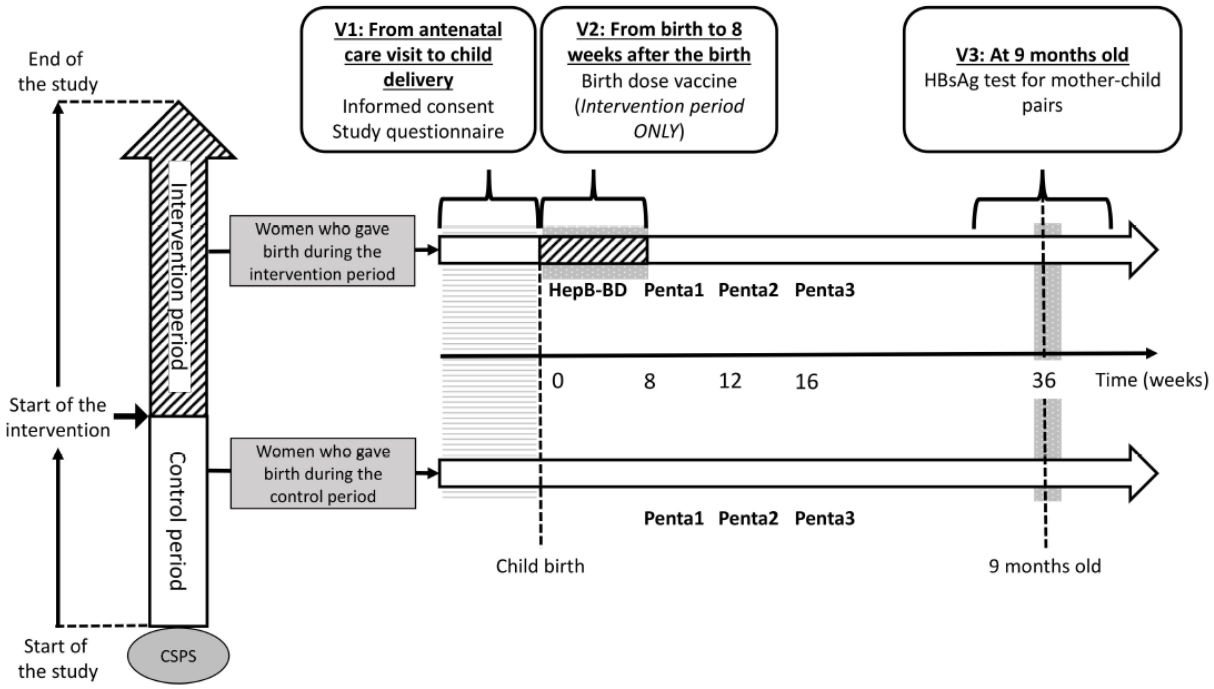


Figure 3.4 - Timeline of visits in the cluster randomised controlled trial of the NeoVac trial in Burkina Faso.

Source: H. Tall et al., Impact of Introducing Hepatitis B Birth Dose Vaccines into the Infant Immunization Program in Burkina Faso: Study Protocol for a Stepped Wedge Cluster Randomized Trial (NéoVac Study). Vaccines. 2021

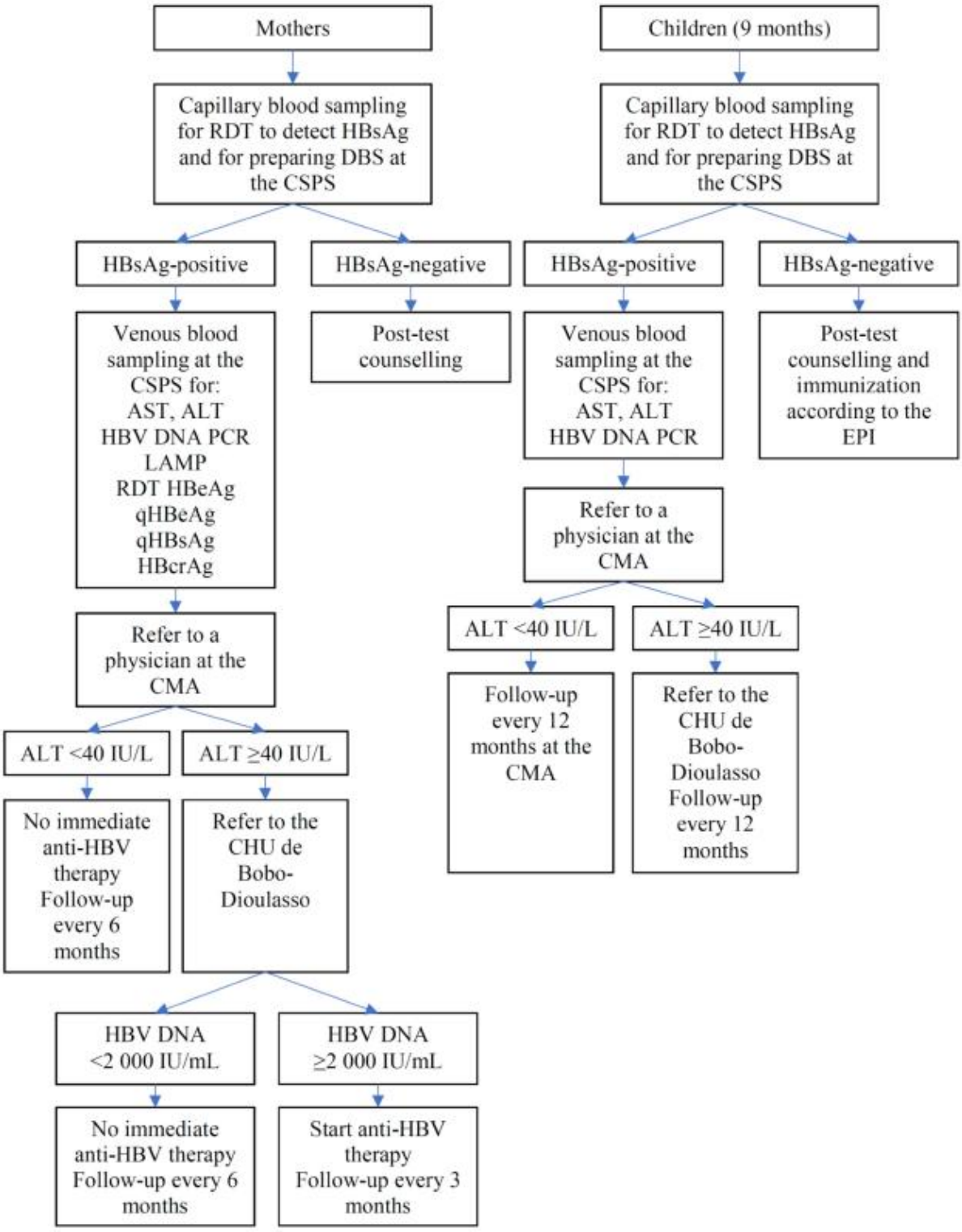


Figure 3.5 - Follow-up of participants who tested positive for HBsAg in the NeoVac cluster randomised controlled trial in Burkina Faso.

Source: H. Tall et al., Impact of Introducing Hepatitis B Birth Dose Vaccines into the Infant Immunization Program in Burkina Faso: Study Protocol for a Stepped Wedge Cluster Randomized Trial (NéoVac Study). Vaccines. 2021

4. Results

4.1. The costs of introducing the hepatitis B birth dose vaccine into the national immunisation programme in Senegal

Gosset A et al. *Vaccines (Basel)*. Published, May 2021. DOI: 10.3390/vaccines9050521

Résumé

En Afrique, certains pays hésitent encore à introduire la dose de naissance du vaccin contre l'hépatite B (HepB-BD) dans leur programme élargi de vaccination (PEV), en raison notamment de contraintes logistiques, économiques et d'un manque d'informations sur les coûts. Afin d'épauler les décideurs de ces pays, nous avons évalué les coûts économiques et financiers de l'introduction de l'HepB-BD ayant eu lieu en 2016 au Sénégal. En 2018, nous avons mené une étude de micro-costing au sein d'un échantillon représentatif des sites du PEV à tous les niveaux au Sénégal. Les informations sur les intrants et les coûts associés aux activités du PEV et de l'HepB-BD ont été recueillies grâce à des questionnaires standardisés et des entretiens semi-structurés. En utilisant la méthode de pondération des probabilités inverses, nous avons calculé les coûts moyens pondérés associés à l'introduction de l'HepB-BD pour chaque niveau du PEV, ainsi que les coûts agrégés au niveau national et les coûts estimés par nouveau-né. Les coûts économiques et financiers ont été estimés du point de vue du gouvernement en dollars américains pour 2015, 2016 et 2017. Les coûts économiques totaux s'élevaient à 143 364 USD en 2015, 759 406 USD en 2016 et 867 311 USD en 2017, tandis que les coûts financiers étaient respectivement de 127 745 USD, 82 519 USD et 29 853 USD. En annualisant les coûts de préintroduction et de formation initiale, le coût économique (financier) par nouveau-né vacciné était de 2,10 USD (0,30 USD) en 2016 et de 1,90 USD (0,20 USD) en 2017. Nos estimations fournissent des informations importantes pour la mise en œuvre de l'HepB-BD dans les pays d'Afrique subsaharienne qui n'ont pas encore intégré ce vaccin dans leur programme de vaccination.

Abstract

Some African countries are still reluctant to introduce the hepatitis B vaccine birth dose (HepB-BD) into their expanded program of immunization (EPI), partly because of logistical, economic, and cost information constraints. To assist decision-makers in these countries, we assessed the economic and financial costs of HepB-BD introduction in Senegal in 2016. We performed a micro-costing study in a representative sample of Senegal's EPI sites at all levels in 2018. Information on EPI and HepB-BD activity-related

inputs and costs was collected using standardized questionnaires and semi-structured interviews. Using inverse probability weighting, we computed weighted average costs associated with HepB-BD introduction for each EPI level, country-level aggregated costs and estimated costs per newborn. Economic and financial costs from a government perspective were estimated in US dollars for 2015, 2016 and 2017. Total economic costs were USD 143,364 in 2015, USD 759,406 in 2016 and USD 867,311 in 2017, while financial costs were USD 127,745, USD 82,519 and USD 29,853, respectively. When annualizing pre-introduction and initial training costs, the economic (financial) cost per vaccinated newborn was USD 2.10 (USD 0.30) in 2016 and USD 1.90 (USD 0.20) in 2017. Our estimates provide valuable information to implement HepB-BD in Sub-Saharan African countries that have not yet integrated this vaccine.

4.1.1. Introduction

Chronic hepatitis B virus (HBV) infection is a major cause of chronic liver disease and mortality in Sub-Saharan Africa (133). Although all African countries have introduced the three-dose infant HBV vaccine (HepB3) into their current expanded program of immunization (EPI) as part of a pentavalent vaccine, prevalence of chronic hepatitis B (CHB) infection is still high in the region (at least 8% in adults and 3% in children under 5 years old in 2015) (133,134).

To reduce the HBV burden in Sub-Saharan Africa, priority must be given to preventing the infection in newborns and young children for the following reasons: (i) HBV transmission mainly occurs during early childhood through perinatal and horizontal transmission, (ii) the risk of developing chronic HBV infection is very high when infection occurs during the first year of life (90%) and then rapidly decreases with age to <5% in adults (7,11), (iii) the risk of developing cirrhosis and hepatocellular carcinoma (HCC) is high when chronic HBV infection is acquired during early childhood, particularly through perinatal transmission (45,135).

Vaccination is the cornerstone of HBV transmission prevention. To effectively prevent perinatal and early horizontal transmission, the current HBV vaccination schedule recommended by the World Health Organization (WHO) is to administer the first dose within 24 h of birth (hepatitis B birth dose vaccine (HepB-BD)), followed by two or three doses during infancy (HepB3) (65).

In 2015, the World Health Assembly adopted a strategy to eliminate viral hepatitis as a major public health threat. Accordingly, the WHO set the goal of achieving an HBV prevalence of 0.1% in children under 5 years of age by 2030. This will require 90% and 80% HepB3 and HepB-BD coverage, respectively, in this population by that time (11). Although these targets for elimination and vaccination coverage have been endorsed by most Sub-Saharan African countries (64), HBV vaccine coverage remains suboptimal in this region, especially for the HepB-BD. Indeed, coverage for the whole WHO African region was estimated at only 4% in 2018 (136). This can be explained at two levels. First, only 13 countries in the region had adopted HepB-BD by 2020. Many of the rest are still reluctant to introduce it because of limited financial and technical resources. These countries also face continued challenges to prioritize resource allocation for HepB-BD and advocate for action and investment in this vaccination strategy because of the lack of reliable information on the economic and financial costs required to integrate HepB-BD into their current EPI. Second, even in countries that have already introduced the HepB-BD into their EPI, coverage of timely HepB-BD administration remains low because of the logistical difficulties in administering the dose as scheduled (i.e., within 24 h of birth) to children born at home (96,99,137).

Senegal is a lower-middle-income country in West Africa with a population of approximately 16 million inhabitants and a yearly gross domestic product of USD 1447 per capita in 2019 (138). In 2018, total health expenditure and government health expenditure per capita were estimated at USD 58.90 and USD 14.00, respectively (139). Prevalence of CHB infection is high, estimated at 8.1% in the general population in 2016

(134). In 2004, Senegal's EPI introduced the HepB3 as part of a pentavalent vaccine (diphtheria, tetanus, whooping cough, HBV, and Hemophilus influenza type B) administrated at 6, 10, and 14 weeks after birth. In 2016, the HepB-BD—using a monovalent hepatitis B vaccine—was added to the schedule. According to WHO/UNICEF, HepB3 coverage was 95% in 2017, while HepB-BD coverage was 58% in 2016 and 72% in 2017 (140).

In this context, we aimed to (i) document the experience of Senegal and the resources needed to implement timely HepB-BD; and (ii) provide accurate estimates of both economic and financial costs involved in Senegal's introduction and implementation to help other countries plan for HepB-BD introduction in the future.

4.1.2. Methods

4.1.2.1. Study Design

This economic study was part of the ongoing Neonatal Vaccination against hepatitis B in Africa (NéoVac) program, aiming to evaluate the feasibility of introducing HepB-BD in three African countries (Burkina Faso/Senegal/Madagascar), and its impact once introduced. The program's protocol was approved by the Clinical Research Committee of the Pasteur Institute in France (no. 2015-069) and the National Ethics Committee in Senegal (SEN18/45).

A micro-costing study was conducted in 2018 to document the quantities and costs of all resources used in Senegal in 2015, 2016 and 2017 for all its EPI activities, including introducing HepB-BD. In line with the country's healthcare system organization, data were collected at each of the following four levels: national, regional, district and first-level health facilities. The latter include health posts (first contact facilities managed by nurses) and health centers (reference facilities at the district level where at least one medical doctor is present). Both health centers and health posts are designated as the primary sites for child immunization. The study was designed to select a representative sample of sites, which were involved in the EPI implementation in the country, as well as to measure variation in costs across the sites.

Following the sampling method proposed by Brenzel (2013) (141), we first selected five regions among Senegal's 14 regions to represent not only the demographic, geographical and economic diversity of the country but also the different HepB-BD coverages observed. The five selected regions were Dakar, Fatick, Kedougou, Saint Louis and Zinguichor. Combined, they cover 6,702,015 inhabitants or 40% of the total population. In each of the five selected regions, we then selected three districts with different HepB-BD coverages. Within each selected district, we randomly selected six primary care facilities (health centers and health posts). We also included two agencies at the national level, specifically the Prevention Department of the Ministry of Health, which is in charge of the EPI at the national level, and the National Medical Supplies Agency, where all the EPI vaccines are stored before being dispatched to regional offices.

The target sample, therefore, included 112 sites, specifically, the 2 agencies at the national level, 5 regional health offices, 15 district health offices within those regions, and 90 primary care facilities within those districts.

4.1.2.2. Data Collection

Data collection for the micro-costing study took place between March and October 2018 in 99 over the 112 target sample sites. We were not able to visit the 12 healthcare facilities initially selected due to the unavailability of staff.

Semi-structured interviews were performed with key informants and standardized data collection forms. We collected detailed information on activities implemented for HepB-BD introduction and EPI management, the corresponding inputs used, and associated costs at the program's four levels. Activities and resources used for implementing HepB-BD and managing the national EPI were identified using a method proposed by the WHO and Brenzel (2013) (141,142).

Specifically, interviews were performed with managers of the Prevention Department of the Ministry of Health, the National Medical Supplies Agency, the regional health offices and district health offices, as well as with EPI managers at the different levels of the program. Collected information included details on the organization of EPI activities (vaccine administration, distribution and storage, program management and supervision), resources used (including human resources and time spent), as well as details on activities specific to introducing HepB-BD (initial training, social mobilization, additional cold chain and distribution equipment) and resources associated with these activities. Semi-structured interviews were also conducted with managers of primary care facilities and staff involved in maternal and child health services to document vaccination-related organization (routine and outreach) and resource use, including the time spent on HepB-BD immunization-related activities.

Besides the semi-structured interviews, forms were filled in at each study site to collect quantitative information on resources used for the EPI and HepB-BD activities (type, quantities, and unit cost).

Data were entered into an Excel spreadsheet and cross-checked by two investigators.

4.1.2.3. Costs Analysis

Overview of the Costing Analysis

Data obtained in the 2018 micro-costing study were used to estimate the incremental economic and financial costs associated with the introduction and implementation of HepB-BD in Senegal. Economic costs included a valuation of all inputs needed for the introduction and routine implementation of HepB-BD, including valuation of time, supplies and equipment already existing in the EPI and used for HepB-BD (as the use of these resources represents an opportunity cost for the EPI) (141,142). Financial costs were defined in terms of how much money was paid for the additional resources used for HepB-BD introduction and implementation (141). Accordingly, no financial cost was considered for activities carried out as part of the overall implementation of the EPI (such as vaccine storage and distribution, program supervision and management, and waste

management) unless additional resources were specifically required for HepB-BD introduction or implementation. Furthermore, capital costs were annualized over their expected lifetime using a discount rate of 3% in the economic approach, and a straight-line depreciation was used in the financial approach.

Annual economic and financial costs were estimated using a government perspective in 2016 US dollars for 2015 (year of HepB-BD pre-introduction and initial training on its administration), 2016 (year of HepB-BD introduction) and 2017 (year of routine HepB-BD implementation).

Using the inverse probability weighting method (see Section 2.3.3. below), we estimated the weighted average economic and financial costs associated with HepB-BD implementation for the regional, district and primary care levels of the EPI. Weighted average costs were multiplied by the corresponding number of sites to generate the total cost for each level of EPI. Costs obtained for each level of the EPI were then aggregated with the costs of the national level to obtain the total cost at the country level. The costs of vaccines and safety supplies were directly estimated for the whole country and reported nationally. Finally, we estimated the financial and economic costs of HepB-BD vaccination per newborn.

Costing Methods to Estimate Costs per Study Site

Activities and input line items included in the costing analysis are described in Table 4.1.1. Additional information on the main characteristics of Senegal and the data used in the costing analysis is presented in Table 4.1.2.

Table 4.1.1: Summary of the activities and input line items considered in the costing analysis covering the 2015–2017 period in Senegal.

Activity	Description	Activity Related to HepB-BD Introduction /Implementation	Input Line Items	Level of the Health System	Comments
1. Pre-introduction	Activities carried out to prepare for HepB-BD introduction, including developing the national plan for the introduction, developing training tools needed, updating and printing immunization-related materials (child immunization cards, registers,	Yes	Recurrent costs: time of salaried labor, per diems, fuel for transportation, stationary, room rental, printing (immunization cards and other immunization related materials)	National	Costs mainly incurred in 2015 and considered as investment costs (annualized over 5 years) Financial costs do not include labor time as no additional staff were hired

	EPI supervision tools, etc.)				
2. Initial training	Initial training and supervision specifically for HepB-BD introduction	Yes	Recurrent costs: staff (provision of services), per diems and transport allowances, fuel for transportation, stationary, room rental	National, regional and district	Costs incurred in 2015 and considered as investment costs (annualized over 2 years)
3. Social mobilization	Social mobilization associated with HepB-BD introduction (during the introduction period and after): development of radio publicity spots and communication tools, broadcast of radio spots and TV shows, organization of special events	Yes	Recurrent: staff (provision of services), per diems and transport allowances, fuel for transportation, room rental for special events, radio time and TV shows to broadcast messages, stationery, printing communication tools (flyers, posters, etc.)	All (national, regional, district and primary care facility)	Costs incurred mainly in 2016 (a small number of costs are reported in 2017)
4. Vaccine administration	Routine facility-based administration of HepB-BD vaccine and outreach vaccination	Yes	Recurrent costs: time taken for a salaried worker to administer the HepB-BD vaccine (6 min per infant), vaccines (number of doses administered), vaccine injection and safety supplies (syringes and safety boxes, etc.), per diems and fuel for outreach vaccination Capital costs: vehicles	National level for vaccines and supplies costs District and first-level health facility levels for labor time related to vaccine administration	Costs incurred in 2016 and 2017 Financial costs do not include labor time as no additional staff were hired
5. Vaccine storage	Cold chain storage of vaccines and storage of injection and safety supplies	No (EPI costs allocated to the HepB-BD based on the share of the HepB-BD volume relative to the total	Recurrent costs: cold chain maintenance and cold chain energy (electricity, gas, ice packs, etc.)	All (national, regional, district and first-level health facility)	Costs incurred in 2016 and 2017 Financial costs only include annualized costs of new cold chain

		volume for all current vaccines	Capital costs: cold chain equipment		equipment purchased in 2015 and 2016
6. Vaccine distribution	Transportation of vaccines, injection and safety supplies	No (EPI costs allocated to the HepB-BD based on the share of the HepB-BD volume relative to the total volume for all current vaccines	Recurrent costs: per diems, fuel for transportation of vaccines and supplies, vehicle maintenance Capital costs: vehicles	All (national, regional, district and first-level health facility)	Costs incurred in 2016 and 2017 Financial costs only include the annualized costs of new vehicles purchased in 2015 and 2016
7. Supervision, monitoring and surveillance	Routine supervision of immunization activities, monitoring and evaluation of immunization data (including surveillance of post-vaccination events)	No: Costs–excluding salary costs-allocated to HepB-BD based on the share of the number of doses for the HepB-BD relative to the total number of vaccines doses in the EPI Salary costs allocated based on time spent	Recurrent costs: time of salaried labor, per diems and transport allowances, fuel for transportation, vehicle maintenance Capital costs: vehicles	All (national, regional, district and first-level health facility)	Costs incurred in 2016 and 2017 No financial costs
8. Management	Planning, budgeting and managing the immunization program (including continuing training)	No: costs-excluding salary costs-allocated to the HepB-BD based on the share of the number of doses for the HepB-BD relative to the total number of vaccines doses in the EPI Salary costs allocated based on time spent	Recurrent costs: time of salaried labor, per diems and transport allowances, fuel for transportation Capital costs: office equipment (computers, printers, etc.)	All (national, regional, district and first-level health facility)	Costs incurred in 2016 and 2017 No financial costs
9. Waste management	Management of HepB-BD vaccine-related waste	No (costs allocated to the HepB-BD based on the share of the HepB-BD volume relative to the total volume for all current vaccines	Recurrent costs: incinerator fuel Capital costs: incinerator	Regional and district levels	Costs incurred in 2016 and 2017 No financial costs

Table 4.1.2: Main data used in the costing analysis of hepatitis B birth dose introduction in Senegal.

Main data	Description	Source
Target population (live births)	541,529 in 2016; 543,126 in 2017	World Bank
HepB-BD coverage rates	58% in 2016; 72% in 2017	WHO/UNICEF
Total number of HepB-BD administered doses	379,999 in 2016; 473,643 in 2017	National database (DVD-MT) used for the management of vaccine stocks in the EPI
Total number of HepB-BD administered doses within 24 h after birth	314,084 in 2016; 391,488 in 2017	WHO/UNICEF
Vaccine type	10-dose vials (Hepavax-Gene®, Berna Biotech Korea Corp., Incheon, South Korea)	Ministry of Health of Senegal
Vaccine wastage rates	5%	Ministry of Health of Senegal
Vaccine unit price	USD 0.20	UNICEF
Vaccine administration	Within 24 h after birth	Ministry of Health of Senegal
Structures where HepB-BD is delivered	• Primary care facilities (public and subsidized private) • Maternity ward in health centers • Maternity ward in regional hospitals	Ministry of Health of Senegal
Personnel in charge of HepB-BD administration	Nurses	
Time needed to administer HepB-BD	6 min	NéoVac study
Discount rate for capital costs	3%	WHO

Resources were classified into the following activities: pre-introduction (development of the national plan for HepB-BD introduction, development of associated training tools, updating and printing of immunization-related materials, including child immunization cards, brochures, information sheets, etc.), initial training, social mobilization, HepB-BD vaccine administration, storage, distribution, supervision, EPI management and waste management. For each activity, we distinguished between recurrent costs (labor, per diems and transport allowances, vaccines and consumables, cold chain energy and maintenance, fuel for transportation and maintenance of vehicles, printing and other operating costs) and capital costs (vehicles, cold chain equipment, incinerators and IT equipment).

Pre-introduction, initial training, social mobilization and HepB-BD vaccine administration were specific to the introduction and implementation of HepB-BD. Accordingly, their whole cost was attributed to HepB-BD both in the economic and financial approach (but the financial costs do not include labor time as no additional staff were hired). The rest of the activities were related to implementing the EPI as a whole. To estimate economic costs, we first estimated the EPI costs associated with each of these activities and then allocated a share of this cost to the HepB-BD implementation using the allocation criteria (Table 4.1.1). To estimate financial costs, we only considered

expenditures related to the purchase of resources specifically required for HepB-BD introduction or implementation.

We estimated economic and financial costs for 2015, 2016 and 2017. Unit costs in CFA franc (CFAF) and in Euros were converted to US dollars (USD), using the World Bank exchange rate for 2016 (1 USD = 592,542 FCFA (143)). For each study site and for each activity, the costs were computed by multiplying the resources used by their unit costs. The total cost was then obtained by summing the costs of the different activities.

Costs Aggregation to Estimate the Total Annual Costs at the Country Level

We used inverse probability weighting to estimate annual average weighted costs for the regional, district and first-level health facility levels. We then aggregated costs at the country level (15). Weights were computed for each study site as the inverse probability of being selected. The respective weighted average costs obtained for each level of the EPI, excluding the national level, were multiplied by the number of sites at the corresponding level to obtain the total annual cost at each level of the EPI for 2015, 2016 and 2017. Finally, the total annual cost at the country level was obtained by summing the respective total annual costs estimated at each level of the health system (i.e., national, regional, district and first-level health facility), as illustrated in **Erreur ! Source du renvoi introuvable.**.

$$[\text{Total annual facility cost}] + [\text{Total annual district cost}] + [\text{Total annual region cost}] + [\text{National admin cost}] + [\text{National vaccine cost}] = [\text{Total annual national cost}]$$

$$[\text{Weighted average region admin cost}] \times [\text{Number of regions (n = 14)}] = [\text{Total annual region cost}]$$

$$[\text{Weighted average district admin cost}] \times [\text{Number of districts (N = 76)}] = [\text{Total annual district cost}]$$

$$[\text{Weighted average primary facility costs} - \text{Vaccines}] \times [\text{Number of primary facilities (N = 1342)}] + [\text{Weighted average health centres costs} - \text{Vaccines}] \times [\text{Number of health centres (N = 98)}] = [\text{Total annual facility cost}]$$

Figure 4.1.1 - Aggregation method for calculating costs of HepB-BD implementation in Senegal.
Source: Adapted from Brenzel L. Common approach for the costing and financing analyses of routine immunization and new vaccine introduction costs (NUVI). Bill and Melinda Gates Foundation; 2013.

Estimation of the Cost per Vaccinated Newborn

As the 2015 annual costs were related to pre-introduction activities and initial training, we considered them as initial investment (i.e., capital) costs. Accordingly, we computed the corresponding annualized costs over five and two years, respectively, as recommended by the WHO (142). Investment annualized costs were then added to the 2016 and 2017 annual costs to obtain annual total costs at the country level, including the cost of initial investment related to pre-introduction activities and initial training.

Finally, we divided the 2016 and 2017 economic and financial total costs estimated at the country level (with and without the annualized cost of initial investment) by the total number of newborns who received the HepB-BD (irrespective of whether or not administration occurred according to the WHO recommendation (i.e., within 24 h of birth)). The latter number was estimated using the database used in the EPI for vaccines stocks management, while the number of newborns who received timely HepB-BD-as per the WHO recommendation-was estimated using data provided by the Ministry of Health of Senegal to WHO/UNICEF (144).

Analyses were conducted using R version 3.6.3 (R Core Team, Vienna, Austria).

4.1.3. Results

4.1.3.1. Introduction and Implementation of HepB-BD in Senegal

Pre-Introduction Activities

In 2014, an HepB-BD introduction plan was developed and discussed at a workshop, which brought together national EPI staff and experts from the WHO and the United States Agency for International Development. A steering committee and several subcommittees were organized to coordinate the preparation, implementation and monitoring of the HepB-BD introduction. In 2015, several specific workshops were held to develop training tools for healthcare workers and communication materials for social mobilization. Training sessions were subsequently organized at each level of the healthcare system for a total of 2000 healthcare workers throughout the country. Social mobilization was then implemented at a national level with the support of the regional and district health offices. The purchase of monovalent HepB-BD vaccines (10-dose vials; Hepavax-Gene®, Berna Biotech Korea Corp., South Korea) was overseen by the Prevention Department of the Ministry of Health. Vaccines were stored in the EPI cold chain at the National Medical Supplies Agency. Using existing EPI supply chains, HepB-BD vaccines were transported from the central EPI store to the regional offices, then from the latter to the district offices, and in turn from the district offices to first-level health facilities. HepB-BD vaccination started in January–February 2016.

HepB-BD Vaccination Strategy

Given the relatively high rate of institutional childbirth (estimated at 61% in 2017 according to the Ministry of Health of Senegal), the Ministry of Health chose fixed facility-based immunization—rather than outreach immunization—as the main strategy to deliver HepB-BD. More specifically, the national strategy aimed to: (i) promote using maternal and child health services and institutional delivery through community sensitization; (ii) ask women who gave birth outside health facilities to bring their newborn(s) to a health facility as soon as possible for postnatal care, including vaccination; (iii) make monovalent hepatitis B vaccines both widely available for HepB-

BD administration, and free of charge in all healthcare facilities providing childbirth, maternal, and child health services.

In addition to the fixed facility-based HepB-BD immunization, first-level health facilities also deliver HepB-BD during routine outreach vaccination activities. These are regularly (most often monthly) conducted to reach populations living more than five km away.

4.1.3.2. Estimations of Weighted Average Costs per Activity

Table A.**1** presents a descriptive analysis of the weighted average economic costs, overall and per activity, for each level of the EPI (excluding the national level). In 2016 (2017), the weighted average economic costs (excluding vaccines costs for healthcare facilities) were USD 2473 (USD 2093) per regional health office, USD 2389 (USD 2396) per district health office, USD 743 (USD 1015) per health center and USD 243 (USD 313) per health post. At the regional and district levels, the activities with the highest costs were supervision and EPI management. In contrast, at the first-level facility level, vaccine administration was the main cost driver.

4.1.3.3. Costs of HepB-BD Implementation at the Country Level

The total economic cost of the HepB-BD implementation in Senegal were estimated at USD 143,364 for 2015, USD 759,406 for 2016 and USD 875,240 for 2017 (Table 4.1.3). Initial training in HepB-BD administration accounted for more than half of the annual costs in 2015 (54%). In 2016 and 2017, vaccine administration (including time spent) was the main cost activity (57%, USD 435,596 in 2016; 63%, USD 556,224 in 2017), followed by supervision of EPI activities (17%, USD 126,648 in 2016; 17%, USD 147,443 in 2017), and EPI management (11%, USD 79,841 in 2016; 11%, USD 96,000 in 2017).

The total financial costs were much lower as they did not account for the opportunity costs of existing EPI resources, mainly human resources already in place and existing equipment. They were estimated at USD 127,745 for 2015, USD 81,940 for 2016 and only USD 29,915 for 2017 (Table 4.1.4). In 2015, the main cost driver was initial training (61% of the total cost). In 2016, social mobilization (74%) was the main cost activity, followed by vaccine administration (23%), while in 2017, the main cost activity was vaccine delivery (82%), followed by social mobilization (11%).

4.1.3.4. Cost per HepB-BD vaccinated Newborn

In 2016 (2017), an estimated 379,999 (473,643) newborns received HepB-BD, including 314,084 (391,488) within 24 h of birth, for total incremental economic and financial costs (including the annualized cost of initial investment) of USD 809,819 (USD 924,185) and USD 130,745 (USD 78,720), respectively (Table 4.1.5).

The economic cost per vaccinated newborn (irrespective of whether or not administration occurred within 24 h of birth) were USD 2.00 in 2016 and USD 1.85 in 2017 (excluding the annualized cost of initial investment), and USD 2.13 in 2016 and USD 1.95 in 2017 (including the annualized cost of initial investment).

The economic costs per newborn vaccinated within 24 h of birth were slightly higher: USD 2.42 (2016) and USD 2.24 (2017) when excluding the annualized cost of initial investment, and USD 2.58 and USD 2.36 when including it.

When, including this cost, the financial costs per vaccinated newborn (irrespective of timing) were USD 0.34 (2016) and USD 0.17 (2017), while the financial costs per newborn vaccinated within 24 h of birth were USD 0.42 (2016) and USD 0.20 (2017).

Table 4.1.3: Aggregated economic costs (in USD 2016) per activity and per study site.

		National			Regional Health Offices			District Health Offices			Health Posts		Health Centers		Total			% per Activity		
		2015	2016	2017	2015	2016	2017	2015	2016	2017	2016	2017	2016	2017	2015	2016	2017	2015	2016	2017
Pre-introduction	Capital	0														0	0			
	Running	65,855														0	0			
	Total	65,855													65,855	0	0	45.9%	0.0%	0.0%
Initial training	Capital		0	0		0	0	0	0	0	0	0	0	0	0	0	0			
	Running		0	0	9272	0	0	68,238	0	0	9	0	0	0	77,510	9	0			
	Total		0	0	9272	0	0	68,238	0	0	9	0	0	0	77,510	9	0	54.1%	0.0%	0.0%
Social mobilization	Capital		0	0		0	0		0	0	0	0	0	0	0	0	0			
	Running		20,653	0		6143	0		31,923	357	1470	1189	688	1645	0	60,877	3191			
	Total		20,653	0		6143	0		31,923	357	1470	1189	688	1645	0	60,877	3191		8.0%	0.4%
Vaccine administration	Capital	0	0	0		0	0		2118	2907	17,326	23,496	0	0	0	19,444	26,402			
	Running	0	98,835	123,191		0	0		2367	3741	245,579	313,652	69,372	89,238	0	416,152	529,821			
	Total	0	98,835	123,191		0	0		4485	6647	262,904	337,147	69,372	89,238	0	435,596	556,224		57.4%	63.6%
Storage	Capital		404	405		2292	2292		3863	4699	15,908	19,761	5351	10,520	0	27,820	37,677			
	Running		2651	2652		928	897		1333	1550	12,466	15,824	232	313	0	17,610	21,236			
	Total		3055	3057		3220	3189		5197	6249	28,374	35,585	5583	10,833	0	45,430	58,913		6.0%	6.7%
Distribution	Capital		634	635		2355	2355		1984	2448	2292	3070	59	84	0	7326	8593			
	Running		701	658		9	9		40	49	2473	3577	233	327	0	3455	4620			
	Total		1335	1293		2364	2364		2024	2496	4766	6647	292	412	0	10,781	13,213	0.0%	1.4%	1.5%
Supervision	Capital		1585	1586		7367	7367		16,943	23,252	7309	11,694	0	0	0	33,204	43,898			
	Running		4856	1333		7360	7617		76,303	88,262	4925	6332	0	0	0	93,443	103,544			
	Total		6441	2918		14,726	14,984		93,246	111,515	12,234	18,026	0	0	0	126,648	147,443		16.7%	16.8%
Management	Capital		94	94		159	159		513	775	1431	1600	222	261	0	2419	2888			
	Running		2442	2442		7933	8515		63,142	73,037	3822	7293	84	1824	0	77,422	93,111			
	Total		2535	2536		8092	8675		63,654	73,812	5252	8892	306	2085	0	79,841	96,000		10.5%	11.1%
Waste management	Capital					94	94		0	0	0	0	0	0	0	94	94			
	Running					0	0		132	162	0	0	0	0	0	132	162			
	Total					94	94		132	162	0	0	0	0	0	226	256	0.0%	0.0%	0.0%
Total		65,855	132,854	132,995	9272	34,640	29,306	68,238	200,660	201,239	315,010	407,487	76,241	104,213	143,364	759,406	875,240	100.0%	100.0%	100.0%
% per site type		45.9%	17.5%	15.2%	6.5%	4.6%	3.3%	47.6%	26.4%	23.0%	41.5%	46.6%	10.0%	11.9%	100.0%	100.0%	100.0%			

Table 4.1.4: Aggregated financial costs (in USD 2016) per activity and per study site.

		National			Regional Health Offices			District Health Offices			Health Posts		Health Centers		Total			% per Activity		
		2015	2016	2017	2015	2016	2017	2015	2016	2017	2016	2017	2016	2017	2015	2016	2017	2015	2016	2017
Pre-introduction	Capital	0													0	0	0			
	Running	50,226													50,226	0	0			
	Total	50,226													50,226	0	0	39.3%		
Initial training	Capital		0	0		0	0	0	0	0	0	0	0	0	0					
	Running		0	0	9272	0	0	68,238	0	0	9	0	0	0	77,519					
	Total		0	0	9272	0	0	68,238	0	0	9	0	0	0	77,519			60.7%		
Social mobilization	Capital		0	0		0	0	0	0	0	0	0	0	0	0	0	0			
	Running		20,653	0		6143	0	0	31,923	357	1470	1189	688	1645	0	60,877	3192			
	Total		20,653	0	0	6143	0	0	31,923	357	1470	1189	688	1645	0	60,877	3192		74.3%	10.7%
Vaccine administration	Capital		0	0	0	0	0	0	0	0	0		0	0	0	0	0			
	Running		0	0	0	0	0	0	2367	3741	16,829	20,875	0	0	0	19,195	24,616			
	Total		0	0	0	0	0	0	2367	3741	16,829	20,875	0	0		19,195	24,616		23.4%	82.3%
Storage	Capital		152	152	0	182	182	0	197	226	159	161	799	928	0	1490	1649			
	Running		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Total		152	152	0	182	182	0	197	226	159	161	799	928	0	1490	1649		1.8%	5.5%
Distribution	Capital		0	0	0	0	0	0	362	439	14	17	2	2	0	378	458			
	Running		0	0		0	0	0	0	0	0	0	0	0	0	0	0			
	Total		0	0	0	0	0	0	362	439	14	17	2	2	0	378	458		0.5%	1.5%
Supervision	Capital		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Running		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Total		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Management	Capital		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Running		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Total		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Waste management	Capital		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Running		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
	Total		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
Total		**50,226**	**20,804**	**152**	**9272**	**6325**	**182**	**68,238**	**34,849**	**4763**	**18,481**	**22,243**	**1490**	**2575**	**127,745**	**81,940**	**29,915**	**100%**	**100%**	**100%**
% site type		39.3%	25.4%	0.5%	7.3%	7.7%	0.6%	53.4%	42.5%	15.9%	22.6%	74.4%	1.8%	8.6%	100%	100%	100%			

Table 4.1.5 : Economic and financial costs (in USD 2016) per HepB-BD vaccinated newborn in Senegal.

		Total Annual Economic Cost	Total Annual Financial Cost	Economic Cost/Vaccinated Children (Irrespective of Timing)	Economic Cost/Vaccinated Children within 24 h	Financial Cost/Vaccinated Children (Irrespective of Timing)	Financial Cost/Vaccinated Children within 24 h
Costs, excluding the annualized costs of initial investment	2016	759 406	81 940	2.00	2.42	0.22	0.26
	2017	875 240	29 915	1.85	2.24	0.06	0.08
Costs, including the annualized costs of initial investment	2016	809 819	130 745	2.13	2.58	0.34	0.42
	2017	924 185	78 720	1.95	2.36	0.17	0.20

4.1.4. Discussion

To our knowledge, this is the first study to document both economic and financial costs associated with introducing the HepB-BD in Sub-Saharan Africa using real-world data. We investigated the experience of Senegal, a country, which successfully introduced this vaccine dose in 2016. Using data from a micro-costing study designed to obtain a representative sample of sites involved in implementing the country's EPI, we identified and valued the resources mobilized for a large range of activities related to the introduction and implementation of the HepB-BD at the different levels of Senegal's health system. The economic costs per HepB-BD vaccinated newborn ranged from USD 2.00 and 2.60 for the first year of introduction (2016) and from USD 1.80 and 2.40 for the subsequent year (2017). Corresponding financial costs were 6 to 11 times lower (ranging from USD 0.20–0.40), mainly because they did not consider the time spent by human resources on pre-introduction activities, HepB-BD administration, EPI management and supervision.

Costs per HepB-BD vaccinated newborn in the current analysis were higher than those reported in a previous study, which we conducted in 2017 in the Dafra district of Burkina Faso using a hypothetical approach (USD 2.94 for the first year of introduction and USD 0.54 for the subsequent year) (145). However, these differences must be interpreted with care given the different methodologies used. The Burkinabe study was hypothetical and used assumptions about resources used, as the country has not yet introduced the HepB-BD into its EPI. In the present study on Senegal, we worked with real-world data collected in the 2018 micro-costing study. Furthermore, unlike the present study, we did not annualize the initial investment costs related to the initial training and pre-introduction activities in the Burkinabe study. This may explain the high (hypothetical) cost per vaccinated newborn found for the first year in Burkina Faso. In addition, EPI management

and supervision costs, which accounted for a substantial proportion of the economic cost in the present study, were not considered in our Burkinabe study.

Furthermore, our cost estimates for Senegal were similar to that Brenzel et al. found in Benin (2015). They reported a cost of USD 2.00 per vaccine dose administrated in that country's EPI (considering all vaccines administrated in the EPI; Benin had not introduced HepB-BD at that time) (146). This would suggest that the HepB-BD has an economic cost similar to other vaccines currently implemented in EPI in West African countries.

The strategy adopted by the Senegalese health authorities was to introduce the HepB-BD as part of the existing routine facility-based vaccination program. Institutional childbirth was particularly promoted to pregnant women. When this was not possible, they were asked to bring their newborn(s) to a healthcare facility for postnatal care and to receive a birth certificate as soon as possible. However, as no clear recommendation was made about whether or not to include HepB-BD in outreach immunization strategy, first-level health facilities implemented different associated practices: some used this strategy to provide HepB-BD to unvaccinated newborns as a catch-up dose. While they may have helped reach some additional newborns, these strategies most likely missed out on vaccinating newborns within the recommended first 24 h after birth and consequently may have not effectively protected newborns against the risk of perinatal infection. Specific studies are needed to evaluate the effectiveness of outreach HepB-BD strategies in Sub-Saharan Africa.

The experience of Senegal described in this work will be useful for other African countries where the HepB-BD has not yet been introduced. This may also be relevant to Gavi, the Vaccine Alliance partnership, which expressed its future support to help countries administer the HepB-BD according to the WHO-recommend schedule (147).

Even after the introduction of HepB-BD into a country's EPI, considerable challenges remain to reach a high level of coverage in the resource-limited African context. First, a recent meta-analysis of HepB-BD coverage in Sub-Saharan African countries where the dose is scheduled in the EPI reported that only 0.3% of babies born in healthcare facilities received the dose within 24 h of birth (137). This highlights the importance of both providing clear guidelines for timely HepB-BD administration in healthcare facilities and ensuring the availability of the HepB-BD at all levels of the healthcare system (96,148). As illustrated by the Senegalese experience, monovalent hepatitis B vaccines must be made available in hospitals' maternity wards. They often do not have a routine EPI vaccination activity. Second, only 60% of women give birth in healthcare facilities in Sub-Saharan Africa (149). Accordingly, even if all infants born in healthcare facilities were to receive the HepB-BD according to the WHO recommendation, achieving the target of 80% HepB-BD coverage by 2030 would be difficult (11). Additional strategies to reach babies not born in healthcare facilities are urgently needed in Sub-Saharan Africa, including the systematic notification of home births to EPI staff by lay community workers (150), increased home-based outreach vaccination using mono-dose vaccines (either in vials or in pre-filled auto-disable injection devices (cPAD)) (151,152), and ambient storage of HepB-BD under a controlled temperature chain (152).

The main limitation of the present study concerns the uncertainty surrounding the definition of allocation criteria used in the analysis of the economic costs to allocate shared costs (i.e., costs associated with activities not specifically carried out for the HepB-BD introduction but, which are carried out as part of the overall implementation of the EPI, and therefore, are of benefit for all EPI vaccines, including the HepB-BD). This is especially the case for EPI management and supervision as well as vaccine storage and distribution. Allocation criteria for labor costs were based on labor time reported by staff, who were asked to both determine the time they spent on the EPI and then, within the EPI, the time spent on the HepB-BD administration component. Because of our exclusive focus on HBV immunization and HepB-BD, time allocations may have been overestimated relative to other services. Consequently, they may have led to an overestimation of labor and economic costs. Another important piece of information used to determine the allocation of shared costs in our study regarded vaccine storage and distribution is the number of vaccine doses delivered as part of the EPI (for the HepB-BD and other vaccines). Although we obtained this information from the database developed by WHO and used in the Senegalese EPI for vaccine stock management, we cannot completely exclude the risk of errors in the source.

Another study limitation regards the estimated number of newborns receiving the HepB-BD dose within the recommended 24 h after birth. As this information was not available in the database used for the EPI vaccine stock management, we used estimated data provided by the Ministry of Health of Senegal for a WHO/UNICEF report (144).

Conclusion

Our costs analyses based on the Senegal context provide important insights for other African countries regarding the types and amount of resources and costs required to introduce HepB-BD. They can help policymakers and other key stakeholders design an effective HepB-BD-introduction program, estimate program-related costs, and develop vaccination strategies in resource-limited contexts. Furthermore, our estimations of the economic costs in Senegal will also be especially useful to estimate and confirm findings from two studies suggesting the cost-effectiveness of introducing HepB-BD into Sub-Saharan African EPI (145,153). Further studies evaluating the effectiveness of complementary strategies to improve HepB-BD coverage and its timely administration are urgently needed in Sub-Saharan Africa.

4.2. Cost-effectiveness of adding a birth dose of hepatitis B vaccine in the Dafra district in the Hauts-Bassins Region in Burkina Faso

Gosset A et al. *Vaccine*. Published, Jul 2021. DOI: 10.1016/j.vaccine.2021.06.059

Résumé

Contexte : L'Organisation mondiale de la santé (OMS) recommande l'administration d'une première dose de vaccin contre l'hépatite B dans les 24 heures suivant la naissance (HepB-BD) pour prévenir la transmission mère-enfant. Très peu d'études ont prouvé la pertinence économique de cette stratégie en Afrique. Nous avons évalué les coûts et le rapport coût-efficacité de l'ajout de l'HepB-BD aux trois doses de pentavalent (HepB3) actuellement administrées dans le district de Dafra, dans la région des Hauts-Bassins au Burkina Faso.

Méthodes : À partir d'un arbre de décision combiné à un modèle de Markov, nous avons estimé le nombre attendu d'années de vie (AV) et d'années de vie corrigées de l'incapacité (AVCI) sauvées, les coûts différentiels et les ratios coût-efficacité différentiels (RCED) de l'HepB-BD + HepB3 par rapport à l'HepB3 seul dans la cohorte de naissance 2017 de Dafra (n = 11 462). La proportion d'accouchements en établissement de santé, la couverture vaccinale et les coûts de vaccination du point de vue du système de santé ont été estimés à partir de données collectées sur le terrain. Nous avons estimé l'efficacité de l'HepB-BD, les probabilités de transition en fonction de l'âge, et les risques de transmission horizontale à partir de données d'études antérieures en Afrique. Les coûts et l'efficacité ont été actualisés à un taux annuel de 3 %. Nous avons effectué des analyses de sensibilité univariées et probabilistes pour évaluer l'incertitude.

Résultats : Dans le scénario de référence sans actualisation, l'HepB-BD + HepB3 permettait de réaliser une économie nette de 18 979 $US et d'éviter 163 AVCI par rapport à l'HepB3 seul. Avec actualisation, l'association HepB-BD + HepB3 par rapport à HepB3 a entraîné un coût supplémentaire de 554$ et 31 AVCI évitées, se traduisant par un RCED de 18$/AVCI évitée. Dans les analyses de sensibilité univariées, l'ajout de l'HepB-BD à l'HepB3 est restée coût-efficace (au seuil de 671$, soit une fois le produit intérieur brut par habitant au Burkina Faso) pour toutes les variations des paramètres. Cependant, les résultats étaient très sensibles aux variations du coût unitaire de l'HepB-BD par nouveau-né vacciné et au risque de transmission périnatale chez les mères porteuses de l'antigène e de l'hépatite B. Les probabilités que l'HepB-BD + HepB3 soient coût-efficace étaient de 71,7 % et 86,7 %, aux seuils de 335$ et 671$, respectivement.

Conclusion : L'introduction de l'HepB-BD au Burkina Faso est susceptible d'être coût-efficace.

Abstract

Background: The World Health Organization (WHO) recommends a first hepatitis B vaccine dose within 24 h of birth (HepB-BD) to prevent mother-to-child transmission. Evidence for this strategy's economic value in Africa is limited. We assessed the costs and cost-effectiveness of adding HepB-BD to the current three-dose pentavalent schedule (HepB3) in the Dafra district of the Hauts-Bassins Region in Burkina Faso.

Methods: Using a decision tree combined with a Markov model, we estimated the expected number of life-years (LY) and disability-adjusted life-years (DALYs) saved, incremental costs, and incremental cost-effectiveness ratios (ICER) of HepB-BD + HepB3 versus HepB3 alone in Dafra's 2017 birth cohort (n = 11,462). Institutional delivery rates, vaccine coverage, and vaccination costs from a health system perspective were estimated from field-collected data. We estimated the effectiveness of HepB-BD, age-specific transition probabilities, and horizontal transmission risks using data from previous African studies. Costs and health outcomes were discounted at an annual rate of 3%. We conducted one-way and probabilistic sensitivity analyses to assess uncertainty.

Results: In the base-case analysis without discounting, HepB-BD + HepB3 yielded a net cost saving of US $18,979 and saved 163 DALYs compared with HepB3 alone. With discounting, HepB-BD + HepB3 compared with HepB3 resulted in an incremental cost of US$554 and 31 DALYs averted, translating into an ICER of US$18/DALY averted. In one-way sensitivity analyses, HepB-BD + HepB3 remained cost-effective (at the cost-effectiveness threshold of US$671 i.e. the Burkina Faso per-capita gross domestic product) for all parameter changes. However, results were very sensitive to variations in HepB-BD unit cost per vaccinated neonate and perinatal transmission risk in mothers carrying the hepatitis B e antigen. The probabilities of HepB-BD + HepB3 being cost-effective were 71.7% and 86.7%, at the cost-effectiveness thresholds of US$335 and US$671, respectively.

Conclusion: Introducing HepB-BD in Burkina Faso is likely to be cost-effective.

4.2.1. Introduction

Hepatitis B virus (HBV) infection is a major global health issue. Of the 257 million people infected worldwide in 2015, 887,000 died from related complications (133). Prevalence is highest in the World Health Organization African region (133), where >8% of adults have chronic HBV infection (CHB) (134). One key intervention to halt the epidemic is vaccination. A three-dose hepatitis B vaccine schedule (HepB3) is incorporated into the Expanded Programme on Immunization (EPI) in all sub-Saharan African (SSA) countries, in the form of a combined vaccine (pentavalent/hexavalent) at either 6, 10, and 14 weeks or 8, 12, and 16 weeks post birth. Although this schedule stops horizontal transmission, it does not prevent all mother-to-child transmissions (MTCT). MTCT may occur perinatally from mothers with high viremia (6).

Before HepB3 was introduced in SSA, horizontal transmission was the most frequent mode of transmission (80-90%) while MTCT accounted for only 10-20% of CHB cases (43,154). MTCT prevention is a priority for three reasons: i) children infected perinatally have a greater risk of developing CHB (90%) than those infected during childhood (30%) (7); ii) children developing CHB after MTCT have a greater risk of cirrhosis and hepatocellular carcinoma (HCC) than those developing CHB after horizontal transmission (45,135); iii) increasing HepB3 coverage without complementary MTCT preventive measures may result in MTCT transmission accounting for a larger proportion of new infections, as horizontal transmission is reduced (44).

In order to prevent perinatal and early horizontal transmission, the WHO recommends the administration of a monovalent hepatitis B vaccine birth dose to all neonates within 24h of birth (HepB-BD) (65). However, in 2020 only 13 countries of SSA had introduced HepB-BD into their EPI (155), and only 6% of infants in the region received it (156). This very low coverage may be explained by i) logistical difficulties to administer the birth dose in low-income settings where home births are common (99,137), ii) limited health budgets, and iii) a lack of financial support from 'Gavi, the Vaccine Alliance' because the current price of the monovalent hepatitis B vaccine per dose is below the alliance's minimum level for co-financing (US$0.20). However, as part of its Vaccine Investment Strategy for the 2021-2025 period, Gavi approved future investment in six new vaccines, including HepB-BD which will be supported by strengthening EPI actions (e.g., human resources, equipment, etc.) (157). Many African countries are therefore considering adding HepB-BD to HepB3 to their EPI. However, there is currently a lack of evidence for the economic value of this schedule (153). We assessed the costs and cost-effectiveness of adding HepB-BD to the current HepB3 schedule in the district of Dafra in the Hauts-Bassins Region of Burkina Faso.

4.2.2. Material and methods

4.2.2.1. Study setting

This study was conducted in Burkina Faso as part of the Neonatal Vaccination against Hepatitis B in Africa (NéoVac) programme, which aims to evaluate the feasibility and

impact of introducing HepB-BD in three African countries (Burkina Faso/Senegal/Madagascar) (132).

A meta-analysis conducted between 1996 and 2017 estimated the prevalence of CHB in Burkina Faso to be 9% (158). HepB3 was introduced in 2006 as the pentavalent vaccine, and is administered at 8, 12 and 16 weeks post-birth.

The present analysis focused on Dafra, one of the eight districts in the Hauts-Bassins Region of the country. Implementing the EPI in Dafra is the responsibility of 16 primary health centres, half of which are located in rural areas. The district covers 337,112 inhabitants, 92% of whom live <5 kilometres from a health centre (159). As part of the NéoVac programme, in February-June 2017, we conducted a population-based demographic survey in Dafra to estimate both the proportion of institutional deliveries and hepatitis B vaccination coverage (Appendix 1). The survey targeted all women 15-50 years old living in areas covered by the district's eight rural health centres. Results showed that 89.6% of births occurred in health facilities (including health centres) and 86.3% of infants completed the HepB3 vaccination schedule (unpublished data). These proportions were quite similar to those reported at the national level in 2015 (the institutional delivery rate was of 82% (160) and the HepB3 coverage rate of 91% (59)), supporting the representativeness of the study findings at a country level.

The NéoVac programme was approved by the Clinical Research Committee of the Pasteur Institute (n°2015-069) and the National Ethics Committee in Burkina Faso (n°2016-10-121).

4.2.2.2. Study Design

In order to estimate the number of perinatal HBV infections with HepB-BD+HepB3, we used a decision tree combined with a Markov model. The latter accounted for horizontal transmissions and simulated lifetime progression and costs of CHB. We used the status-quo as a comparator (i.e., the current EPI situation where the first HepB3 dose is administered from week 8 after birth). The target population was the Dafra district's 2017 birth cohort, whose size was estimated using the number of inhabitants (N=337,112) and the district's crude birth rate (34/1000) (159). In the base-case analysis, we used the HepB3 coverage rate estimated from the abovementioned population-based demographic survey in Dafra (86.3%). Assuming that every child born in a health facility in Dafra was vaccinated at birth, we hypothesized an HepB-BD coverage rate in the district of 89.6%. The following outcomes were assessed with HepB-BD+HepB3 and with HepB3 alone: number of perinatal HBV infections, number of CHB cases, number of life-years (LY), number of disability-adjusted life-years (DALYs) and costs. We used a lifetime horizon of 85 years, reflecting the 2016 WHO life tables for Burkina Faso (161), and discounted health outcomes and costs at an annual rate of 3% (162).

4.2.2.5. Model description

Figure 4.2.1 presents the decision tree to estimate the number of perinatal infections. At the end of their first life-year, infants were classified into one of the three following initial health states: i) perinatally infected through MTCT, ii) fully immunized (i.e., they

received all three doses of HepB3), or iii) susceptible to HBV infection (i.e. they did not receive all three doses of HepB3), depending on maternal HBV serostatus and administration or not of HepB-BD, and completion or not of HepB3. The risk of perinatal transmission was defined according to maternal serostatus as follows: hepatitis B surface antigen (HBsAg)-positive and e antigen (HBeAg)-positive (high risk); HBsAg-positive and HBeAg-negative (low risk); HBsAg-negative (no risk). Using a Markov model, we then simulated infants' lifetime progression according to their initial health states. The model included two absorbing health states (HBV-related and HBV-unrelated deaths) and five transient health states: horizontally acquired HBV infection, resolved HBV infection, CHB without advanced liver disease, decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) (Figure 4.2.2). In line with previous Markov models to simulate the natural history of CHB (163), we set the cycle duration to one year and applied half-cycle corrections (164).

We made the following assumptions: i) infants who did not have perinatal transmission and completed HepB3 as scheduled were fully immunized without any risk of horizontal transmission as the vaccine efficacy against chronic HBV infection is close to 100% in the absence of perinatal MTCT (165); ii) HBV immunization presented no serious adverse event (166); iii) susceptible children had a risk of HBV infection through horizontal transmission until 20 years of age. New infections beyond this age were not considered, as the risk of developing CHB is very low in adults (<5%) and therefore has limited impact on morbidity and mortality (7). Irrespective of transmission mode (i.e., perinatal or horizontal), HBV-infected individuals could either resolve their HBV infection, progress to CHB, or die from fulminant hepatitis within one year after the infection. During the lifetime, we did not assume any risk of reactivation related to immunosuppressive therapy in those who spontaneously resolved their infection, as access to this treatment is very limited in Burkina Faso. Individuals with CHB but without advanced liver disease could either remain in this health state, resolve their HBV infection, or progress to DC or HCC. Due to limited access to HBV screening and treatment in Burkina Faso, CHB is generally diagnosed only when the disease becomes symptomatic (103). Accordingly, we assumed that only those who progressed to DC or HCC sought medical care and benefited from antiviral treatment.

The model was built using R version 3.5.1.

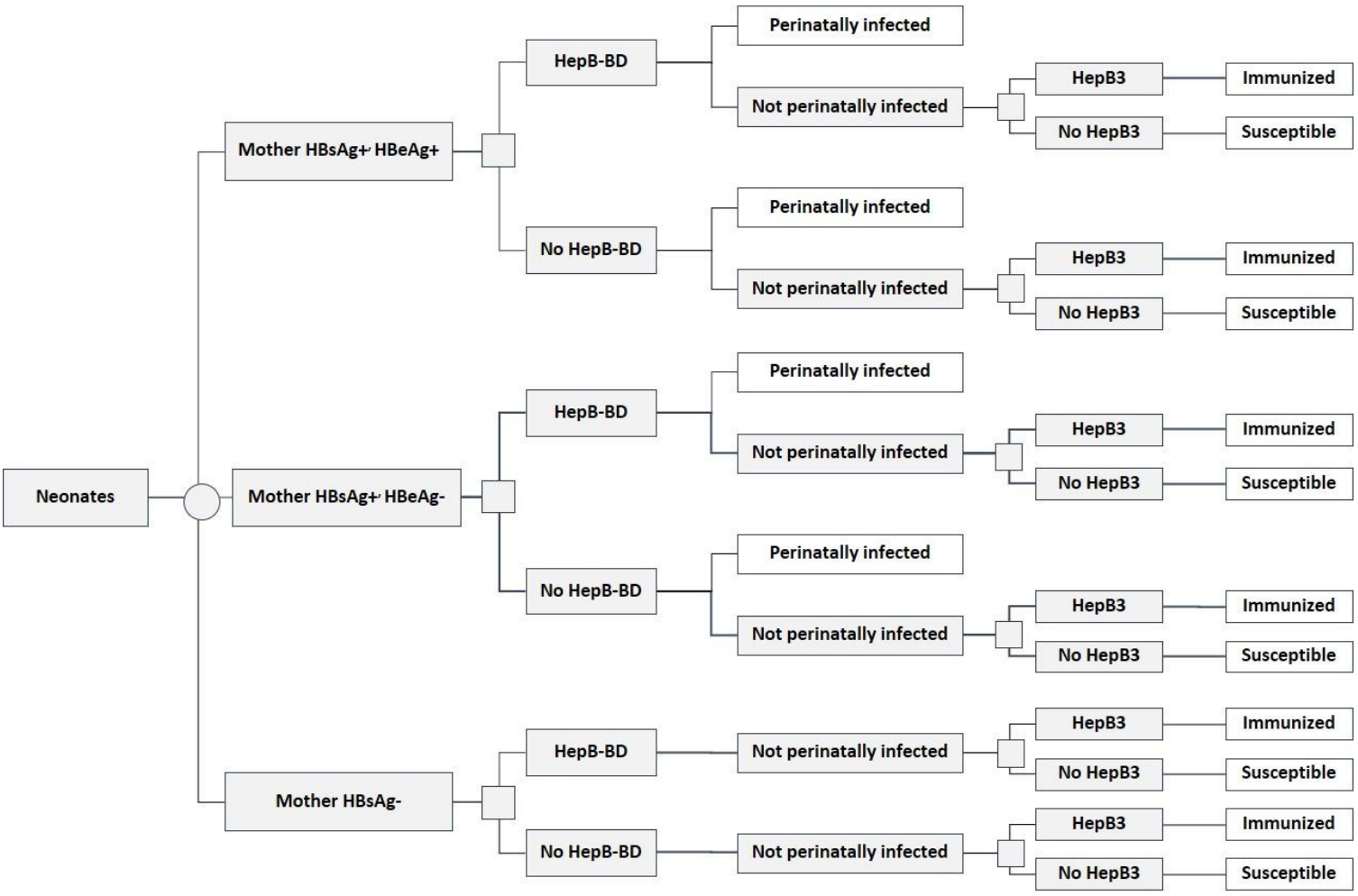


Figure 4.2.1 - Decision tree representing perinatal infections according to maternal HBV serostatus, HepB-BD, and HepB3 administration

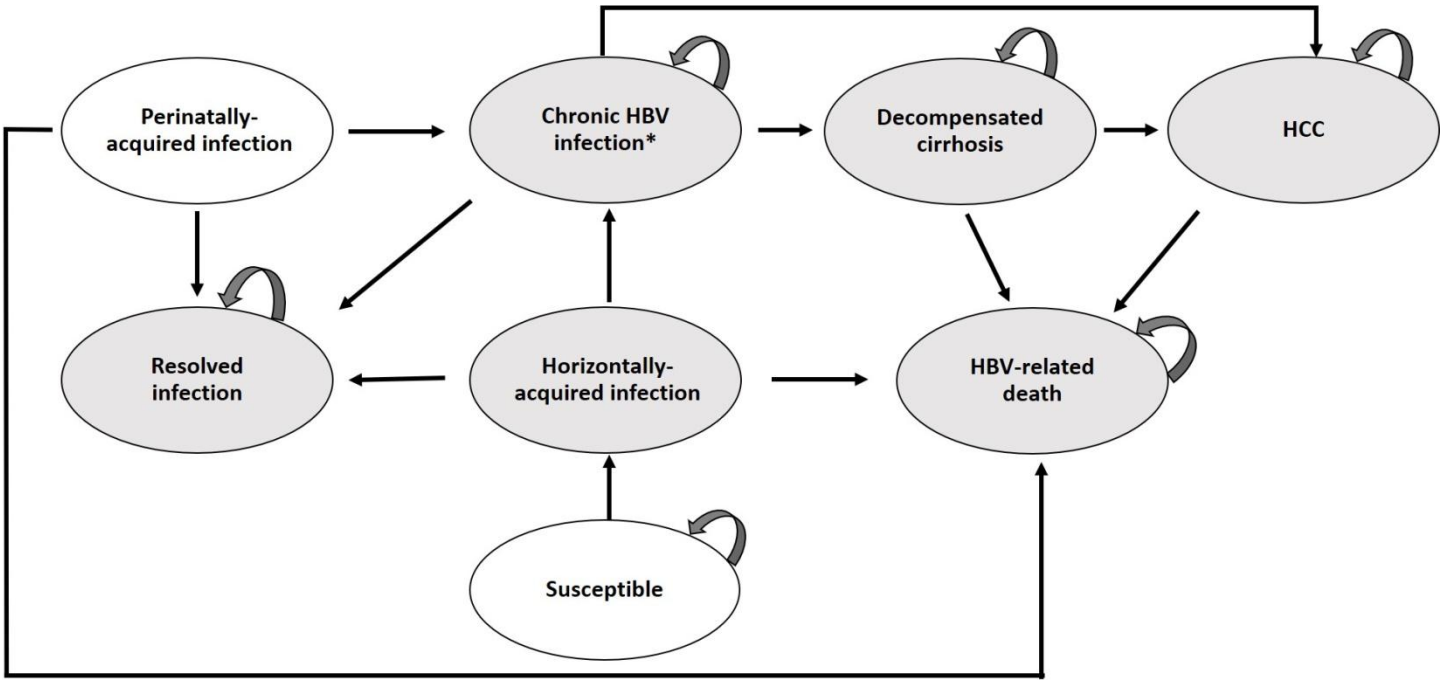


Figure 4.2.2 - Diagram of the Markov model used to simulate disease progression and associated costs

The two white oval boxes represent infants' initial health states obtained from the decision tree model: i) 'perinatally-acquired chronic HBV infection', or ii) 'susceptible to HBV infection' i.e., did not complete all three doses of the pentavalent hepatitis B vaccine (the third initial health state 'fully immunized' is not represented as we assumed that infants completing all three doses of the pentavalent hepatitis B vaccine had no risk of horizontal transmission). The grey oval boxes represent the different health states of the model. The model accounted for "natural mortality" (people had a risk of HBV-unrelated death in all health states which depended on age) but for purpose of simplification, the health state 'HBV-unrelated death' is not represented in the diagram. Arrows denote the transition between health states.

4.2.2.6. Model parameters

Epidemiological data

Parameters on the risks of perinatal infection were primarily obtained from African studies (6,167), or from Asian and European studies when African data were missing (23) (Table 4.2.1, Appendix B2). Annual health states transition probabilities to simulate the natural history of CHB were mainly estimated using data from SSA studies (Table 4.2.1, Appendix B3). Except for DC and HCC mortality rates, transition probabilities varied according to the individual's age and HBV transmission mode (i.e., perinatal or horizontal). The latter was considered to account for a higher risk of liver complications in individuals with perinatal-acquired CHB (versus horizontal-acquired CHB) (43,135).

Costs

Costs were assessed using a health system perspective. All costs were computed in CFA franc and converted into 2017 US$ using the 2017 average annual exchange rate (168).

HBV vaccination costs

HBV vaccination costs were estimated using data from a 2017 micro-costing study conducted in Dafra which documented the quantities and unit costs of all resources used

in 2016-2017 for EPI activities (Appendix B4). Using standardized methods (141,142), we estimated the costs of the following activities separately for HepB-BD and HepB3: i) vaccine administration (syringes, safety boxes and human resources), ii) vaccine distribution and storage (including transport, cold chain equipment, operating costs), iii) waste management, and iv) advanced strategies for boosting HepB-BD coverage. In the base-case analysis, we assumed an HepB-BD coverage rate of 89.6%, and in the sensitivity analyses, we varied the HepB-BD coverage rate from 50 to 95%. Advanced strategies for boosting HepB-BD coverage included community mobilization and reinforced communication activities among pregnant women to reach a coverage rate of 89.6%, and notification of births (in addition of community mobilization and reinforced communication activities) to reach a coverage rate of 95%. Vaccine and consumable unit costs came from the UNICEF Supply Division (169). For the monovalent vaccine, we considered two different formats: single-dose and 10-dose vials with respective unit prices of US$0.38 and US$0.17. We defined the total cost for routine HepB-BD and HepB3 immunization, respectively, as the sum of the costs related to each previously mentioned activity. We then computed the HepB-BD (HepB3) unit cost per vaccinated neonate as the total cost for routine HepB-BD (HepB3) divided by the number of vaccinated neonates in 2017 in Dafra. Detailed information is provided in Appendix 4 on the micro-costing study, as well as on the approaches used to estimate both the costs of each above-mentioned activity, and the cost per vaccinated neonate.

Cost of care for HBV-related complications

As hospital-based specialized care is not available in Dafra, we estimated the healthcare cost of CHB patients with DC or HCC at the national level using annual healthcare resource use and respective unit cost data, obtained from expert interviews in a referral hospital (Appendix 5). Care practices for CHB patients with DC or HCC followed WHO guidelines (65).

DALYs

DALYs were calculated for symptomatic acute hepatitis, DC and HCC, using previously published disability weights (Table 4.2.1) (170).

4.2.2.7. Economic and sensitivity analyses

The methods employed in the economic analysis were in line with international guidelines (164,171). ICERs were calculated as the difference in total costs between the two strategies (HepB-BD+HepB3 *versus* HepB3 alone) divided by the corresponding difference in health benefits. We considered two cost-effectiveness thresholds to assess the cost-effectiveness of the HepB-BD+HepB3 as follows: i) the Burkina Faso per-capita gross domestic product (GDP) (172) (US$671 in 2017 (173)) and 0.5 times the country's per-capita GDP (US$335) (174).

We assessed uncertainty in model parameters using a probabilistic sensitivity analysis (PSA). Model parameters were sampled from their distributions (Table 4.2.1) over 10,000 Monte Carlo simulations. The 10,000 pairs of incremental costs and DALYs obtained in

the simulations were plotted in the cost-effectiveness plan and their respective distributions were used to estimate the 95% confidence intervals (CI). To account for uncertainty in the value of the cost-effectiveness threshold, the 10,000 Monte Carlo simulations were also used to derive the cost-effectiveness acceptability curve (CEAC) (175).

Furthermore, we conducted one-way deterministic sensitivity analyses (DSA) to investigate the impact of each parameter on the cost-effectiveness. Parameter variations considered in the analysis are presented in Table 4.2.1 and results depicted using a Tornado Diagram.

Table 4.2.1: Model parameters

Parameters	Base-case values	Range for sensitivity analysis	Distribution	Source
Epidemiological parameters				
HBsAg prevalence in pregnant women (%)	10.0	8.0 – 12.0	Beta (86.83, 781.48)	(158,176,177)
HBeAg prevalence in HBsAg+ pregnant women (%)	15.0	10.0 – 20.0	Beta (29.62, 167.84)	(176,177)
HepB3 coverage rate (%)	86.3		Beta (512.16, 81.30)	NéoVac (2017)
HepB-BD coverage rate (%)	89.6	50.0 – 95.0	Beta (3.51, 0.41)	Hypothesis, NéoVac (2017)
Number of neonates estimated for 2017 in Dafra health district	11,462			(159)
Perinatal infection risk in mothers HBeAg-positive and with HepB-BD (%)	32.4	10.2-58.3	Beta (4.25, 8.86)	(6)
Perinatal infection risk in mothers HBeAg-positive but no HepB-BD (current situation) (%)	58.8	36.0 - 78.0	Beta (11.42, 8.00)	(6,167)
Perinatal infection risk in mothers HBeAg-negative and with HepB-BD (%)	0.7	0.0-2.1	Beta (1.61, 228.99)	(23)
Perinatal infection risk in mothers HBeAg-negative but no HepB-BD (current situation) (%)	5.0	1.0 - 15.0	Beta (1.49, 28.36)	(6)
Annual heath state transition probabilities				
Susceptible to horizontally acquired infection (up to 20 years of age)	0.031	0.020 – 0.040	Beta (37.52, 1172.73)	(178)
Perinatally-acquired infection to chronic infection	0.885	0.700-1.000	Beta (18.68, 2.43)	(7)
Horizontally-acquired infection to chronic infection	$\exp(-0.645age^{0.455})$			(7)
0-4 years old		0.200-0.600	Beta (5.82, 11.84)	
5-9 years old		0.150-0.300	Beta (18.06, 75.57)	
10-14 years old		0.080-0.200	Beta (14.05, 96.59)	
15-19 years old		0.050-0.150	Beta (10.99, 109.85)	
Perinatally-acquired infection to death (fulminant hepatitis)	$13x10^{-6}$	0 – 0.006	Beta (0.04, 3158.07)	(179)
Horizontally-acquired infection to death (fulminant hepatitis)	0.001	0 – 0.006	Beta (0.34, 337.31)	(179)

Chronic HBV infection to resolved infection (HBsAg seroconversion)				(43)
0-9 years old	0.0010	0 – 0.003	Beta (1.63, 1629.70)	
10-19 years old	0.0046	0.002 – 0.007	Beta (13.94, 3015.81)	
20-29 years old	0.0101	0.005 – 0.014	Beta (20.98, 2056.06)	
30-39 years old	0.0105	0.005 – 0.016	Beta (14.55, 1371.50)	
40-49 years old	0.0232	0.012 – 0.033	Beta (19.51, 821.52)	
50+ years old	0.0239	0.012 – 0.036	Beta (15.47, 631.87)	
Chronic infection to decompensated cirrhosis for people with perinatally-acquired HBV				(180)
0-4 years old	0.0003	0.0001 – 0.0004	Beta (1.01, 3374.57)	
5-9 years old	0.0001	0 – 0.0002		
10-14 years old	0.0001	0 – 0.0002		
15-19 years old	0.0003	0.0001 – 0.0004		
20-24 years old	0.0004	0.0002 – 0.0006		
25-29 years old	0.0008	0.0004 – 0.0011		
30-34 years old	0.0012	0.0006 – 0.0018	Beta (7.81, 5198.75)	
35-39 years old	0.0018	0.0010 – 0.0027		
40-44 years old	0.0029	0.0016 – 0.0043	Beta (11.60, 3504.92)	
45-49 years old	0.0037	0.0020 – 0.0054		
50-54 years old	0.0051	0.0027 – 0.0074	Beta (11.18, 1852.85)	
55-59 years old	0.0068	0.0036 – 0.0098		
60-64 years old	0.0123	0.0065 – 0.0178	Beta (14.76, 1120.34)	
65-69 years old	0.0138	0.0073 – 0.0199		
70-74 years old	0.0173	0.0091 – 0.0250	Beta (12.93, 667.82)	
75-79 years old	0.0206	0.0109 – 0.0299		
80-84 years old	0.0240	0.0126 – 0.0347	Beta (12.38, 453.10)	
85+ years old	0.0292	0.0154 – 0.0422		
Chronic infection to decompensated cirrhosis for people with horizontally-acquired HBV				(180)
0-4 years old	0.0001	0 – 0.0001	Beta (0.51, 12630.32)	
5-9 years old	$1x10^{-5}$	0 – $2x10^{-5}$		
10-14 years old	$1x10^{-5}$	0 – $2x10^{-5}$		
15-19 years old	$5x10^{-5}$	0 – 0.0001		
20-24 years old	0.0001	0 – 0.0002		
25-29 years old	0.0001	0.0001 – 0.0002		
30-34 years old	0.0002	0.0001 – 0.0003	Beta (5.62, 22484.78)	
35-39 years old	0.0003	0.0002 – 0.0005		
40-44 years old	0.0005	0.0003 – 0.0008	Beta (11.12, 18523.68)	
45-49 years old	0.0007	0.0004 – 0.0010		
50-54 years old	0.0009	0.0005 – 0.0014	Beta (11.24, 10205.00)	
55-59 years old	0.0012	0.0007 – 0.0018		

60-64 years old	0.0023	0.0012 – 0.0034	Beta (13.27, 5514.15)	
65-69 years old	0.0025	0.0013 – 0.0038		
70-74 years old	0.0032	0.0017 – 0.0047	Beta (12.55, 3572.52)	
75-79 years old	0.0038	0.0020 – 0.0056		
80-84 years old	0.0044	0.0023 – 0.0065	Beta (11.47, 2328.37)	
85+ years old	0.0053	0.0029 – 0.0080		
Chronic infection to HCC for people with perinatally-acquired HBV				(181)
0-14 years old	$1x10^{-5}$	0 – $2x10^{-5}$	Beta (0.51, 5051.12)	
15-39 years old	0.0003	0.0002 – 0.0005		
40-44 years old	0.0012	0.0006 – 0.0019	Beta (10.77, 7684.88)	
45-49 years old	0.0015	0.0007 – 0.0023		
50-54 years old	0.0020	0.0010 – 0.0030	Beta (10.24, 4645.11)	
55-59 years old	0.0024	0.0012 – 0.0037		
60-64 years old	0.0022	0.0011 – 0.0033		
65-69 years old	0.0034	0.0017 – 0.0052	Beta (6.07, 1313.39)	
70-74 years old	0.0058	0.0029 – 0.0089		
75+ years old	0.0096	0.0048 – 0.0146	Beta (15.16, 1564.13)	
Chronic infection to HCC for people with horizontally-acquired HBV				(181)
0-14 years old	0.0000	0 – $1x10^{-5}$	Beta (0.83, 16598.04)	
15-39 years old	0.0001	0 – 0.0002		
40-44 years old	0.0003	0.0001 – 0.0004	Beta (9.36, 31192.85)	
45-49 years old	0.0003	0.0002 – 0.0005		
50-54 years old	0.0004	0.0002 – 0.0006	Beta (11.39, 22771.51)	
55-59 years old	0.0005	0.0003 – 0.0008		
60-64 years old	0.0005	0.0003 – 0.0008		
65-69 years old	0.0008	0.0004 – 0.0011	Beta (8.61, 7822.49)	
70-74 years old	0.0013	0.0008 – 0.0019		
75+ years old	0.0022	0.0012 – 0.0031	Beta (21.75, 9863.58)	
Decompensated cirrhosis to HCC	0.07	0.01 – 0.2	Beta (1.65, 21.97)	(182)
Decompensated cirrhosis to death	0.15	0.05 – 0.5	Beta (0.90, 5.10)	(182)
HCC to death	0.90	0.5 –1.0	Beta (3.39, 0.38)	(183)
Disability weights				
Symptomatic acute infection	0.051[a]	0.03 – 0.08	Beta (14.65, 272.67)	(170)
Decompensated cirrhosis	0.178	0.15 – 0.25	Beta (36.39, 168.03)	(170)
HCC	0.54[b]	0.4 – 0.7	Beta (22.20, 18.91)	(170)
Costs				
Total HepB-BD cost per administered dose - 10-dose vial if coverage rate=89.6% (50%-95%) (US $)	0.60	0.50-0.97	Gamma (25, 41.667)	NéoVac (2017)

Total HepB-BD cost per administered dose - Single-dose vial (50%-95%) (US $)	–	1.08-1.64	–	NéoVac (2017)
Total HepB3 cost per immunized child (US $)	3.09	–	Point estimate	NéoVac (2017)
Persons at advanced stage of disease (DC and HCC) receiving care (%)	100.0	50.0 – 100.0	Point estimate	Hypothesis
Decompensated cirrhosis				
Initial screening performed during 1st hospitalization	25.8		Gamma (25, 0.969)	NéoVac (2017)
Hospitalization for patients with ascites[c] (annual cost - 3 per year)	543.7		Gamma (25, 0.046)	NéoVac (2017)
Hospitalization for patients without ascites[c] (annual cost - 3 per year)	533.1		Gamma (25, 0.047)	NéoVac (2017)
Cost of drugs for patients with ascites[c] (annual cost - 365.25 days of treatment)	369.6		Gamma (25, 0.068)	NéoVac (2017)
Cost of drugs for patients without ascites[c] (annual cost - 365.25 days of treatment)	229.4		Gamma (25, 0.109)	NéoVac (2017)
HCC				
Costs of initial screening (only for people not coming from the cirrhosis health state (i.e., diagnosed with CHB at HCC stage)	25.8		Gamma (25, 0.969)	NéoVac (2017)
Costs of initial check-up (only for people not coming from the cirrhosis health state)	146.0		Gamma (25, 0.171)	NéoVac (2017)
Costs of monitoring check-up (annual cost; 1 check-up per year for people diagnosed at HCC stage; 2 check-ups per year for the others)	72.2		Gamma (25, 0.346)	NéoVac (2017)
Cost of drugs for patients already diagnosed with CHB (cost for 90 days of treatment)	143.3		Gamma (25, 0.174)	NéoVac (2017)
Cost of drugs for patients diagnosed with CHB at HCC stage (cost for 90 days of treatment)	52.3		Gamma (25, 0.478)	NéoVac (2017)

[a] According to the WHO, acute infection usually lasts 0.25 years. Therefore, we used an annual disability weight of 0.013 (65). We only applied a disability weight to symptomatic acute HBV infections, which represent 1% of perinatally-infected individuals, 10% of children infected between 1 and 5 years of age, and 30% of individuals infected after the age of 5 years (184).

[b] We applied the annual disability weight considering that 50% of individuals diagnosed with HCC died within 3 months (183).

[c] We considered that 48% of patients had ascites (185).

4.2.3. Results

4.2.3.1. Base-case analysis

Cost related to HepB-BD

In the base-case analysis, assuming an HepB-BD coverage rate of 89.6%, the incremental cost related to HepB-BD immunization was US$6,113 for 10-dose vials and US$12,125 for the single-dose format (Table 4.2.2). The largest cost item for 10-dose and single-dose vials was 'vaccines and injection supplies', accounting for US$2,630.1 (43% of the total) and US$4,702.1 (38.8% of the total), respectively. The second largest cost item for the former format was human resources (US$1,499.1, 24.5% of the total) and vaccine storage (US$2,621.2, 21.6% of the total) for the latter, due to the larger volume required. The total HepB-BD cost per administered dose was US$0.60 and US$1.18 for the 10-dose and single-dose vials, respectively. When assuming that the HepB-BD coverage decreased

(increased) to 50% (95%), the total HepB-BD cost per administered dose was US$0.50 (US$0.97) for the 10-dose format and US$1.08 (US$0.1.64) for the single-dose format.

Costs related to care provided for HBV complications

Without discounting, total healthcare costs for caring and treating HBV-related liver complications over the lifetime of HBV-infected cases were US$33,164 with HepB-BD+HepB3 and US$58,255 with HepB3 alone. When discounted at 3%, these costs decreased to US$7,161 and US$12,719, respectively.

Effectiveness

Without discounting, HepB-BD+HepB3 prevented 67 CHB cases and 8 HBV-related deaths, and resulted in 157 LYS and 163 DALYs averted compared with HepB3 alone (Table 4.2.3). When discounting HepB-BD benefits, the number of LYS and DALYs averted fell by 29 and 31, respectively.

Cost-effectiveness of HepB-BD+HepB3 (10-dose format)

Without discounting, HepB-BD+HepB3 compared with HepB3 alone generated net cost-savings of US$18,979, and resulted in 157 LYS, and 163 DALYs averted (Table 4.2.3). With a 3% discount rate, HepB-BD+HepB3 compared with HepB3 resulted in an incremental cost of US$554, 29 LYS, and 31 DALYs averted, translating into an ICER of US18/DALY averted.

The 10,000 Monte Carlo simulations are displayed in Figure 4.2.3a and the CEAC in Figure 4.2.3b. Without discounting, HepB-BD+HepB3 was cost-saving in 84.1% of simulations; it was cost-effective in 96.4% of the simulations at the cost-effectiveness threshold of US$335, and in 97.3% at the cost-effectiveness threshold of US$671. With discounting, HepB-BD+HepB3 was cost-saving in 23.2% of the simulations, and was cost-effective in 71.7% and 86.7% of the simulations at the cost-effectiveness thresholds of US$335 and US$671, respectively.

Table 4.2.2: Routine immunization economic costs of HepB-BD in the Dafra district, Burkina Faso, according to vaccine vial format (10- or single-dose) and coverage rate (N=11,462)

Cost category	HepB-BD coverage rate of 50%			HepB-BD coverage rate of 89.6%			HepB-BD coverage rate of 95%		
	Routine immunization economic cost (US$)	Cost/dose (US$)	Total (%)	Routine immunization economic cost (US$)	Cost/dose (US$)	Total (%)	Routine immunization economic cost (US$)	Cost/dose (US$)	Total (%)
10-dose vial									
Vaccines and injection supplies[a]	1,467.8		51.3	2,630.1		43.0	2,788.7		26.5
Human resources for vaccine administration	836.5		29.2	1,499.1		24.5	1,589.4		15.1
Vaccine storage	296.4		10.4	531.1		8.7	563.1		5.4
Vaccine distribution	214.0		7.5	383.5		6.3	406.7		3.9
Waste management	48.3		1.7	86.6		1.4	91.8		0.9
Advanced strategies for boosting HepB-BD coverage[c]	0.0		0.0	982.0		16.1	5,077.7		48.3
Total	**2,863.1**	**0.50**	100.0	**6,112.5**	**0.60**	100.0	**10,517.5**	**0.97**	100.0
Single-dose vial									
Vaccines and injection supplies[a]	2,623.9		42.2	4,702.1		38.8	4,985.4		29.5
Human resources for vaccine administration	836.5		13.5	1,499.1		12.4	1,589.4		9.4
Vaccine storage[b]	1,462.7		23.5	2,621.2		21.6	2,779.3		16.5
Vaccine distribution[b]	1,056.3		17.0	1,892.8		15.6	2,006.9		11.9
Waste management	238.6		3.8	427.5		3.5	453.3		2.7
Advanced strategies for boosting HepB-BD coverage[c]	0.0		0.0	982.0		8.1	5,077.7		30.1
Total	**6,218.0**	**1.08**	100.0	**12,124.8**	**1.18**	100.0	**16,892.0**	**1.64**	100.0

[a] The unit cost of HepB-BD was US$0.38 for a single-dose vial and US$0.17 for a 10-dose vial.
[b] The volume (in cm^3) of one packaged hepatitis B vaccine birth dose was 2.8 cm^3 per dose for 10-dose vials and 14.4 cm^3 per dose for single-dose vials.
[c] Advanced strategies include community mobilization activities and reinforced communication to reach a coverage rate of 89.6% (base-case analysis) and notification of births (in addition of community mobilization activities and reinforced communication) to reach a coverage rate of 95%.
Abbreviation: HepB-BD=Hepatitis B vaccine dose within 24 hours of birth.

Table 4.2.3: Base-case results for the cost-effectiveness analysis of HepB-BD+HepB3 versus HepB3 alone in the fictive birth cohort of Dafra, Burkina Faso (N=11,462)

	Total cost, US$	Total number of chronic HBV infections	Total number of HBV-related deaths	Total life-years	Total DALYs	Incremental cost (95%CI[a]), US$	Life-years saved (95%CI[a])	DALYs averted (95%CI[a])	ICER (95%CI[a]), US$ per life-year saved	ICER (95%CI[a]), US$ per DALY averted
HepB3 alone (current EPI situation)										
Undiscounted results	88,868	260	20	714,761	265,257					
Discounted results (3%)	43,331			308,544	48,286					
HepB-BD+HepB3										
Undiscounted results	69,889	193	12	714,918	265,094	-18,979 (-104,883 to 8,504)	157 (8 to 384)	163 (8 to 401)	Cost-saving (cost-saving to 270)	Cost-saving (cost-saving to 259)
Discounted results (3%)	43,886			308,573	48,255	554 (-15,045 to 10,523)	29 (1 to 78)	31 (2 to 81)	19 (cost-saving to 2,468)	18 (cost-saving to 2,286)

[a] The 95% confidence intervals were estimated as the range between observations at percentiles 2.5 and 97.5 from the results of the 10,000 Monte Carlo simulations.

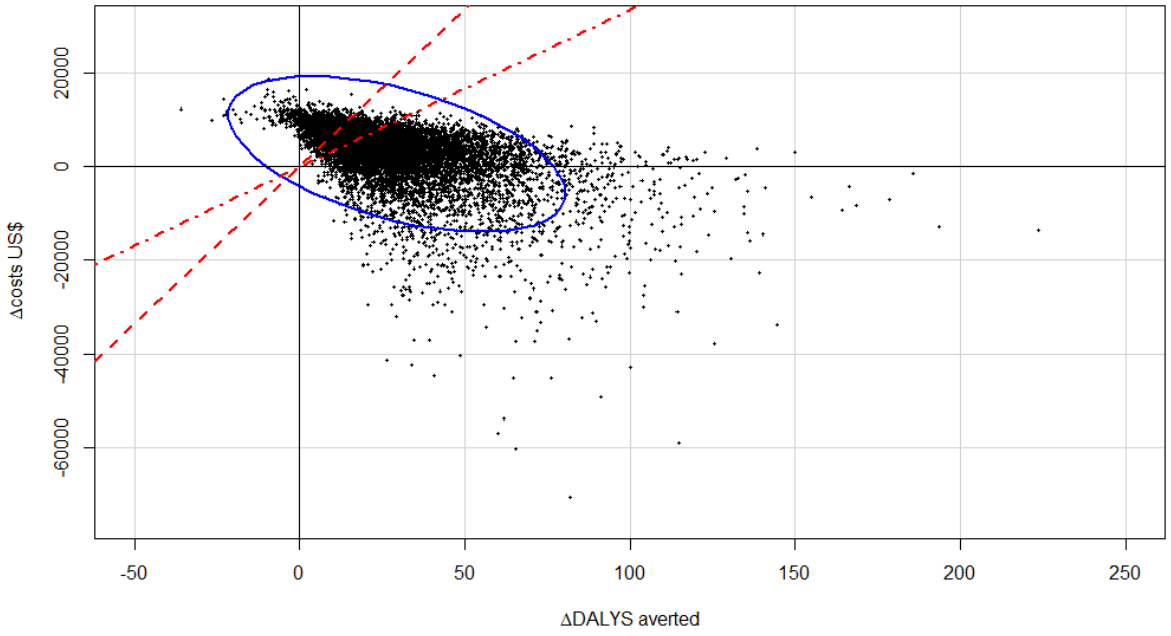
Abbreviations: HepB-BD= Hepatitis B vaccine dose within 24 hours of birth; HepB3=three doses of pentavalent vaccine; HBV= hepatitis B virus; EPI= Expanded Program on Immunization; DALYs=disability-adjusted life-years; ICER=incremental cost-effectiveness ratio.

4.2.3.2. Deterministic sensitivity analysis (DSA)

Results from the DSA are presented in Figure 4.2.4 and in Table B1 in Appendix B.

When varying HepB-BD coverage rate from 50% to 95%, the number of DALYs averted by HepB-BD+HepB3 compared with HepB3 alone ranged from 17 to 33 (Table B1). However, the incremental cost of HepB-BD+HepB3 varied greatly according to HepB-BD coverage rate and vaccine format, as they are interrelated with HepB-BD cost per administrated dose. For 10-dose vials, HepB-BD generated net cost-savings of US$238 when HepB-BD coverage rate was 50%, and an incremental cost of US$4,624 when HepB-BD coverage rate was 95%, translating into an ICERs of US$152/DALY averted. For single-dose vials, incremental cost of HepB-BD ranged from US$3,116 to US$12,017 when varying HepB-BD coverage rate from 50% to 95%, i.e. an ICER of US$182 and US$367/DALY averted, respectively.

Furthermore, the DSA shows that the cost-effectiveness results were very sensitive to perinatal infection risks with and without the HepB-BD. Transition probabilities from CHB to DC, and from DC to death, were also very sensitive parameters. However, Figure 4.2.4 shows that HepB-BD+HepB3 remained cost-effective for all variations in parameters considered in the DSA at the cost-effectiveness threshold of US$671. In addition, HepB-BD+HepB3 remained cost saving as long as the cost of HepB-BD per administered dose was <US$0.54, and cost effective as long as the cost of HepB-BD per administered dose was <US$1.55 at the cost-effectiveness threshold of US$335, or < US$2.55 at the cost-effectiveness threshold of US$671.



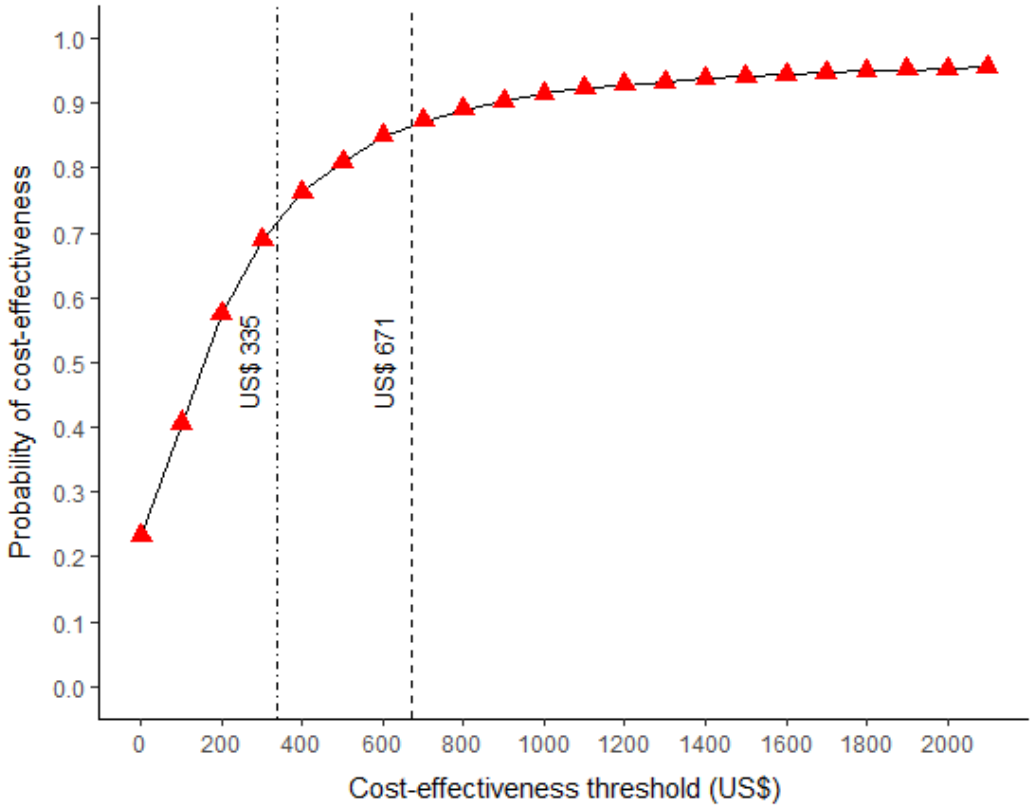


Figure 4.2.3 - Scatter plot of estimated joint density of incremental costs and incremental effects of HepB-BD+HepB3 versus HepB3 alone, obtained by Monte Carlo simulation in the fictive birth cohort (N=11,462) of Dafra, Burkina Faso (a) and cost-effectiveness acceptability curve (b)

The dashed line indicates the cost-effectiveness threshold of 1 times the Burkina Faso GDP/capita in 2017 (US$671/DALY), while the dashed-dotted line indicates the cost-effectiveness threshold of 0.5 times the Burkina Faso GDP/capita in 2017 (US$335/DALY).

The cost-effectiveness acceptability curve shows the probability that HepB-BD+HepB3 is cost-effective compared with HepB3 alone over a range of cost-effectiveness thresholds from US$0 to US$2,100/DALY.

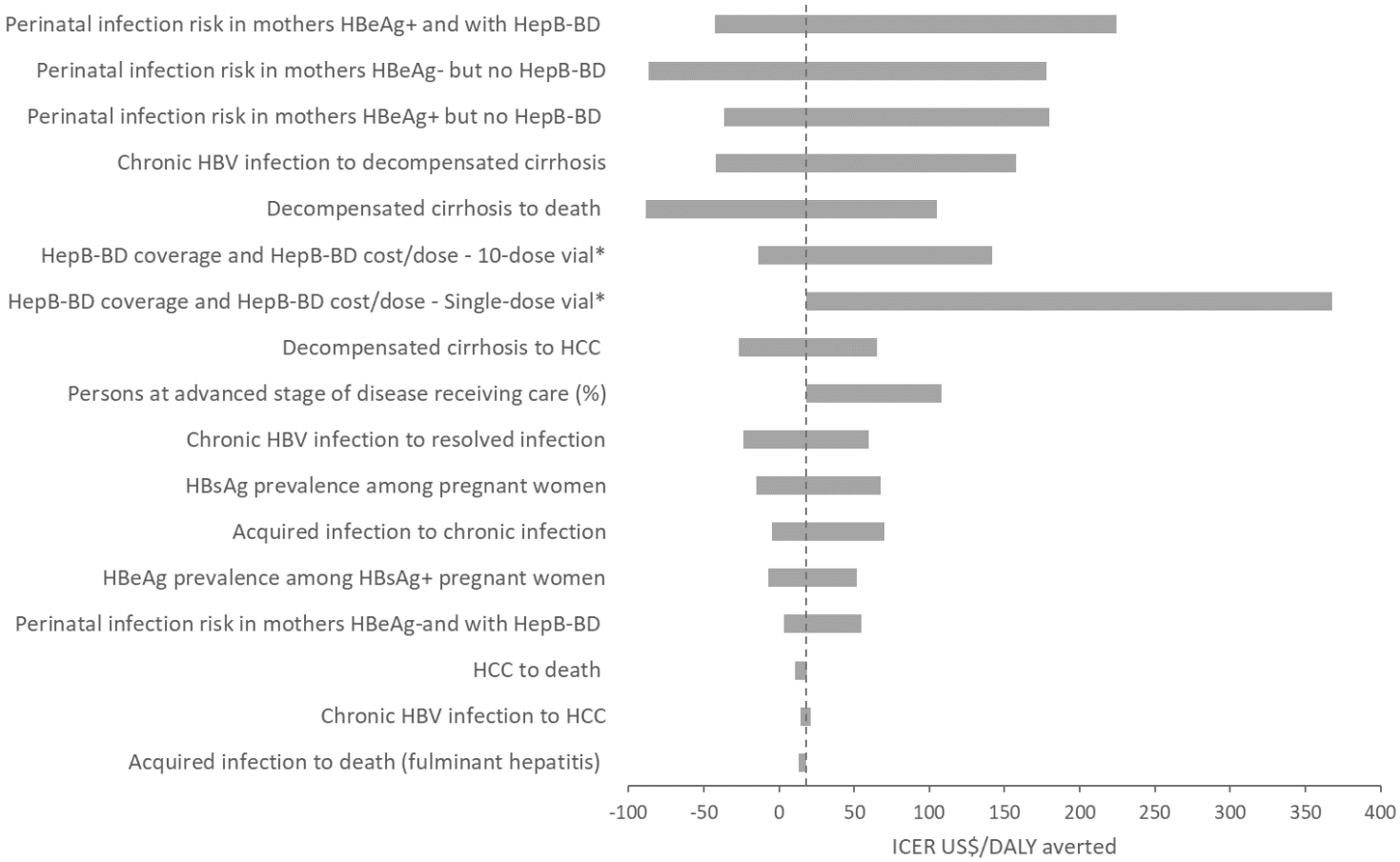


Figure 4.2.4 - One-way sensitivity analyses of the incremental cost-effectiveness ratio

* The total HepB-BD cost per administered dose depended on HepB-BD coverage, therefore the two variables varied simultaneously.

The horizontal axis shows variations in incremental cost-effectiveness ratios (in US dollars per disability-adjusted life-year) for each variation in the parameters listed on the vertical axis. The dashed vertical line shows the ICER of the HepB-BD+HepB3 in the base-case analysis. Negative ICERs indicate that HepB-BD+HepB3 yielded net costs savings.

The diagram illustrates results only when parameter variation had an impact on the ICER >US1/DALY averted.

4.2.4. Discussion

Using modelling based on parameters derived from African data, this study provides evidence that implementing HepB-BD in addition to HepB3 in Dafra in the Hauts-Bassins Region in Burkina Faso could be of economic value. Adding HepB-BD to the current EPI is cost-effective and could even be cost-saving, as the additional cost related to vaccination at birth could be counterbalanced by future avoided healthcare costs thanks to avoided CHB in perinatally HBV-infected children. However, the results varied greatly according to discounting, which reflects time preferences. The PSA, which simultaneously took into account uncertainty in all model parameters, showed that with discounting, the probabilities of HepB-BD+HepB3 being cost-effective were 71.7 and 86.7%, at the cost-effectiveness thresholds of US$335 and US$671, respectively. However, without

discounting, the probabilities of being cost-effective greatly increased to 96.4 and 97.3%, for the same cost-effectiveness thresholds. The gap between undiscounted and discounted results reflects the fact that the health benefits of HepB-BD only become evident several decades after vaccination, as CHB-related cirrhosis or HCC usually develop in adulthood. The way decision makers will appreciate these benefits, and accordingly, use our cost-effectiveness results for policy decisions, will depend on their time preferences (186).

Furthermore, the DSA highlighted that cost-effectiveness results were particularly sensitive to two key parameters: total HepB-BD cost per administered dose and MTCT risk with and without the HepB-BD. There was considerable variation in the total cost of HepB-BD per administered dose according to the vaccine format (US$0.60 for 10-dose vials *versus* US$1.18 for single-dose vials), because of the higher unit price of the single-dose format (US$0.38 per dose compared with US$0.17) and the higher volume it requires for storage and transport. However, the DSA showed that when the total cost of HepB-BD per administered dose increased to US$1.64, the ICER was estimated at US$367/DALY, which remains below the cost-effectiveness threshold of US$671. Moreover, HepB-BD+HepB3 remained cost-effective, as long as the total cost of HepB-BD was <US$1.55 per administered dose at the cost-effectiveness threshold of US$335, or <US$2.55 at the cost-effectiveness threshold of US$671. With regard to the effectiveness of HepB-BD for reducing MTCT risk, there is still uncertainty in SSA due to the small number of related studies. One study, by Ekra et al. in Côte d'Ivoire, found that 37.5% of neonates with HBeAg-positive mothers were infected despite HepB-BD. Similarly, a recent study in Cameroon found that 28.9% of children of HBeAg-positive mothers carried HBsAg despite HepB-BD (167,187). These findings need to be confirmed in larger studies (132). We assessed this uncertainty related to HBV MTCT risks using one-way sensitivity analyses which confirmed that HepB3-BD+HepB3 could remain cost-effective when considering a large range of variations in these parameters.

To date, a small number of studies have assessed the cost-effectiveness of HepB-BD (188–190) but only one has examined the economic value of adding HepB-BD to HepB3 in the EPI of a sub-Saharan African country (153). It was conducted in Mozambique and showed that universal HepB-BD was highly cost-effective, with an ICER estimated at US$250.95 per DALY averted, compared with HepB3 alone. The study model was limited by its heavy dependency on non-African specific data. More specifically, rates of perinatal/horizontal transmission and natural history of CHB differ markedly between geographical regions due to virological, environmental, cultural and socioeconomic differences, including differences in HBV genotypes (8) and local standard of care (103). In contrast with previous models, ours took into account the risk of horizontal transmission by using transition probabilities specific to age and HBV transmission mode defined using SSA-specific data.

Our study has limitations. First, the model we built omitted the health state related to compensated cirrhosis as we did not identify any cohort data for CHB patients in SSA which would have allowed us to measure the incidence of compensated cirrhosis. Nevertheless, the omission of compensated cirrhosis should have minimal impact on our

results as this health state is generally asymptomatic, and therefore has little effect on DALYs and mortality (170). Similarly, the impact on costs to care of compensated cirrhosis may be marginal in SSA, because CHB patients often seek medical care only when they develop severe symptoms from decompensated cirrhosis or HCC (191). Second, we modelled a static birth cohort without taking into account the dynamicity of HBV transmission over time and herd immunity induced by the intervention. The omission of these effects could have led to an underestimation of the health benefits and therefore the cost-effectiveness of HepB-BD. Third, cost-effectiveness was estimated specifically for the Dafra district, not for Burkina Faso nationally or for the whole SSA region. Nevertheless, the Dafra district is representative of the Burkina Faso in terms of demography and EPI performance (i.e., coverage rate and costs). Furthermore, most epidemiological parameters used in our models (MTCT risks with/without HepB-BD and transition probabilities to simulate disease evolution) were not specific to this district but derived using West African data, or SSA data when the former were unavailable. Finally, variations in the parameters covering regional differences were accounted for in the deterministic and probabilistic sensitivity analyses. Results showed that HepB-BD+HepB3 remained cost-effective for all variations in the parameters in the DSA and has a >95% probability of being cost-effective without discounting, and >85% with discounting at the cost-effectiveness threshold of US$671 (i.e. Burkina Faso per-capita GDP). Given all these points, we believe that our findings may be generalizable to all Burkina Faso and neighbouring countries in West Africa with similar living standards, especially given the high prevalence of HBV throughout the region (43).

Conclusion

Despite uncertainty about the magnitude of HepB-BD effectiveness, this study provides evidence that adding HepB-BD to HepB3 would be cost-effective in Burkina Faso - a nation where HBV is highly endemic.

4.3. Costs of integrating hepatitis B screening and antiviral prophylaxis into routine antenatal care in Burkina Faso: Prophylaxis for All versus targeted strategies

Gosset A et al. *International Journal of Gynecology and Obstetrics*. Published, Apr. 2024. DOI: http://doi.org/10.1002/ijgo.15515

Résumé

Objectif : L'élimination de la transmission mère-enfant (TME) du virus de l'hépatite B (VHB) dans les pays africains hautement endémiques présente des incertitudes quant à sa faisabilité économique. La prévention de la TME (PTME) nécessite le dépistage de l'antigène de surface de l'hépatite B (AgHBs) chez les femmes enceintes, l'identification des porteuses d'une charge virale élevée ou de l'antigène e de l'hépatite B (AgHBe), et l'administration d'une prophylaxie au ténofovir aux femmes à haut risque de transmission. Nous avons estimé les coûts de l'intégration des services de PTME dans les soins prénataux au Burkina Faso, en utilisant quatre stratégies différentes pour sélectionner les femmes pour la prophylaxie au ténofovir : 1) ADN du VHB (≥200 000 UI/mL), 2) AgHBe, 3) test de diagnostic rapide de l'antigène core de l'hépatite B (TDR-AgHBcr), 4) toutes les femmes positives à l'AgHBs ("Prophylaxis for All").

Méthodes : À partir d'une approche de micro-costing, nous avons estimé le coût économique supplémentaire de l'intégration de chaque stratégie dans les soins prénataux de routine en 2024, par rapport à la vaccination néonatale seule. Les analyses de sensibilité ont exploré les variations de la prévalence, de la couverture des interventions, des prix des tests et du ténofovir.

Résultats : La stratégie TDR-AgHBcr s'est avérée la moins coûteuse, avec un coût économique total de 3 959 689$, comparée à l'ADN du VHB (6 128 875$), à l'AgHBe (4 135 233$) et au Aall (4 141 206$). Le coût par femme enceinte recevant une prophylaxie au ténofovir variait de 61,88$ (Prophylaxis for All) à 1 071,05$ (ADN du VHB). La stratégie Prophylaxis for All présentait le coût marginal le plus bas en raison du plus grand nombre de femmes sous ténofovir (66 928) par rapport à l'ADN du VHB (5 722), à l'AgHBe (10 020) et au TDR-AgHBcr (7 234). Dans les analyses de sensibilité, la stratégie Prophylaxis for All devenait moins coûteuse lorsque le prix du ténofovir diminuait.

Conclusion : Le TDR-AgHBcr minimise les ressources et les coûts, représentant 0,61% du budget de santé 2022 du Burkina Faso. Cette étude souligne la faisabilité économique potentielle de ces stratégies et fournit des informations précieuses pour la réalisation d'analyses coût-efficacité.

Abstract

Objective: Economic feasibility of eliminating mother-to-child transmission (MTCT) of hepatitis B virus (HBV) in highly-endemic African countries remains uncertain. Prevention of MTCT (PMTCT) involves screening pregnant women for hepatitis B surface antigen (HBsAg), identifying those with high viral loads or hepatitis B e antigen (HBeAg), and administering tenofovir prophylaxis to high-risk women. We estimated the costs of integrating PMTCT services into antenatal care in Burkina Faso, based on four different strategies to select women for tenofovir prophylaxis: 1) HBV DNA (≥200,000 IU/mL), 2) HBeAg, 3) hepatitis B core-related antigen rapid diagnostic test (HBcrAg-RDT), 4) all HBsAg-positive women.

Methods: Using a micro-costing approach, we estimated the incremental economic cost of integrating each strategy into routine antenatal care in 2024, compared to neonatal vaccination alone. Sensitivity analyses explored variations in prevalence, service coverage, test and tenofovir prices.

Results: HBcrAg-RDT strategy was the least expensive, with a total economic cost of US$3,959,689, compared to HBV DNA (US$6,128,875), HBeAg (US$4,135,233), and Prophylaxis for All (US$4,141,206). The cost per pregnant woman receiving tenofovir prophylaxis varied from US$61.88 (Prophylaxis for All) to US$1,071.05 (HBV DNA). The Prophylaxis for All strategy had the lowest marginal cost due to a higher number of women on tenofovir (66,928) compared to HBV DNA (5,722), HBeAg (10,020), and HBcrAg-RDT (7,234). In sensitivity analyses, the Prophylaxis for All strategy became less expensive when the tenofovir price decreased.

Conclusion: HBcrAg-RDT minimizes resource use and costs, representing 0.61% of Burkina Faso's 2022 health budget. This study highlights the potential economic feasibility of these strategies and provides valuable resources for conducting cost-effectiveness analyses.

4.3.1. Introduction

West Africa is one of the regions most affected by hepatitis B virus (HBV) infection, with prevalence of chronic hepatitis B (CHB) infection ranging from 6% to 17% in 2022 (17). Mother-to-child transmission (MTCT) of HBV is particularly concerning, with infected newborns having a 90% risk of developing chronic infection (7) and increased risk of developing liver cirrhosis and hepatocellular carcinoma (135).

While administration of hepatitis B birth dose vaccine (HepB-BD) within 24 hours of birth is the primary intervention to prevent MTCT (PMTCT), a residual risk remains in highly-viremic pregnant women (21). In addition to HepB-BD, the World Health Organization (WHO) recommends antenatal screening for hepatitis B surface antigen (HBsAg) and administration of tenofovir disoproxil fumarate (TDF) prophylaxis to HBsAg-positive pregnant women having high HBV DNA levels exceeding 200,000 IU/mL or hepatitis B e antigen (HBeAg) (24).

However, HBV DNA testing remains unaffordable and inaccessible for most pregnant women living in resource-limited countries. HBeAg testing, while less expensive than HBV DNA testing, requires a laboratory-based immunoassay and current rapid diagnostic tests (RDTs) to detect HBeAg lack sensitivity (35). To ensure high coverage of HBV PMTCT, alternative strategies need to be explored, such as the use of a rapid diagnostic test for hepatitis B core-related antigen (HBcrAg-RDT), a novel new assay that does not yet have regulatory approval (39). This test only requires a drop of capillary blood, without the need for electricity or centrifugation, to identify HBV-infected women eligible for TDF prophylaxis within 45 minutes (192). Another strategy being considered is to provide TDF prophylaxis to all HBsAg-positive pregnant women (40,193).

Addressing HBV PMTCT is a key healthcare priority in Burkina Faso, a West African country with a high prevalence of CHB infection (10.1% in 2010) (194). In 2022, HepB-BD was integrated into the national immunization program. The country also developed an ambitious plan for the triple elimination of MTCT of HIV, syphilis and hepatitis B in 2021-2025 (195). Despite the national plan's intention to offer free HBV screening to all pregnant women, the cost of the test is still borne by the women. The plan also considers the possibility of universal treatment for all HBsAg-positive pregnant women, given the limited availability of HBV DNA testing or laboratory-based HBeAg assays at the national level.

To inform decision-makers on the economic implications of the HBV PMTCT strategies, we estimated the costs of integrating HBV screening and TDF prophylaxis into routine antenatal care at primary healthcare centers (PHCs) in Burkina Faso. We considered four alternative strategies for selecting HBsAg-positive pregnant women for TDF prophylaxis: 1) HBV DNA ≥200,000 IU/mL, 2) HBeAg-positive, 3) positive for HBcrAg-RDT, and 4) all HBsAg-positive women.

4.3.2. Materials and methods

Using a micro-costing approach, we estimated the projected incremental economic costs associated with the integration of each strategy into the existing antenatal care

system in Burkina Faso, compared to the current situation in which HepB-BD, along with three subsequent pentavalent vaccines, is administered. The analysis is conducted for the year 2024, considering the national health system perspective.

4.3.2.1. Study setting

Burkina Faso has approximately 20.5 million people, with 79.3% living in rural areas. The country consists of 13 regions, organized into 70 health districts, with 2041 PHCs in 2020. All regions have a high prevalence of CHB infection, ranging from 6.6% to 11.0% in 2010 (194). In 2021, 98% of pregnant women received antenatal care from skilled health workers, and 72% completed the four antenatal visits as per the national recommendation. In 2019, 88% of pregnant women were screened for HIV, and 100% of HIV-positive pregnant women received antiretroviral therapy (120). However, HIV screening remains the only test universally offered during antenatal care visits; rapid test for syphilis or dual test with HIV, as well as HBV screening, are not yet part of routine antenatal care.

We conducted this study as part of the Neonatal Vaccination against Hepatitis B in Africa (NéoVac) program, which aims to assess the impact and cost-effectiveness of integrating HepB-BD into the immunization program in Burkina Faso (132,196). An ancillary study called "Performance of Diagnostic Test for Hepatitis B in Africa (PREDICT-B)" evaluated the performance of HBcrAg-RDT to identify pregnant women with high HBV DNA levels (≥200,000 IU/mL) (192). The study was approved by the institutional review board of the Institut Pasteur (IRB2018/12) and the Ethics Committee for the Health Research in Burkina Faso (N°2018-12-155). All the participants in the NéoVac and PREDICT-B study provided an informed consent.

4.3.2.2. Strategies for selecting HBsAg-positive women for TDF prophylaxis

In all strategies, we assumed that pregnant women receiving routine antenatal care at PHCs are systematically screened for HBsAg. This screening procedure involves collecting capillary blood by finger prick and using an on-site RDT (SD Bioline HBsAg RDT, Abbott, USA) to provide same-day results. Conversely, eligibility for TDF prophylaxis varied according to the specific strategy considered.

Strategy-1: HBV DNA

Following HBsAg screening, pregnant women with a positive result undergo venipuncture at the PHCs. Blood samples are sent to a regional laboratory for HBV DNA quantification using a real-time PCR. Pregnant women later return to the PHC to receive results. TDF prophylaxis is administered to those with HBV DNA levels ≥200,000 IU/mL.

Strategy-2: HBeAg

Similar to the HBV DNA strategy, this strategy involves collecting venous blood samples from HBsAg-positive pregnant women and sending them to the regional laboratory. HBeAg is detected using an enzyme-linked immunosorbent assay (ELISA). Pregnant

women return to the PHC to receive results. Only those positive for HBeAg undergo TDF prophylaxis.

Strategy-3: HBcrAg-RDT

A single finger prick yields two drops of capillary blood: one for HBsAg screening, and the second is placed into a tube containing a pre-treatment solution (39). When the HBsAg screening test turns positive, the pre-treated sample is dropped on an HBcrAg-RDT cassette (Espline, Fujirebio, Japan). HBcrAg-RDT results are available within 30 minutes. Women who test positive for HBcrAg-RDT initiate TDF prophylaxis on the same day as HBsAg screening.

Strategy-4: Prophylaxis for All

Following HBsAg screening test, no secondary testing is performed. All pregnant women testing positive for HBsAg start TDF prophylaxis.

4.3.2.3. Cost estimates

We calculated the total economic costs of each strategy by considering that each resource required for the strategy implementation has an opportunity costs as it is no longer available for an alternative use (121).

In each strategy, we categorized resources into the following activities: pre-introduction, social mobilization, supervision and monitoring, training, transportation and storage of consumables, screening (comprising both HBsAg screening and the second test), treatment, and health information system. This classification methodology was adapted from a previous cost estimate (196). For each of these activities, we considered both recurrent costs (including consumables and salaries) and capital costs, referring to equipment with a lifespan of one year or more. Pre-introduction costs, allocated for the first year of intervention implementation, were considered as capital costs (121). Table 4.3.1 provides detailed information about the activities, resources, and unit costs.

We allocated the costs associated with transportation, storage, and waste management as the proportion of the total annualized cost linked to HBV screening and treatment. We estimated this proportion as the volume required for the HBV tests and treatment relative to the total volume used. We assumed an 80% equipment capacity utilization (197), and annualized capital costs using a 3% discount rate. Given the one-year time frame, no further discounting was required. We assumed a wastage factor of 1% for tests and TDF drugs. We allocated the target population to each PHC in Burkina Faso based on the proportion of the national population covered by each PHC. We initially valued all costs in CFA francs and subsequently converted them to 2022 US$ using the average annual exchange rate for 2022 (US$ 1 = FCFA 623.76) (105). We performed cost analyses using R version 4.3.1.

4.3.2.4. Data collection

We used several sources to collect data. Semi-structured interviews with key informants and the Action Plan of the Dafra Health District, 2022, allowed us to understand the organization of the health system and to collect type, quantity, and prices

of the resources regarding pre-introduction, social mobilization, training, monitoring, supervision, screening, and health information system activities. Key informants included public health experts involved in the national program for the elimination of mother-to-child transmission of HIV, syphilis, and hepatitis B, clinical experts, and NéoVac field coordinators. We obtained unit prices for consumables required for screening and treatment from quotations provided by the Central Purchasing Agency for Essential Generic Medicines and Medical Consumables (CAMEG). However, for the HBV DNA test and HBeAg test, we used average laboratory prices, and for the HBcrAg-RDT, we obtained the price from the manufacturer.

Data on storage, transportation and waste management activities were derived from a previous study on the costs of HepB-BD implementation in Burkina Faso (196), and from various reports (198–203). To estimate transportation costs, we calculated the total distance in kilometres: from Ouagadougou, the central level, to each of the ten regional CAMEG agencies responsible for transportation and storage; from the regional agencies to each district depot; and from the district depot to each primary healthcare centers (PHCs). We also calculated the distance from PHCs to the capital of their respective regional level to estimate costs of transporting blood samples from PHCs to regional laboratories in the HBV DNA and HBeAg scenarios. We used Google Maps and Mapcarta to estimate the distance in kilometres.

We used a linear regression model to estimate the expected number of PHCs in 2024. This model considered the number of PHCs from 2016 to 2020 (118) as the dependent variable, and the estimated total population in the same years (46) as the independent variable.

The number of pregnant women is estimated to align with the projected number of births in Burkina Faso for the year 2024 (46), with the assumption that each birth corresponds to one single woman.

Lastly, we obtained data from the literature on the HBV prevalence in pregnant women, the proportion of high viral loads in HBV-infected pregnant women, and test performance (Table 4.3.2). The diagnostic performance of HBcrAg-RDT was obtained from the estimates in Burkina Faso (192).

4.3.2.5. Base-case analysis and sensitivity analyses

In the base-case analysis, we assumed 90% HBsAg screening coverage for pregnant women. For the first three 'targeted' strategies, we assumed that 90% of HBsAg-positive pregnant women would undertake the second test. Then, we assumed that 90% of eligible women would receive TDF prophylaxis in all strategies, and that all would receive three bottles of 30 TDF tablets to cover the period from the 28th week of pregnancy until delivery.

For sensitivity analyses, we varied each of the following: HBsAg screening coverage rates (80-95%), the second test uptake rates (80-100%), the TDF uptake among eligible women (80-100%), HBsAg prevalence (8-12%), the proportion of HBsAg-positive pregnant women with a high viral load (6-15%), and the prices of screening tests and TDF

(variation of ±25%). Finally, we included a scenario in which pregnant women receive TDF up to one month after delivery, necessitating four TDF bottles (120 tablets).

Table 4.3.1: Overview of cost components, resources and unit costs

Activity	Description	Level of the health system	Basic assumptions	Resource type	Cost type	Unit cost (US$)
Pre-introduction	Advocacy	Central	2 days meeting in Ouagadougou			
			1 DRS per region + 1 hepatologist per CHU and CHR + 3 communicators	Per diem /day	Capital	16.03
			2 support staff + 1 administrator	Per diem /day	Capital	8.02
				Meeting room rental /day	Capital	80.19
				Coffee break + lunch /person and day	Capital	8.02
				Fuel /km	Capital	0.16
	Advocacy	District	1 day meeting in each district.		Capital	
			Participants are per health district			
			2 communicators	Per diem /day	Capital	16.03
			1 MCD + 1 deputy + 2 physicians + 1 support staff + 1 driver	Per diem /day	Capital	8.02
				Meeting room rental /day	Capital	32.07
				Coffee break + lunch /person and day	Capital	5.61
				Fuel /km	Capital	0.16
	Two reinforced supervisions during the first year	PHC	Supervisors can visit 2 PHC per day		Capital	
			2 supervisors	Per diem /day	Capital	16.03
			1 driver	Per diem /day	Capital	8.02
				Fuel /km	Capital	0.16

Social mobilisation	Posters and leaflets to raise awareness of the importance of HBV screening in pregnant women.	PHC	1 poster + 1 leaflet per health facility	Printout of a poster	Recurrent - consumable	0.48
				Printout of a brochure (10 pages)	Recurrent - consumable	1.36
	Daily talks to answer pregnant women's questions, concerns and raise awareness	PHC	Talks led by midwifes or skilled birth attendants who work 2346 hours per year 10 min/day to talk about HBV screening on consultation days	Midwife average salary /hour	Recurrent - Salary	2.33
	ASBC		1 day/month in each of the 8228 villages	ASBC salary average /year	Recurrent - Salary	384.76
Monitoring and supervision	Monitoring activities of health districts	District	Monitoring activities are semi-annual and last one day per district, we assumed half a day for HBV alone			
			1 monitor	Per diem /day	Recurrent - Salary	43.28
			1 driver shared by four monitors for different activities	Per diem /day	Recurrent - Salary	25.65
	Monitoring activities of PHC	PHC	Monitoring activities are semi-annual and last half a day per PHC, we assumed that half of this time is dedicated to HBV alone			
			1 monitor	Per diem /day	Recurrent - Salary	32.07
			1 driver shared by four monitors for different activities	Per diem /day	Recurrent - Salary	8.02
	Specific supervision for the elimination of mother-to-child transmission (including HIV, HBV, syphilis) at the district level	District	Supervision is semi-annual and lasts one day per district, we assumed half a day for HBV alone			

			2 supervisors	Per diem /day	Recurrent - Salary	43.28
			1 driver	Per diem /day	Recurrent - Salary	25.65
	Specific supervision for the elimination of mother-to-child transmission (HIV, HBV, syphilis) at the PHC level	PHC	Supervision is quarterly. Supervisors can visit 2 PHC per day. We assumed that half of the time is specifically for HBV			
			2 supervisors	Per diem /day	Recurrent - Salary	16.03
			1 driver	Per diem /day	Recurrent - Salary	8.02
	Supervision of ASBCs	PHC	Supervision is semi-annual and lasts one day per PHC. We assumed half a day for HBV alone			
			2 supervisors + 2 OBCs	Per diem /day	Recurrent - Salary	4.01
			1 RPS	Per diem /day	Recurrent - Salary	48.11
	For each of the monitoring and supervision activity	All levels		Fuel /km	Recurrent - consumable	0.16
Training	Training of trainers	Central	2-day training specific to the elimination of mother-to-child transmission of HBV.			
			4 people train the trainers	Per diem /day	Recurrent - Salary	40.09
			3 trainers per region	Per diem /day	Recurrent - Salary	43.28
				Meeting room rental /day	Recurrent - consumable	80.19
				Office supplies /person	Recurrent - consumable	7.22
				Coffee break + lunch /person and day	Recurrent - consumable	8.02
	Training at the district level	District	2-day training in each district			
			3 trainers	Per diem /day	Recurrent - Salary	43.28
			3 administrators + 3 participants/ PHC (head nurse, head of maternity ward, midwife)	Per diem /day	Recurrent - Salary	16.03 8.02

			5 resident participants from the district management team	Per diem /day	Recurrent - Salary	8.02
				Office supplies /person	Recurrent - consumable	7.22
				Coffee break + lunch /person and day	Recurrent - consumable	5.61
				Fuel /km	Recurrent - consumable	0.16
	ASBC training at the PHC level	PHC	2-day training in each PHC:			
			2 trainers/ PHC	Per diem /day	Recurrent - Salary	8.02
			2 OBC/ PHC	Per diem /day	Recurrent - Salary	4.01
			9 ASBS/ PHC	Per diem /day	Recurrent - Salary	2.41
				Coffee break + lunch /person and day	Recurrent - consumable	4.81
Transportation and storage	Transport of screening tests and TDF at the regional level	Central	Transport from CAMEG central agencies to CAMEG regional agencies once a month			
			1 driver	Per diem /day	Recurrent - Salary	16.03
			1 apprentice	Per diem /day	Recurrent - Salary	8.02
				Truck 13T (50m3)	Capital	89,188.72
				Vehicle maintenance /year	Recurrent - consumable	9,622.68
				Fuel /km	Recurrent - consumable	0.16
	Transport of screening tests and TDF at the district level	Region	Transportation from regional to district level, once a month			
			1 driver	Per diem /day	Recurrent - Salary	8.02
				Van (20m3)	Capital	36,290.61
				Vehicle maintenance /year	Recurrent - consumable	5% of vehicle cost

			Fuel /km	Recurrent - consumable	0.16
Transport of screening tests and TDF at the PHC level	PHC	Transportation from district to PHC level, once a month			
		Head nurse	Head nurse average salary /year	Recurrent - Salary	2,108.77
			Moto	Capital	2,405.64
			Vehicle maintenance /year	Recurrent - consumable	5% of vehicle cost
			Fuel /km	Recurrent - consumable	0.06
Storage of screening tests and TDF at the central level	Central	Surface of a central storage area = 4000m² equivalent to an available storage volume of 20,000m3	Construction price /m2	Capital	80.19
		Staff in charge of stock management:			
		2 pharmacists	Pharmacist average salary /year	Recurrent - Salary	5,963.83
		2 pharmacy assistants	Pharmacy assistant average salary /year	Recurrent - Salary	4,809.54
Storage of screening tests and TDF at the regional level	Region	Surface of a regional storage area = 2000m²	Construction price /m2	Capital	80.19
		Staff in charge of stock management:			
		2 pharmacists	Pharmacist average salary /year	Recurrent - Salary	5,963.83
		2 pharmacy assistants	Pharmacy assistant	Recurrent - Salary	4,809.54

				average salary /year		
	Storage of screening tests and TDF at the district level	District	Surface of a district storage area = 45m²	Construction price /m2	Capital	80.19
			Staff in charge of stock management:			
			1 pharmacist	Pharmacist average salary /year	Recurrent - Salary	4,809.54
	Storage of screening tests and TDF at the PHC	PHC	Surface of a PHC storage area = 11m²	Construction price /m2	Capital	80.19
			Staff in charge of stock management:			
			1 manager	Average salary /year	Recurrent - Salary	384.76
	For the storage of consumables at all levels	All levels	Electric consumption (lighting + air conditioning) 250 kWh/m²/year	Electricity /kWh	Recurrent - consumable	0.44
	HBsAg screening test		Volume of a test=0.000021m3			
			Volume of a lancet=0.0000075m3			
	HBcrAg-RDT		Volume of a test= 0.000201m3			
	HBeAg, and HBV DNA tests		Volume of a tube 0.5 ml= 0.000084 m3			
			Volume of a needle= 0.000011m3			
	For HBsAg, HBeAg, and HBV DNA tests		Unit volume of consumables (cotton, alcohol, gloves) = 0.0000143m3			
	Tenofovir		Volume per tablet pack = 0.000123m3			
Screening - HBsAg	HBsAg screening test	PHC	SD Bioline HBsAg test	Test	Recurrent - consumable	2.17
				Lancet	Recurrent - consumable	0.05

			Working time: 3 min for administrating the test + 3 min for reading the result	Midwife average salary /hour	Recurrent - Salary	2.33
Screening – 2nd test	HBeAg test	PHC	ELISA HBeAg test For these tests, blood samples are collected at the PHCs and sent to the regional laboratory	Test	Recurrent - consumable	9.62
			Working time: 5 min for the blood sample + 3 min for labelling and storing in the fridge + an additional consultation of 10 minutes for the results	Midwife average salary /hour	Recurrent - Salary	2.33
	HBV DNA test	PHC	Real-time PCR test. For these tests, blood samples are collected at the PHCs and sent to the regional laboratory	Test	Recurrent - consumable	40.09
			Working time: 5 min for the blood sample + 3 min for labelling and storing in the fridge + an additional consultation of 10 minutes for the results	Midwife average salary /hour	Recurrent - Salary	2.33
	For HBeAg and HBV DNA tests	PHC		Vacutainer needle	Recurrent - consumable	0.11
				Tube	Recurrent - consumable	0.11
				Tourniquet	Capital	3.21
				Tray	Capital	16.03
				55l fridge	Capital	1,547.69
				Tube holder	Capital	6.41
			10L cooler can hold 2 x 40 tube holders, or 80 tubes.	10L cooler	Capital	24.05
				Cold accumulator	Capital	2.00
				Courier /day	Recurrent - Salary	13.15
				Fuel /km	Recurrent - consumable	0.16

	HBcrAg-RDT	PHC	HBcrAg-RDT (Espline, Fujirebio, Japan)	Test (unit)	Recurrent - consumable	10.00
			Working time: 3 min for administrating the test + 3 min for reading the result	Midwife average salary /hour	Recurrent - Salary	2.33
	For HBsAg, HBeAg, and HBV DNA tests	PHC	1g consumption per unit	Cotton /500g	Recurrent - consumable	3.72
			2ml consumption per unit	Alcohol /L	Recurrent - consumable	1.05
				Glove /unit	Recurrent - consumable	0.15
Screening – all tests	Waste management	All health facilities	1 incinerator per PHC. Incineration capacity = 75kg/day	Incinerator	Capital	6,577.64
			Fuel consumption 1080L/ year	Fuel /L	Recurrent - consumable	1.12
				Landfill costs /year	Recurrent - consumable	272.17
				Water and electricity /year	Recurrent - consumable	192.45
				Maintenance technician salary /year	Recurrent - Salary	1,154.29 on Ouagadougou and Bobo-Dioulasso, 577.15 outside
				Incinerator maintenance	Recurrent - consumable	48.11
Treatment delivery	Tenofovir prophylaxis	PHC	1 tablet daily	Tenofovir 300mg /30 tablets	Recurrent - consumable	4.48
	Consultation time	PHC	15 min consultation for all eligible pregnant women	Midwife average salary /hour	Recurrent - Salary	2.33
Health information system	Reporting activities data	Districts	Supply of materials and data validation workshop: we considered 1/12th of the costs for HBV screening.	Supply of materials /year and district	Recurrent - consumable	7,698.14
				Data validation workshops	Recurrent - consumable	3,144.90

			/year and district		
	All health facilities	5 min to report each HBsAg-positive case per midwife	Midwife average salary /hour	Recurrent - Salary	2.33
		5 min to report each eligible case to TDF per midwife	Midwife average salary /hour	Recurrent - Salary	2.33
		5 minutes per midwife for notification of each pregnant woman on tenofovir	Midwife average salary /hour	Recurrent - Salary	2.33
		2 persons from district staff in charge of data management (2 PHC visited per day): we considered 1/12th of the costs for HBV screening.	Per diem /day	Recurrent - Salary	8.02

Table 4.3.2: Key demographic, epidemiological, and screening information

	Input	Source
Total number of pregnant women in 2024	810,065	(46)
Prevalence of HBsAg in pregnant women	10.2	(158)
Proportion of HBsAg-positive pregnant women with high viral load (≥ 200,000 IU/mL)	9.5	(204)
Sensitivity of HBsAg RDT to detect the presence of HBsAg	1	
Specificity of HBsAg RDT to detect the presence of HBsAg	1	
Sensitivity and specificity of the tests to detect HBV DNA ≥ 200,000 IU/mL:		
Viral load quantification (real-time PCR) - Sensitivity	1	
Viral load quantification (real-time PCR) - Specificity	1	
HBeAg test (ELISA) - Sensitivity	0.846	(35)
HBeAg test (ELISA) - Specificity	0.905	(35)
HBcrAg test (RDT) - Sensitivity	0.826	(39)
HBcrAg test (RDT) - Specificity	0.954	(39)
Number of primary health care facilities in 2024	2,302	Estimated using a linear regression from the number of PHC facilities from 2016 to 2020 and the estimated total population (46)
Coverage rate of HBsAg screening among pregnant women	90%	
Uptake of the second test among HBsAg-positive women	90%	
Uptake of tenofovir prophylaxis among eligible pregnant women	90%	

4.3.3. Results

4.3.3.1. Target population

Table 4.3.3 presents the care cascade and cost estimates. In the base-case scenario for 2024, a total of 729,059 pregnant women in Burkina Faso are estimated to undergo HBsAg screening, of whom 74,364 test positive. Subsequently, 66,928 women receive the second test. Finally, the number of women starting TDF prophylaxis is 5,722 (HBV DNA strategy), 10,020 (HBeAg), 7,234 (HBcrAg-RDT), and 66,928 (Prophylaxis for All).

4.3.3.2. Cost estimates and drivers

The total economic cost in 2024 is estimated at $6,128,875 (HBV DNA strategy), $4,135,233 (HBeAg), $3,959,689 (HBcrAg-RDT), and $4,141,206 (Prophylaxis for All) (Table 4.3.3). The economic cost per pregnant woman screened for HBsAg is estimated at $8.41 (HBV DNA), $5.67 (HBeAg), $5.43 (HBcrAg-RDT), and $5.68 (Prophylaxis for All). The economic cost per woman receiving TDF prophylaxis is estimated at $1,071.05 (HBV DNA), $412.71 (HBeAg), $547.36 (HBcrAg-RDT), and $61.88 (Prophylaxis for All).

Recurrent costs associated with consumables are the predominant contributor to the total economic cost in all strategies, accounting for 82.8% (HBV DNA), 74.3% (HBeAg), 75.7% (HBcrAg-RDT), and 75.7% (Prophylaxis for All) (Table 4.3.4). Recurrent costs associated with salaries accounted for 14.2% (HBV DNA), 21.2% (HBeAg), 21.1% (HBcrAg-RDT), and 21.0% (Prophylaxis for All). To implement each strategy effectively, the additional number of healthcare workers required at the PHC level would be 125 (HBV DNA), 127 (HBeAg), 119 (HBcrAg-RDT), and 181 (Prophylaxis for All).

The screening activity, including both the HBsAg screening test and the second test, was the primary cost driver, accounting for 78.7%, 66.8%, 66.1%, and 46.5% of the total cost in the HBV DNA, HBeAg, HBcrAg-RDT, and the Prophylaxis for All strategies, respectively (Figure 4.3.1). Specifically, the cost of the HBsAg screening accounted for 26.1% (HBV DNA), 38.7% (HBeAg), 40.4% (HBcrAg-RDT), and 38.6% (Prophylaxis for All) of the total cost, while the second test represented 44.2% (HBV DNA), 15.7% (HBeAg), and 17.1% (HBcrAg-RDT).

4.3.3.3. Sensitivity analyses

For all strategies, the economic cost per pregnant woman screened for HBsAg was most sensitive to variations in the prices of the HBsAg screening test and the second test (Table 4.3.5). For all variations in the parameters considered, the HBcrAg strategy was the least expensive, except when the TDF price decreased by 25%, in which case the Prophylaxis for All strategy became the least expensive.

For the cost per pregnant woman receiving TDF prophylaxis, sensitivity analyses showed that variations in the proportion of HBsAg-positive pregnant women with a high viral load had the greatest impact in the HBV DNA, HBeAg, and HBcrAg-RDT strategies. In the Prophylaxis for All strategy, variations in the HBsAg prevalence had the greatest impact.

Table 4.3.3: Cost estimates and the cascade of screening and treatment for each strategy

	HBV DNA strategy	HBeAg strategy	HBcrAg-RDT strategy	Prophylaxis for All strategy
Total incremental economic cost	6,128,875	4,135,233	3,959,689	4,141,206
Number of pregnant women screened for HBsAg	729,059	729,059	729,059	729,059
Cost per pregnant woman screened for HBsAg	8.41	5.67	5.43	5.68
Number of pregnant women screened HBsAg+	74,364	74,364	74,364	74,364
Cost per HBsAg+ pregnant woman	82.42	55.61	53.25	55.69
Number of pregnant women screened with a 2nd test	66,928	66,928	66,928	-
Cost per pregnant woman screened with a 2nd test	91.57	61.79	59.16	-
Number of pregnant women positive at 2nd test	6,358	11,133	8,038	-
Cost per pregnant woman positive at 2nd test	963.94	371.44	492.62	-
Number of pregnant women receiving TDF prophylaxis	5,722	10,020	7,234	66,928
Cost per pregnant woman receiving TDF prophylaxis	1,071.05	412.71	547.36	61.88

Table 4.3.4: Cost estimates by cost component and cost type for each strategy

Cost component	HBV DNA strategy		HBeAg strategy		HBcrAg-RDT strategy		Prophylaxis for All strategy	
	US$	(%)	US$	(%)	US$	(%)	US$	(%)
Pre-introduction								
Subtotal	71,940	(1.17)	71,940	(1.74)	71,940	(1.82)	71,940	(1.74)
Social mobilisation								
Recurrent - consumables	4,244	(0.07)	4,244	(0.10)	4,244	(0.11)	4,244	(0.10)
Recurrent - salaries	188,886	(3.08)	188,886	(4.57)	188,886	(4.77)	188,886	(4.56)
Subtotal	193,130	(3.15)	193,130	(4.67)	193,130	(4.88)	193,130	(4.66)
Supervision & monitoring								
Recurrent - consumables	79,494	(1.30)	79,494	(1.92)	79,494	(2.01)	79,494	(1.92)
Recurrent - salaries	173,855	(2.84)	173,855	(4.20)	173,855	(4.39)	173,855	(4.20)
Subtotal	253,349	(4.13)	253,349	(6.13)	253,349	(6.40)	253,349	(6.12)
Training								
Recurrent - consumables	304,562	(4.97)	304,562	(7.37)	304,562	(7.69)	304,562	(7.35)
Recurrent - salaries	251,315	(4.10)	251,315	(6.08)	251,315	(6.35)	251,315	(6.07)
Subtotal	555,877	(9.07)	555,877	(13.44)	555,877	(14.04)	555,877	(13.42)
Transportation & storage								
Recurrent - consumables	14,858	(0.24)	15,438	(0.37)	17,307	(0.44)	20,407	(0.49)
Recurrent - salaries	8,766	(0.14)	9,109	(0.22)	10,211	(0.26)	12,061	(0.29)
Capital	46,718	(0.76)	48,542	(1.17)	54,416	(1.37)	64,276	(1.55)

Subtotal	70,343	(1.15)	73,088	(1.77)	81,934	(2.07)	96,744	(2.34)
Screening								
Recurrent – consumables for HBsAg screening	1,754,342	(28.62)	1,754,342	(42.42)	1,754,342	(44.31)	1,754,342	(42.36)
Recurrent - salaries for HBsAg screening	171,908	(2.80)	171,908	(4.16)	171,908	(4.34)	171,908	(4.15)
Capital for HBsAg screening	386	(0.01)	386	(0.01)	386	(0.01)	386	(0.01)
Subtotal – HBsAg screening	1,926,636	(31.44)	1,926,636	(20.20)	1,926,636	(17.47)	1,926,636	(46.52)
Recurrent – consumables for the 2nd test	2,773,454	(45.25)	714,219	(17.27)	676,036	(17.07)	-	-
Recurrent – salaries for the 2nd test	53,287	(0.87)	53,287	(1.29)	15,781	(0.40)	-	-
Capital for the 2nd test	67,999	(1.11)	67,999	(1.64)	35	(<0.01)	-	-
Subtotal –2nd test	2,894,740	(47.23)	835,505	(46.59)	691,853	(48.66)	-	-
Subtotal	4,821,376	(78.67)	2,762,141	(66.80)	2,618,489	(66.13)	1,926,636	(46.52)
Treatment								
Recurrent - consumables	77,644	(1.27)	135,956	(3.29)	98,159	(2.48)	908,123	(21.93)
Recurrent - salaries	3,698	(0.06)	6,476	(0.16)	4,676	(0.12)	43,256	(1.04)
Subtotal	81,343	(1.33)	142,431	(3.44)	102,835	(2.60)	951,379	(22.97)
Health information system								
Recurrent - consumables	63,219	(1.03)	63,219	(1.53)	63,219	(1.60)	63,219	(1.53)
Recurrent - salaries	18,299	(0.30)	20,058	(0.49)	18,918	(0.48)	28,933	(0.70)
Subtotal	81,518	(1.33)	83,277	(2.01)	82,136	(2.07)	92,152	(2.23)
Subtotal recurrent - consumables	5,071,818	(82.75)	3,071,473	(74.28)	2,997,363	(75.70)	3,134,391	(75.69)

Subtotal recurrent - salaries	870,014	(14.20)	874,893	(21.16)	835,548	(21.10)	870,213	(21.01)
Subtotal capital	187,043	(3.05)	188,867	(4.57)	126,778	(3.20)	136,602	(3.30)
TOTAL	**6,128,875**	(100.00)	**4,135,233**	(100.00)	**3,959,689**	(100.00)	**4,141,206**	(100.00)

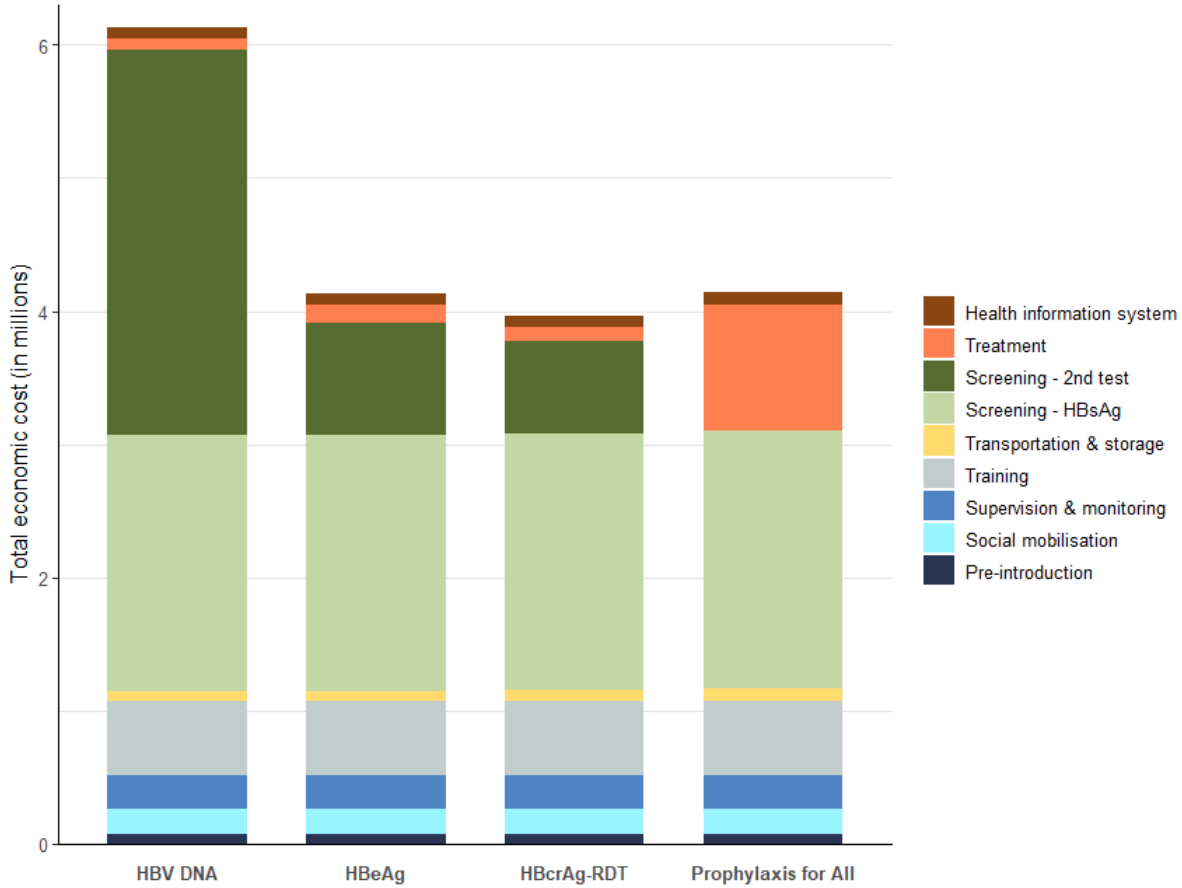


Figure 4.3.1 - Distribution of costs by cost component for each strategy

Table 4.3.5 : Results of the sensitivity analyses

	HBV DNA strategy	HBeAg strategy	HBcrAg-RDT strategy	Prophylaxis for All strategy
95% coverage for HBsAg and 2nd test screening and TDF prophylaxis				
Total incremental economic cost	6,578,671	4,361,191	4,171,253	4,364,513
Cost per pregnant woman screened for HBsAg	8.55	5.67	5.42	5.67
Cost per HBsAg+ pregnant woman	83.81	55.56	53.14	55.60
Cost per pregnant woman screened with a 2nd test	88.22	58.48	55.94	-
Cost per pregnant woman positive at 2nd test	928.64	351.58	465.75	-
Cost per pregnant woman receiving TDF prophylaxis	977.52	370.09	490.27	58.53
80% coverage for HBsAg and 2nd test screening and TDF prophylaxis				
Total incremental economic cost	5,286,522	3,705,865	3,555,602	3,712,441
Cost per pregnant woman screened for HBsAg	8.16	5.72	5.49	5.73
Cost per HBsAg+ pregnant woman	79.98	56.06	53.79	56.16
Cost per pregnant woman screened with a 2nd test	99.97	70.08	67.24	-
Cost per pregnant woman positive at 2nd test	1,052.32	421.29	559.85	-
Cost per pregnant woman receiving TDF prophylaxis	1,315.40	526.61	699.81	70.20
90% coverage of HBsAg and 100% coverage of the 2nd test and TDF prophylaxis				
Total incremental economic cost	6,463,892	4,256,374	4,064,280	4,248,298
Cost per pregnant woman screened for HBsAg	8.87	5.84	5.57	5.83
Cost per HBsAg+ pregnant woman	86.92	57.24	54.65	57.13
Cost per pregnant woman screened with a 2nd test	86.92	57.24	54.65	-

Cost per pregnant woman positive at 2nd test	914.97	344.09	455.07	-
Cost per pregnant woman receiving TDF prophylaxis	914.97	344.09	455.07	57.13
Prevalence of HBsAg+ pregnant women = 8%				
Total incremental economic cost	5,495,327	3,931,686	3,778,517	3,920,884
Cost per pregnant woman screened for HBsAg	7.54	5.39	5.18	5.38
Cost per HBsAg+ pregnant woman	94.22	67.41	64.78	67.23
Cost per pregnant woman screened with a 2nd test	104.69	74.90	71.98	-
Cost per pregnant woman positive at 2nd test	1,101.98	450.27	599.35	-
Cost per pregnant woman receiving TDF prophylaxis	1,224.43	500.30	665.95	74.69
Prevalence of HBsAg+ pregnant women = 12%				
Total incremental economic cost	6,647,266	4,301,804	4,107,921	4,321,470
Cost per pregnant woman screened for HBsAg	9.12	5.90	5.63	5.93
Cost per HBsAg+ pregnant woman	75.98	49.17	46.95	49.40
Cost per pregnant woman screened with a 2nd test	84.42	54.63	52.17	-
Cost per pregnant woman positive at 2nd test	888.66	328.44	434.40	-
Cost per pregnant woman receiving TDF prophylaxis	987.39	364.93	482.67	54.88
Proportion of HBsAg+ pregnant women with high viral load = 6%				
Total incremental economic cost	6,096,697	4,111,067	3,934,590	4,141,204
Cost per pregnant woman screened for HBsAg	8.36	5.64	5.40	5.68
Cost per HBsAg+ pregnant woman	81.98	55.28	52.91	55.69
Cost per pregnant woman screened with a 2nd test	91.09	61.43	58.79	-
Cost per pregnant woman positive at 2nd test	1,518.23	438.57	633.50	-

Cost per pregnant woman receiving TDF prophylaxis	1,686.93	487.30	703.89	61.88
Proportion of HBsAg+ pregnant women with high viral load = 15%				
Total incremental economic cost	6,179,441	4,173,207	3,999,131	4,141,209
Cost per pregnant woman screened for HBsAg	8.48	5.72	5.49	5.68
Cost per HBsAg+ pregnant woman	83.10	56.12	53.78	55.69
Cost per pregnant woman screened with a 2nd test	92.33	62.35	59.75	-
Cost per pregnant woman positive at 2nd test	615.54	300.28	366.58	-
Cost per pregnant woman receiving TDF prophylaxis	683.93	333.65	407.32	61.88
Price of all screening tests increased by 25%				
Total incremental economic cost	7,206,189	4,697,738	4,528,633	4,541,141
Cost per pregnant woman screened for HBsAg	9.88	6.44	6.21	6.23
Cost per HBsAg+ pregnant woman	96.90	63.17	60.90	61.07
Cost per pregnant woman screened with a 2nd test	107.67	67.66	70.19	-
Cost per pregnant woman positive at 2nd test	1,133.38	421.96	563.40	-
Cost per pregnant woman receiving TDF prophylaxis	1,259.32	468.85	626.00	67.85
Price of all screening tests decreased by 25%				
Total incremental economic cost	5,051,560	3,572,727	3,390,746	3,741,272
Cost per pregnant woman screened for HBsAg	6.93	4.90	4.65	5.13
Cost per HBsAg+ pregnant woman	67.93	48.04	45.60	50.31
Cost per pregnant woman screened with a 2nd test	75.48	53.38	50.66	-
Cost per pregnant woman positive at 2nd test	794.51	320.91	421.84	-
Cost per pregnant woman receiving TDF prophylaxis	882.78	356.57	468.71	55.90

25% price increase for HBsAg screening test				
Total incremental economic cost	6,528,809	4,535,167	4,359,624	4,541,141
Cost per pregnant woman screened for HBsAg	8.96	6.22	5.98	6.23
Cost per HBsAg+ pregnant woman	87.80	60.99	58.63	61.07
Cost per pregnant woman screened with a 2nd test	97.55	67.76	65.14	-
Cost per pregnant woman positive at 2nd test	1,026.85	407.36	542.38	-
Cost per pregnant woman receiving TDF prophylaxis	1,140.94	452.62	602.64	67.85
25% price decrease for HBsAg screening test				
Total incremental economic cost	5,728,940	3,735,298	3,559,755	3,741,272
Cost per pregnant woman screened for HBsAg	7.86	5.12	4.88	5.13
Cost per HBsAg+ pregnant woman	77.04	50.23	47.87	50.31
Cost per pregnant woman screened with a 2nd test	85.60	55.81	53.19	-
Cost per pregnant woman positive at 2nd test	901.04	335.51	442.87	-
Cost per pregnant woman receiving TDF prophylaxis	1,001.16	372.79	492.07	55.90
25% price increase for 2nd test				
Total incremental economic cost	6,806,255	4,297,804	4,128,698	4,141,206
Cost per pregnant woman screened for HBsAg	9.34	5.90	5.66	5.68
Cost per HBsAg+ pregnant woman	91.53	57.79	55.52	55.69
Cost per pregnant woman screened with a 2nd test	101.70	64.22	61.69	-
Cost per pregnant woman positive at 2nd test	1,070.48	386.04	513.65	-
Cost per pregnant woman receiving TDF prophylaxis	1,189.43	428.93	570.72	61.88
25% price decrease for 2nd test				

Total incremental economic cost	5,451,495	3,972,661	3,790,680	4,141,206
Cost per pregnant woman screened for HBsAg	7.48	5.45	5.20	5.68
Cost per HBsAg+ pregnant woman	73.31	53.42	50.97	55.69
Cost per pregnant woman screened with a 2nd test	81.45	59.36	56.64	-
Cost per pregnant woman positive at 2nd test	857.41	356.83	471.59	-
Cost per pregnant woman receiving TDF prophylaxis	952.67	396.48	523.99	61.88
25% increase in TDF price				
Total incremental economic cost	6,148,286	4,169,221	3,984,229	4,368,237
Cost per pregnant woman screened for HBsAg	8.43	5.72	5.46	5.99
Cost per HBsAg+ pregnant woman	82.68	56.07	53.58	58.74
Cost per pregnant woman screened with a 2nd test	91.86	62.29	59.53	-
Cost per pregnant woman positive at 2nd test	967.00	374.49	495.67	-
Cost per pregnant woman receiving TDF prophylaxis	1,074.44	416.10	550.75	65.27
25% decrease in TDF price				
Total incremental economic cost	6,109,464	4,101,244	3,935,149	3,914,176
Cost per pregnant woman screened for HBsAg	8.38	5.63	5.40	5.37
Cost per HBsAg+ pregnant woman	82.16	55.15	52.92	52.64
Cost per pregnant woman screened with a 2nd test	91.28	61.28	58.80	-
Cost per pregnant woman positive at 2nd test	960.89	368.38	489.57	-
Cost per pregnant woman receiving TDF prophylaxis	1,067.66	409.32	543.96	58.48
Eligible pregnant women receive four 30-tablet packs of TDF (until 1 month postpartum)				
Total incremental economic cost	6,155,975	4,182,685	3,993,949	4,458,149

Cost per pregnant woman screened for HBsAg	8.44	5.74	5.48	6.11
Cost per HBsAg+ pregnant woman	82.78	56.25	53.71	59.95
Cost per pregnant woman screened with a 2nd test	91.98	62.50	59.68	-
Cost per pregnant woman positive at 2nd test	968.21	375.70	496.88	-
Cost per pregnant woman receiving TDF prophylaxis	1,075.79	417.44	552.09	66.61

4.3.4. Discussion

Our results indicate that the HBcrAg-RDT strategy was the least expensive, costing approximately half as much as the HBV DNA strategy and slightly less than the HBeAg and Prophylaxis for All strategies. The substantial cost disparity between the HBV DNA strategy and the other strategies primarily arises from the higher unit cost of the HBV DNA test ($40.0), which is approximately four times that of the HBeAg immunoassay ($9.6) or HBcrAg-RDT ($10.0). The HBcrAg-RDT, despite its slightly higher unit cost compared to the HBeAg test, incurred lower consumable costs due to eliminating the need for venepuncture and sample transport to laboratories.

The Prophylaxis for All strategy offers the lowest marginal cost per pregnant woman receiving TDF and becomes competitive when the unit price of the cost of TDF decreases. Recent modelling studies have investigated the cost-effectiveness of the Prophylaxis for All strategy in sub-Saharan Africa (40,193). In South Africa, an upper-middle-income country, Mokaya and colleagues (193) found that the Prophylaxis for All strategy was cost-effective compared to no HBsAg screening and no TDF prophylaxis, while the HBeAg strategy incurred higher costs and prevented fewer infections than the Prophylaxis for All strategy. According to a global model by Nayagam and colleagues (40), PMTCT strategies based on different eligibility criteria (HBV DNA, HBeAg, or Prophylaxis for All) could be cost-effective compared to HepB-BD alone in a few sub-Saharan African countries, but not in Burkina Faso.

In 2022, Burkina Faso allocated $650 million to its health budget. Compared to this national budget, the total economic costs of implementing the HBV PMTCT strategies are expected to be relatively modest, with HBV DNA projected to account for 0.94%, HBeAg for 0.64%, HBcrAg for 0.61%, and the Prophylaxis for All strategy for 0.64% of the national health budget. We did not estimate financial costs, which would reflect the actual expenses for additional resources and are more informative for government budgeting. Nevertheless, most of our economic cost estimates should align with the financial costs, except for transportation and storage, for which Burkina Faso's existing capacities should be sufficient.

It is important to note that the current Burkina Faso's healthcare workforce density (0.9 nurses and midwives per 1,000 people (105)) falls short of the Sustainable Development Goals' target of 2.3 healthcare workers per 1,000 people (108). Integrating HBV PMTCT into the routine antenatal care without reinforcing the healthcare workforce could severely strain current PHC capacities. The Prophylaxis for All strategy would require more healthcare workers (n=181) than the targeted strategies (n=125 for HBV DNA, n=127 for HBeAg, and n=119 for HBcrAg-RDT).

Our study has limitations. First, we could not account for geographical variations in costs, such as midwives' salaries, for which we had to rely on the national average salary. Second, the assumption of equipment availability for HBV DNA or HBeAg analysis at the regional level might have overestimated the costs associated with transporting blood samples. In Burkina Faso, some districts now have access to point of care HBV DNA assays, such as GeneXpert®. Third, there are no real-world data in Burkina Faso on the feasibility

and acceptability of the different strategies to select women for TDF prophylaxis. A recent study in Uganda described the care cascade for HBV PMTCT based on the HBV DNA strategy (205). While all pregnant women enrolled in the study accepted HBsAg screening, and 93% of HBsAg-positive women accepted HBV DNA testing, only 73% returned for their results due to the long turnaround time from sample collection to receipt of HBV DNA results (median: 46 days). The use of strategies with same-day initiation of TDF prophylaxis, such as HBcrAg-RDT or Prophylaxis for All, could potentially overcome this challenge. However, it is uncertain whether a similar proportion of women would adhere to TDF prophylaxis once they fully understand its risks and benefits, compared to situations where communication might be more challenging under the Prophylaxis for All strategy. Finally, our study did not account for Burkina Faso's ongoing security crisis, which may affect the cost and coverage of the interventions.

Our cost estimation indicates that the economic costs required to integrate HBV PMTCT into routine antenatal care are likely to be modest in relation to Burkina Faso's total annual health budget. Conducting a cost-effectiveness and budget impact analysis is crucial to provide more robust guidance to the country in selecting the optimal strategy. This study provides robust data for such analyses, not only for Burkina Faso, but also for other highly HBV-endemic countries considering adopting similar strategies.

4.4. Implementing decentralised HBV screening and antiviral prophylaxis for pregnant women in Burkina Faso - A dynamic modelling study on health impact and cost-effectiveness

Résumé

Contexte : La prévention de la transmission mère-enfant (TME) du virus de l'hépatite B (VHB) est une préoccupation majeure en Afrique de l'Ouest, où la prévalence de l'infection chronique par l'hépatite B variait de 6 à 17% en 2022. Avant 2024, les recommandations préconisaient une prophylaxie au ténofovir pour les femmes enceintes ayant un ADN du VHB ≥200 000 UI/mL ou une positivité à l'antigène HBe (AgHBe). Depuis 2024, les recommandations ont été élargies pour inclure toutes les femmes enceintes positives à l'antigène de surface de l'hépatite B (AgHBs) dans les contextes où le test de l'ADN du VHB ou de l'AgHBe n'est pas disponible. Cependant, la couverture des femmes enceintes éligibles à une prophylaxie antivirale en Afrique de l'Ouest reste alarmante. Cette étude a évalué l'impact sanitaire et le rapport coût-efficacité de l'implémentation du dépistage du VHB et de la prophylaxie au ténofovir dans les soins prénataux de routine dans les centres de soins de santé primaires (CSPS) au Burkina Faso, en termes de morbidité liée au VHB, en particulier en relation avec la TME. Nous avons évalué quatre stratégies alternatives pour identifier les femmes enceintes positives à l'AgHBs éligibles à la prophylaxie par le TDF : 1) ADN du VHB ≥200 000 UI/mL, 2) AgHBe-positif, 3) positif pour un test de diagnostic rapide (TDR) alternatif pour détecter l'antigène HB core (TDR-AgHBcr), et 4) traitement de toutes les femmes HBsAg-positives ("Prophylaxis for All").

Méthode : Nous avons utilisé un modèle dynamique déterministe à compartiments, stratifié par âge, sexe et mode de transmission (horizontale ou mère-enfant). Nous avons calibré les paramètres du modèle en utilisant des données existantes issues d'une revue de la littérature afin de s'aligner avec les tendances épidémiologiques au Burkina Faso ou dans d'autres pays d'Afrique de l'Ouest. Nous avons évalué les coûts du point de vue du système de santé du gouvernement du Burkina Faso. Nous avons utilisé une approche de micro-costing pour déterminer les coûts de mise en œuvre des stratégies d'intervention lors des visites prénatales de routine dans les CSPS. Nous avons également inclus les coûts de la vaccination contre le VHB (HepB3), la dose à la naissance (HepB-BD) et les coûts des soins pour les patients dans les stades avancés de la maladie. Un modèle épidémiologique a implémenté les stratégies de 2024 à 2124, tandis qu'un modèle coût-efficacité a inclus l'implémentation des stratégies en 2024 avec une évaluation de l'efficacité sur un horizon de 100 ans. La stratégie de référence était la situation actuelle au Burkina Faso où l'HepB-BD est administré en même temps que l'HepB3. Nous avons considéré un seuil coût-

efficacité de 416,5$. Nous avons effectué des analyses de sensibilité déterministes et probabilistes.

Résultats : En 2023, avant l'implémentation des stratégies, le taux de prévalence estimé était de 6,5% [IC 95% = 3,8 ; 10,7], 85,8% des cas étant dus à la transmission horizontale et 14,1% à la TME. La prévalence estimée du VHB chez les femmes enceintes était de 10,9% [6,0% ; 17,4%]. Dans le modèle coût-efficacité, la stratégie Prophylaxis for All dominait largement, avec un ratio coût-efficacité incrémental de 60,9$ par AVCI évitée à un taux d'actualisation de 3%. Les résultats étaient plus sensibles aux taux de transition vers une cirrhose décompensée et à l'efficacité de l'HepB-BD chez les mères ayant une charge virale élevée. La stratégie Prophylaxis for All avait une probabilité de 91,8% d'être coût-efficace. En comparaison à la stratégie de référence, l'implémentation de cette stratégie de 2024 à 2124 pourrait éliminer la TME du VHB d'ici 2034 et réduire les cas de VHB chronique, les décès et les AVCI attribuables à la TME de 12,1% [4,9% ; 13,9%], 10,0% [4,1% ; 13,2%] et 11,4% [5,6% ; 16,0%], respectivement.

Conclusion : L'implémentation du dépistage universel de l'AgHBs et de la prophylaxie au ténofovir dans les CSPS au Burkina Faso est prometteuse pour réduire la transmission du VHB, en particulier la TME. La stratégie optimale à mettre en œuvre dans les soins prénataux semble être une stratégie Prophylaxis for All.

Abstract

Background: Preventing mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is a major concern in West Africa, where the prevalence of chronic hepatitis B infection ranged from 6% to 17% in 2022. Prior to 2024, guidelines recommended tenofovir prophylaxis for pregnant women with HBV DNA ≥ 200,000 IU/mL or HBe antigen (HBeAg) positivity. Since 2024, the recommendations have been expanded to include all HBsAg-positive pregnant women in settings where HBV DNA or HBeAg testing is unavailable. However, the coverage of eligible pregnant women receiving antiviral prophylaxis in West Africa remains alarmingly low. This study assessed the health impact and cost-effectiveness of implementing HBV screening and tenofovir prophylaxis in routine antenatal care in primary healthcare centres (PHCs) in Burkina Faso, in terms of HBV burden, particularly its association with MTCT. We evaluated four alternative strategies for identifying hepatitis B surface antigen (HBsAg)-positive pregnant women eligible for TDF prophylaxis: 1) HBV DNA ≥200,000 IU/mL, 2) HBeAg-positive, 3) positive for an alternative rapid diagnostic test (RDT) to detect HB core antigen (HBcrAg), and 4) treatment of all HBsAg-positive women.

Method: We used a deterministic compartmental dynamic model stratified by age, sex, and transmission mode (horizontal or mother-to-child). We calibrated the model parameters using existing data from a literature review to align epidemiological trends in Burkina Faso or other West African countries. We assessed costs from the perspective of the Burkina Faso government health system. We used a micro-costing approach to determine the costs of implementing the intervention strategies during routine antenatal visits at PHCs. We also included costs of HBV vaccination (HepB3), birth dose (HepB-BD),

and care costs for patients with advanced HBV disease. An epidemiological model implemented the strategies from 2024 to 2124, while a cost-effectiveness model included strategy implementation in 2024 with a health impact assessment over a 100-year horizon. The baseline strategy was the current situation in Burkina Faso where HepB-BD is administered alongside HepB3. We considered a cost-effectiveness threshold of US$416.5. We conducted deterministic and probabilistic sensitivity analyses.

Results: In 2023, before implementation of strategies, the estimated prevalence rate was 6.5% [95% CI=3.8; 10.7], with 85.8% due to horizontal transmission and 14.1% due to MTCT. The estimated HBV prevalence among pregnant women was 10.9% [6.0%; 17.4%]. In the cost-effectiveness model, the Prophylaxis for All strategy strongly dominated, with an incremental cost-effectiveness ratio of US$60.9 per DALY averted at a 3% discount rate. Results were most sensitive to transition rates to decompensated cirrhosis and HepB-BD efficacy in mothers with high viral load. The Prophylaxis for All strategy had an 91.8% probability of being cost-effective. Compared with the baseline strategy, implementing the Prophylaxis for All strategy from 2024 to 2124 could eliminate HBV MTCT by 2034, and reduce chronic HBV cases, deaths, and DALYs attributable to MTCT by 12.1% [4.9%; 13.9%], 10.0% [4.1%; 13.2%], and 11.4% [5.6%; 16.0%], respectively.

Conclusion: Implementation of universal antenatal HBsAg screening and tenofovir prophylaxis in PHCs in Burkina Faso is promising for reducing HBV transmission, especially MTCT. The optimal strategy to implement in antenatal care appears to be the Prophylaxis for All strategy.

4.4.1. Introduction

With prevalence rates of chronic hepatitis B (CHB) infection ranging from 6-17% in 2022 (17), West Africa is one of the highest HBV burdened regions in the world. CHB infection is a major driver of morbidity and mortality primarily, through its leading role in causing cirrhosis and hepatocellular carcinoma (HCC). The World Health Organization (WHO) has made HBV control a priority, aiming to significantly reduce HBV-related mortality and incidence by 2030 (11).

One of the highest priorities in HBV control is the prevention of mother-to-child transmission (MTCT), as infants infected through this route face a 90% risk of developing CHB (7). In addition, these infants have higher rates of progression to significant liver fibrosis compared to those who acquire HBV infection horizontally (43), underscoring the critical need for timely and effective interventions targeting pregnant women.

While the deployment of hepatitis B birth dose (HepB-BD) remains a cornerstone of MTCT prevention, its efficacy has shown limitations particularly in highly viremic pregnant women (6,21). Prior to 2024, guidelines recommended tenofovir disoproxil fumarate (TDF) prophylaxis, consisting of a daily 300mg tablet from 28 weeks' gestation until at least delivery, for pregnant women with high viral load (HBV DNA ≥ 200,000 IU/mL) or HBe antigen (HBeAg) positivity in the absence of viral load screening (24). Since 2024, the recommendations have been expanded to include all HBsAg-positive pregnant women in settings where HBV DNA or HBeAg testing is unavailable (19). Despite the hyperendemic status of HBV in West Africa, the coverage of eligible pregnant women receiving antiviral prophylaxis remained alarmingly low in 2016 (134).

In many African countries, HBV screening is not routinely available in antenatal care, but remains limited to centralised laboratories within the health system. Furthermore, in most cases, pregnant women currently bear the financial burden of HBV screening and TDF prophylaxis. Burkina Faso, has recently stepped up its efforts to eliminate MTCT of HIV, syphilis, and hepatitis B, committing to reduce HBV prevalence in children from 2.6% to 0.1% by 2025, and to provide free HBV screening to all pregnant women (195).

There is an urgent need for Burkina Faso, as well as its endemic counterparts in Africa, to find accessible, affordable, and sustainable solutions for integrating HBV screening into routine antenatal care as a critical step towards achieving HBV MTCT elimination. Current viral load tests are prohibitively expensive, while the more affordable HBeAg test requires specialised equipment to analyse blood samples, and existing rapid diagnostic tests (RDTs) for HBeAg diagnosis lack performance (35). Alternative strategies such as the use of HB core antigen (HBcrAg) RDTs (206) or the extension of TDF prophylaxis to all HBV-positive pregnant women could offer potential solutions.

This study assesses the health impact of HBV burden, with a focus on HBV burden associated with MTCT, and examines the cost-effectiveness of implementing HBV screening in pregnant women and TDF prophylaxis in routine antenatal care at primary healthcare centres (PHCs) in Burkina Faso. We considered four alternative strategies to identify hepatitis B surface antigen (HBsAg) positive pregnant women eligible for TDF

prophylaxis: 1) HBV DNA ≥200,000 IU/mL, 2) HBeAg-positive, 3) positive for HBcrAg-RDT, and 4) all HBsAg-positive women.

4.4.2. Methods

4.4.2.1. Current situation in Burkina Faso

In 2022, Burkina Faso's population was approximately 22.7 million (105), with 73.9% living in rural areas (114). Utilisation of antenatal care by pregnant women was high, with 98% receiving care from skilled health workers and 72% attending the recommended four antenatal visits in 2021 (119). Gross domestic product (GDP) per capita was US$ 832.9 in 2022 (105).

Since 2022, Burkina Faso has incorporated HepB-BD within the Expanded Programme on Immunisation. This addition complements the administration of the three standard HBV vaccine doses (HepB3) at 8, 12, and 16 weeks post-birth, a practice established since 2006.

Currently, HBV screening for pregnant women can be prescribed during antenatal visits. However, access to HBV screening requires a visit to a laboratory, usually at regional and sometimes district level, at a cost borne by the women. TDF prophylaxis for eligible pregnant women has not been implemented. Within the existing antenatal care framework, universal screening for HIV is standard practice. In 2019, 88% of pregnant women underwent HIV screening and 100% of HIV-positive pregnant women received antiretroviral therapy (120).

4.4.2.2. Comparative strategies and base-case assumptions

Table 4.4.1 shows the parameters used in the base-case analysis. The baseline strategy is the current situation in Burkina Faso, where HepB-BD is administered alongside HepB3. In the year of introduction in 2022, HepB-BD coverage was 53% (207). We assumed 90% coverage in subsequent years. HepB3 coverage was derived from existing data (207).

We compared this baseline strategy with four intervention strategies that were evaluated in the context of routine antenatal care in PHCs. In these strategies, pregnant women are screened for HBsAg, and eligibility for TDF prophylaxis varies according to specific criteria.

Strategy 1: HBV DNA

Pregnant women with a positive HBsAg screening test undergo venipuncture at the PHCs. Blood samples are sent to a regional laboratory for HBV DNA quantification using a real-time PCR. TDF prophylaxis is given to those with HBV DNA levels ≥200,000 IU/mL.

Strategy 2: HBeAg

Similar to the HBV DNA strategy, HBsAg-positive pregnant women provide venous blood samples for laboratory analysis. HBeAg is detected by enzyme-linked immunosorbent assay (ELISA), and only HBeAg-positive cases receive TDF prophylaxis.

Strategy 3: HBcrAg-RDT

In this strategy, only a single finger prick is needed to perform both the HBsAg and HBcrAg-RDT screening test. If the HBsAg screening test is positive, an additional HBcrAg-RDT test is performed using a drop of blood placed in a tube containing a pre-treatment solution (39). Women testing positive for HBcrAg-RDT initiate TDF prophylaxis.

Strategy 4: Prophylaxis for All

Following HBsAg screening test, all pregnant women who test positive for HBsAg are eligible for TDF prophylaxis without secondary testing.

For the base-case analysis, we assumed a 90% HBsAg screening coverage among pregnant women, with 90% of HBsAg-positive women undergoing secondary testing in relevant strategies. We also assumed that 90% of eligible pregnant women would receive TDF prophylaxis.

4.4.2.3. HBV model structure

We used a deterministic compartmental dynamic model to project the trajectory of HBV transmission and disease burden at the national level of Burkina Faso, and to capture both the direct and indirect effects of the different intervention strategies. This model was constructed based on previous HBV models (44,208). It provides a simplified yet comprehensive representation of the natural history of HBV infection (163) and comprises eight health states: susceptible, acute infection, HBeAg-positive, HBeAg-negative, compensated cirrhosis, decompensated cirrhosis, HCC, and seroconversion/immune (Figure 4.4.1). Our model was stratified by age, sex, and mode of transmission (horizontal or mother-to-child). Newborns entering the model were classified as either susceptible or infected through MTCT. To simulate transitions between health states and account for aging effects, we employed partial derivatives at 6-month intervals. Given Burkina Faso's endemic HBV status, we initiated the model's timeline back to 1850 to reach an endemic equilibrium. Subsequently, we calibrated the model's parameters using existing data obtained from a literature review to align the model with epidemiological trends in Burkina Faso or other West African studies (Supplementary appendix).

4.4.2.4. Cost analyses

We assessed all costs from the perspective of the Burkina Faso government health system. We assessed the economic costs of screening and treating pregnant women, assuming the integration of the four intervention strategies into routine antenatal visits at PHCs. We used a micro-costing approach to identify the types, quantities, and unit prices of resources required to implement these intervention strategies. We gathered

information through semi-structured interviews, examination of relevant reports, and references to previous studies. All costs were initially valued in CFA francs and subsequently converted to US$ 2022 using the average annual exchange rate for 2022 (US$1 = FCFA 623.76) (105). More cost analysis details are published elsewhere (209).

Additionally, we included the economic costs per child vaccinated associated with administration of HepB-BD and HepB3, based on previous studies (196,210). The HepB-BD cost was originally derived from a study conducted in Senegal in 2017. We adjusted this cost for relevance to Burkina Faso using the 2017 parity power-purchasing conversion factor (105). Both HepB-BD and HepB3 costs were initially determined in 2017 prices. We adjusted for inflation to present our cost estimates in 2022 prices by applying annual inflation rates from 2017 to 2022 (105).

In Burkina Faso, diagnosis of CHB typically occurs when the disease becomes symptomatic (103). Accordingly, we assumed that only individuals who progressed to decompensated cirrhosis or HCC would seek medical care and receive antiviral treatment outside of pregnancy. Care practices for CHB patients with DC or HCC followed WHO guidelines (65). To determine the costs associated with the use of healthcare resources for CHB patients with decompensated cirrhosis or HCC, we conducted interviews with experts working in two university hospitals of Burkina Faso: Yalgado Ouédraogo in Ouagadougou and Sourô SANOU in Bobo Dioulasso. University hospitals are the main facilities for the treatment of advanced liver disease and serve as the primary training centres for gastroenterologists and hepatologists in the country.

4.4.2.5. Epidemiological and cost-effectiveness outcomes

We conducted two models to comprehensively assess the outcomes of the implemented strategies: one focused on the long-term epidemiological impact and another on the cost-effectiveness of these strategies.

In the epidemiological model, the strategies were implemented over the period 2024-2124. Over this time horizon, we estimated epidemiological outcomes considering both overall HBV transmission and, specifically, MTCT. These outcomes included the year of HBV transmission elimination —defined as the year when incidence per year falls below 1/100,000 population —, HBV incidence, prevalence, and mortality rates, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) attributable to HBV.

In contrast, in the cost-effectiveness model, the strategies were only implemented for the year 2024. We captured the long-term health outcomes associated with the immediate implementation of the strategy by examining their effects over a 100-year horizon, based on the United Nations Statistics Division 2022 life tables for Burkina Faso (211). For each strategy, we calculated the incremental cost-effectiveness ratio (ICER) compared to the current situation. We identified optimal strategies by constructing cost-effectiveness efficiency frontiers. We presented both undiscounted and discounted outcomes at an annual rate of 3%. The cost-effectiveness threshold was set at 0.5 times Burkina Faso's per-capita GDP in 2022 (i.e. US$416.5) (174).

4.4.2.6. Sensitivity analyses

To fully capture uncertainties, we used the Latin hypercube method (212) to generate 500 samples from the probability distributions of the epidemiological and economic parameters outlined in Table 4.4.1. These samples were used to derive 95% confidence intervals (CI) in the epidemiological and cost-effectiveness model and to derive cost-effectiveness acceptability curves in the cost-effectiveness model (175).

We also performed one-way deterministic sensitivity analyses to explore the impact of variations in key parameters on the cost-effectiveness outcomes over the range of values specified in Table 4.4.1. The results were illustrated using a Tornado diagram.

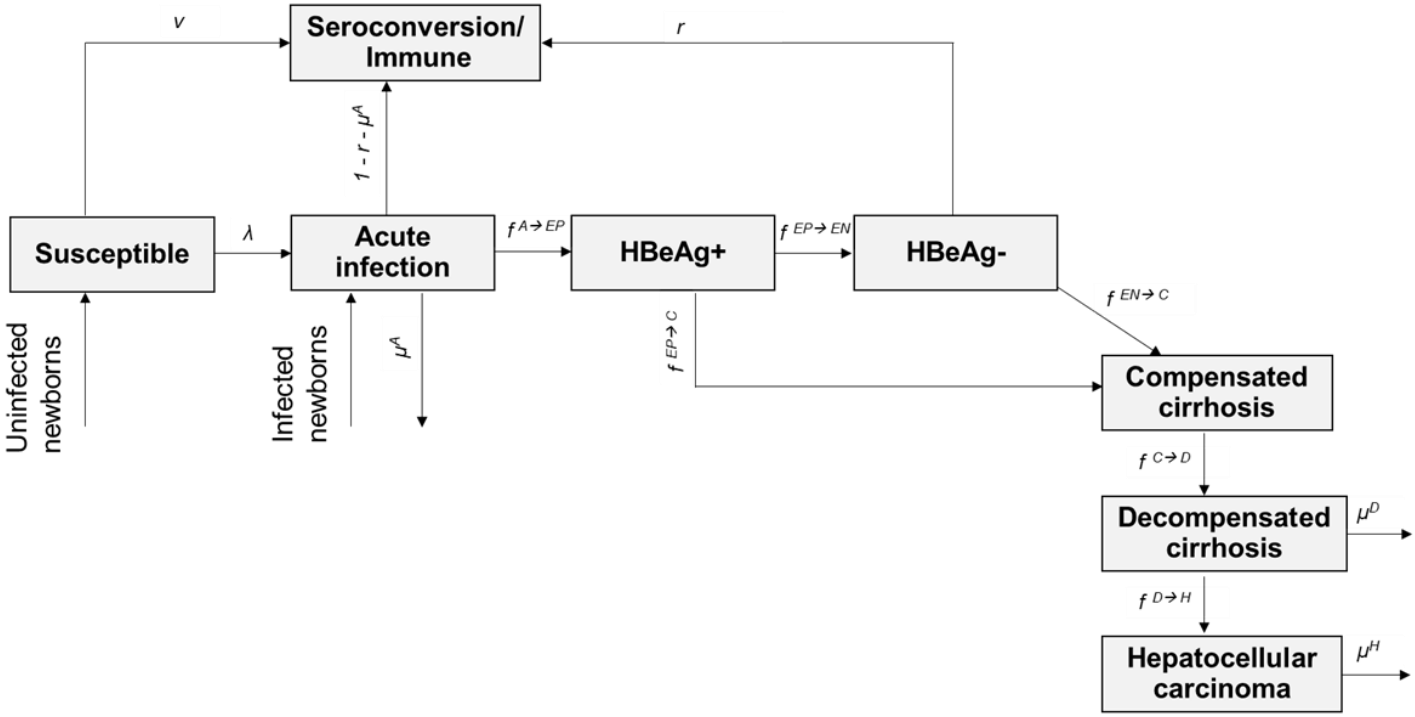


Figure 4.4.1 - Natural history of hepatitis B in the deterministic compartmental model

Table 4.4.1: Parameters of the epidemiological and cost-effectiveness models

Parameters	Description	Value for the base-case analysis	Range for sensitivity analysis	Distribution	Sources
Demography					
$f(a, t)$	Fertility rates	Time-varying[a]			(211)
τ_{births}	Male-to-female birth ratios	1.046			(211)
$m_g(a,t)$	Death rates	Time-varying[a]			(211)
$n_g(a,t)$	Migration rates	Time-varying[a]			(211)
Introduction year of interventions					
	HepB3	2006			
	HepB-BD	2022			
	Screening in pregnant women and antiviral treatment	2024			
Coverage of interventions					
$v_{cov}(a,t)$[b]	HepB3 coverage rate	Time-varying[a]			(59)
HepBBD_cov	HepB-BD coverage	Time-varying[a]	0.50 – 0.95	Beta(3.4,0.4)	(207)
$test_cov_{HBsAg}$	HBsAg screening coverage	0.9	0.50 – 0.95	Beta(3.4,0.4)	
$test_cov_{HBVDNA}$	Viral load screening coverage among HBsAg+ pregnant women	0.9	0.50 – 0.95	Beta(3.4,0.4)	
$test_cov_{HBeAg}$	HBeAg screening coverage among HBsAg+ pregnant women	0.9	0.50 – 0.95	Beta(3.4,0.4)	
$test_cov_{HBcrAg}$	HBcrAg screening coverage among HBsAg+ pregnant women	0.9	0.50 – 0.95	Beta(3.4,0.4)	
TDF_{cov}	Antiviral treatment coverage among eligible pregnant women	0.9	0.50 – 0.95	Beta(3.4,0.4)	
Efficacy of interventions					

v_{eff}	HepB3 efficacy	0.95			(178)
	Relative MTCT risk reduction if mother has high viral load:				
eff_{HV_BD}	HepB-BD	0.522	0.19 – 0.81	Beta(4.2,3.9)	(21,167)
eff_{HV_TDF}	Antiviral treatment	0.510	0.19 – 0.81	Beta(4.2,4.0)	(213–216)
$eff_{HV_BD_TDF}$	HepB-BD + antiviral treatment	1	0.83 – 1	Beta(19.7,1.0)	(31,32)
	Relative MTCT risk reduction if mother has low viral load:				
eff_{LV_BD}	HepB-BD	0.94	0.55 – 1	Beta(2.7,0.2)	(21)
eff_{LV_TDF}	Antiviral treatment	1	0.83 – 1	Beta(19.7,1.0)	(213–216)
$eff_{LV_BD_TDF}$	HepB-BD + antiviral treatment	1	0.83 – 1	Beta(19.7,1.0)	(31,32)
Screening test performance					
	HBsAg diagnostic test (RDT)				
$sens_{HBsAg}$	Sensitivity	1	0.97 – 1	Beta(121.2,1.0)	
$spec_{HBsAg}$	Specificity	1	0.97 – 1	Beta(121.2,1.0)	
	Viral load quantification (qRT-PCR) for detecting HBV DNA ≥ 200,000 IU/mL:				
$sens_{HBVDNA}$	Sensitivity	1	0.97 – 1	Beta(121.2,1.0)	(217,218)
$spec_{HBVDNA}$	Specificity	1	0.97 – 1	Beta(121.2,1.0)	(217,218)
	HBeAg diagnostic test (RDT) for detecting HBV DNA ≥ 200,000 IU/mL:				
$sens_{HBeAg}$	Sensitivity	0.846	0.77 – 0.90	Beta(105.6, 19.2)	(35)
$spec_{HBeAg}$	Specificity	0.905	0.86 – 0.93	Beta(234.5,24.6)	(35)
	HBcrAg diagnostic test (RDT) for detecting HBV DNA ≥ 200,000 IU/mL:				
$sens_{HBcrAg}$	Sensitivity	0.886	0.73 – 0.97	Beta(21.5,2.8)	(39)
$spec_{HBcrAg}$	Specificity	0.935	0.89 – 0.97	Beta(129.0,9.0)	(39)
p_{HV_EP}	Proportion of HBeAg+ pregnant women with high viral load	0.866	0.81 – 0.93	Beta(111.9, 17.3)	(21)

p_{HV_EN}	Proportion of HBeAg- pregnant women with high viral load	0.024	0.01 – 0.04	Beta(11.7,483.3)	(21)
Transmission parameters					
βi	Contact rates between infectious and susceptible individuals	Fitted			
α	Relative infectiousness of HBeAg+ compared to HBeAg- carriers in horizontal transmission	15	13-17	Beta' (855.6, 56.0)	(44,208)
δEN	Mother-to-child transmission risk from an HBeAg- mother at birth	0.05	0.01 – 0.15	Beta (1.49, 28.36)	(6)
δEP	Mother-to-child transmission risk from an HBeAg+ mother at birth	0.588	0.36 – 0.78	Beta (11.42, 8.00)	(6,167)
Transitions between states					
$\sigma(a)$[b]	Transition risk from acute infection to HBeAg+ state	$\sigma(a)$	0.84-0.93, a≤0.5 r^c=[0.59-0.71], a>0.5	Beta(173.6, 22.6), a≤0.5 r^c= Beta(157.9, 86.9), a>0.5	(7)
τ_{HBeAg+}	Female-to-male ratio of the annual transition risk from acute infection to HBeAg+ state	Fitted			
$f_g^{A\to EP}(a)$	Annual transition rate from acute infection to HBeAg+ state	Calculated from $\sigma(a)$ and τ_{HBeAg+}			
$f_{g,z}^{A\to R}(a)$	Annual transition rate from acute infection to immune	Calculated from $\sigma(a)$ and μ_z^A			
$f^{EP\to EN}$	Annual transition rate from HBeAg+ to HBeAg-	0.051 for ages <10, 0.087 for ages [10-20[, 0.086 for ages ≥20	0.04 – 0.07 0.065 – 0.13 0.065 – 0.13	Beta (39.7, 738.5) Beta (22.9, 240.7) Beta (22.2, 235.7)	(43)
$f_z^{EP\to C}$	Annual transition rate from HBeAg+ to compensated cirrhosis	$l(a)$			
$f_z^{EN\to C}$	Annual transition rate from HBeAg- to compensated cirrhosis	0.04*m(a)*			(208)
$\omega_{\text{cirrhosis}}$	Ratio of MTCT developing cirrhosis compared to horizontal transmission	16	1 – 31	Beta' (436.58, 26.22)	(135)
$\tau_{\text{cirrhosis}}$	Ratio of males developing cirrhosis compared to females	2	1.4 – 3.3	Beta'(15.79, 6.39)	(43)
$f^{EN\to R}(a)$	Annual transition rate from HBeAg- to immune	0.0010 for ages <10, 0.0046 for ages [10-20[,	0–0.003 0.002–0.007	Beta (1.63, 1629.7) Beta (13.94, 3015.8)	(43)

		0.0101 for ages [20-30[, 0.0105 for ages [30-40[, 0.0232 for ages [40-50[, 0.0239 for ages ≥ 50	0.005–0.014 0.005–0.016 0.012–0.033 0.012–0.036	Beta (20.98, 2056.1) Beta (14.6, 1371.5) Beta (19.5, 821.5) Beta (15.5, 631.9)	
$f^{C \to D}$	Annual transition rate from compensated cirrhosis to decompensated cirrhosis	0.04	0.01 – 0.06	Beta(30.0, 720.2)	(182)
$f^{D \to H}$	Annual transition rate from decompensated cirrhosis to hepatocellular carcinoma	0.0376	0.01 – 0.12	Beta(1.3, 34.3)	(182)
μ_z^A	Annual HBV-related mortality rate from acute infection	10^{-5} if z = horizontal 10^{-7} if z = MTCT	0 – 0.006	Beta (0.34, 337.3) if z = horizontal Beta (0.04, 3158.1) if z = MTCT	(179)
μ_z^D	Annual HBV-related mortality from decompensated cirrhosis	0.1880	0.08 – 0.22	Beta(26.2, 113.4)	(219)
μ_z^H	Annual HBV-related mortality from hepatocellular carcinoma	0.5450	0.3 – 0.9	Beta(5.1, 4.2)	(219)
Disability weights					
	Symptomatic acute infection	0.051[d]	0.032 – 0.074		(220)
	Decompensated cirrhosis without anaemia[e]	0.178	0.123 – 0.25		(220)
	Decompensated cirrhosis with mild anaemia[e]	0.181	0.126 – 0.252		(220)
	Decompensated cirrhosis with moderate anaemia[e]	0.22	0.156 – 0.298		(220)
	Decompensated cirrhosis with severe anaemia[e]	0.3	0.212 – 0.404		(220)
	Hepatocellular carcinoma	0.54	0.377 – 0.687		(220)
Costs					
	Average structural cost of implementing HBV screening and TDF prophylaxis per health facility (US $)	494.81	371.11 – 618.51	Gamma (16, 0.03)	
	Additional structural cost of implementing HBV DNA and HBeAg strategies per health facility (US $)	29.52	22.14 – 36.90	Gamma (16, 0.54)	
	Average economic cost of HBsAg screening per woman screened for HBsAg (US $)	2.74	2.05 – 3.42	Gamma (16, 5.85)	

Average economic cost of 2nd test screening per woman screened for 2nd test (US $):				
HBV DNA strategy	42.44	31.83 – 53.05	Gamma (16, 0.38)	
HBeAg strategy	11.69	8.77 – 14.61	Gamma (16, 1.37)	
HBcrAg strategy	10.71	8.03 – 13.39	Gamma (16, 1.49)	
Average economic cost of TDF prophylaxis per woman on TDF prophylaxis (US $)	15.05	11.29 – 18.81	Gamma (16, 1.06)	
Average economic cost of HepB-BD per vaccinated newborn (US $)	1.82	1.4 – 2.3	Gamma (16, 8.79)	(210)
Average economic cost of HepB3 per immunized child (US $)	3.69	2.8 – 4.6	Gamma (16, 4.34)	(196)
Cost of initial check-up per patient with decompensated cirrhosis (US$)	42.5	31.9 – 53.1	Gamma (16, 0.38)	
Annual cost of care per patient with decompensated cirrhosis without ascites[f] (US$)	831.3	623.5 – 1,039.1	Gamma (16, 0.01)	
Annual cost of care per patient with decompensated cirrhosis and ascites[f] (US$)	962.1	721.6 – 1,202.6	Gamma (16, 0.01)	
Cost of initial check-up per patient with hepatocellular carcinoma (US$)	67.3	50.5 – 84.1	Gamma (16, 0.24)	
Annual cost of care per patient with hepatocellular carcinoma (US$)	45.4	34.1 – 56.8	Gamma (16, 0.35)	
Discount rate	0.03	0.01 - 0.05	Beta(9.01, 291.4)	

[a] For parameters marked as time-varying, year-specific data were used in the model.

[b] Parameters that mark the transition between health states and are presented as risks (or proportions) were considered as the cumulative proportion of people experiencing an event after one year. These risks were derived as mean annual rates using the following relationship (131): $rate = -\ln(1 - risk)$

[c] r is the parameter of the function $\sigma(a)=exp(-ra^s)$

[d] According to the WHO, acute infection usually lasts 0.25 years. Therefore, we used an annual disability weight of 0.013 (65). We only applied a disability weight to symptomatic acute HBV infections, which represent 1% of perinatally-infected individuals, 10% of children infected between 1 and 5 years of age, and 30% of individuals infected after the age of 5 years (184).

[e] We considered that among individuals with CHB and decompensated cirrhosis 60% did not have anaemia, and among those with anaemia: 70.7% had mild anaemia , 23.9% had moderate anaemia, 30% had severe anaemia (221–224)

[f] We considered that 48% of patients with decompensated cirrhosis had ascites (185).

4.4.3. Results

4.4.3.1. Prevalence and health outcomes before strategy implementation

In Burkina Faso in 2023, before the implementation of interventions, the estimated prevalence was 6.5% [95% CI=3.8; 10.7] (Figure 4.4.2), of which 99.0% was chronic. Horizontal transmission accounted for 85.8% of prevalent cases in the total population, and MTCT for 14.1%. Prevalence of HBV in infants aged 1 year was 0.97%. The HBV incidence rate was 308.7 per 100,000 people [223.5; 452.3], and MTCT incidence rate was 16.3 per 100,000 people [1.9; 41.9]. MTCT accounted for 47.7% and horizontal transmission for 52.3% of chronic incident cases. The impact of HBV infection included 15,029 [7,253; 29,940] DALYs and 15,182 [8,505; 27,272] HBV-related deaths. Horizontal transmission accounted for 81% of the DALYs and HBV-related deaths, and MTCT for 19%.

The estimated prevalence of HBV among pregnant women in 2023 was 10.9% [6.0%; 17.4%]. Within this population, 8,622 [1,095; 19,294] women had a high viral load (HVL), while 80,296 [47,216; 129,594] women had a low viral load (LVL).

In the baseline strategy, the model predicted HBV transmission elimination by 2120 and HBV MTCT elimination by 2044.

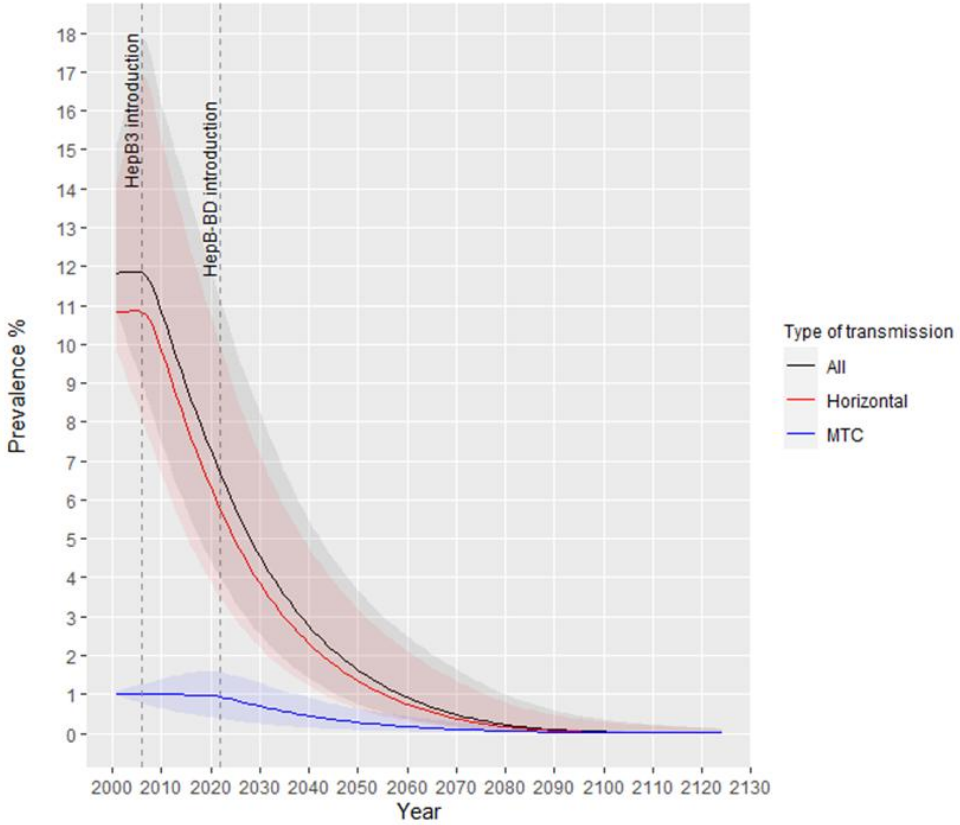


Figure 4.4.2 - Evolution of HBV prevalence rate overall, and by mode of transmission according to the current situation in Burkina Faso

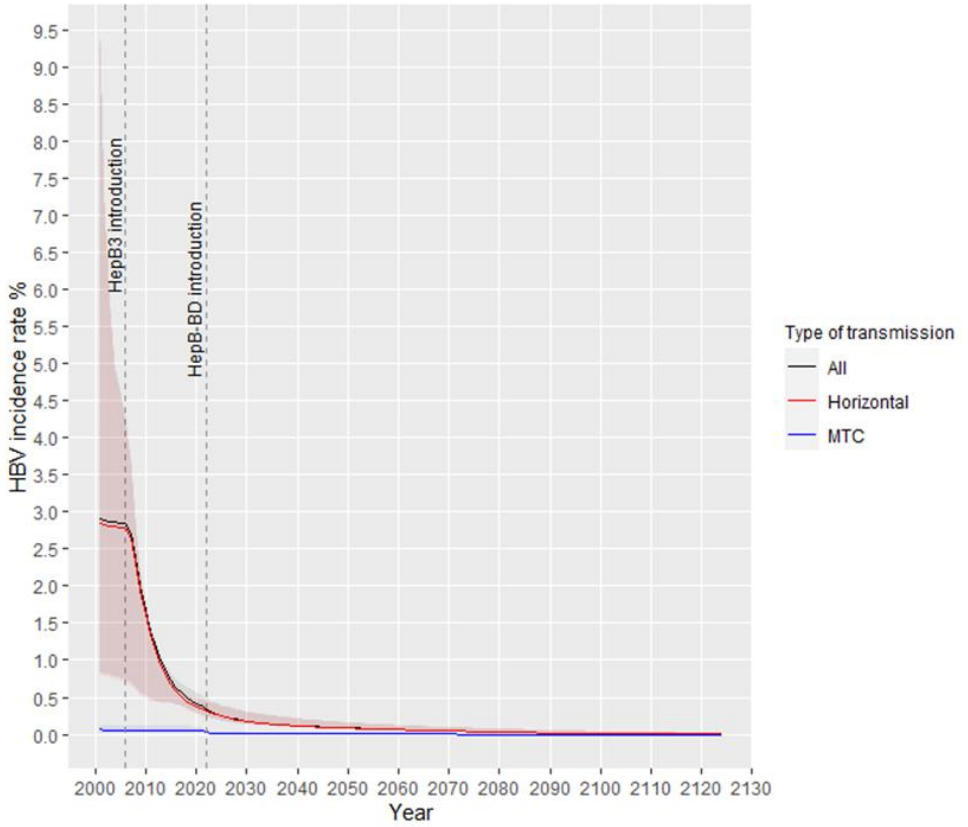


Figure 4.4.3 - Evolution of HBV incidence rate overall, and by mode of transmission according to the current situation in Burkina Faso

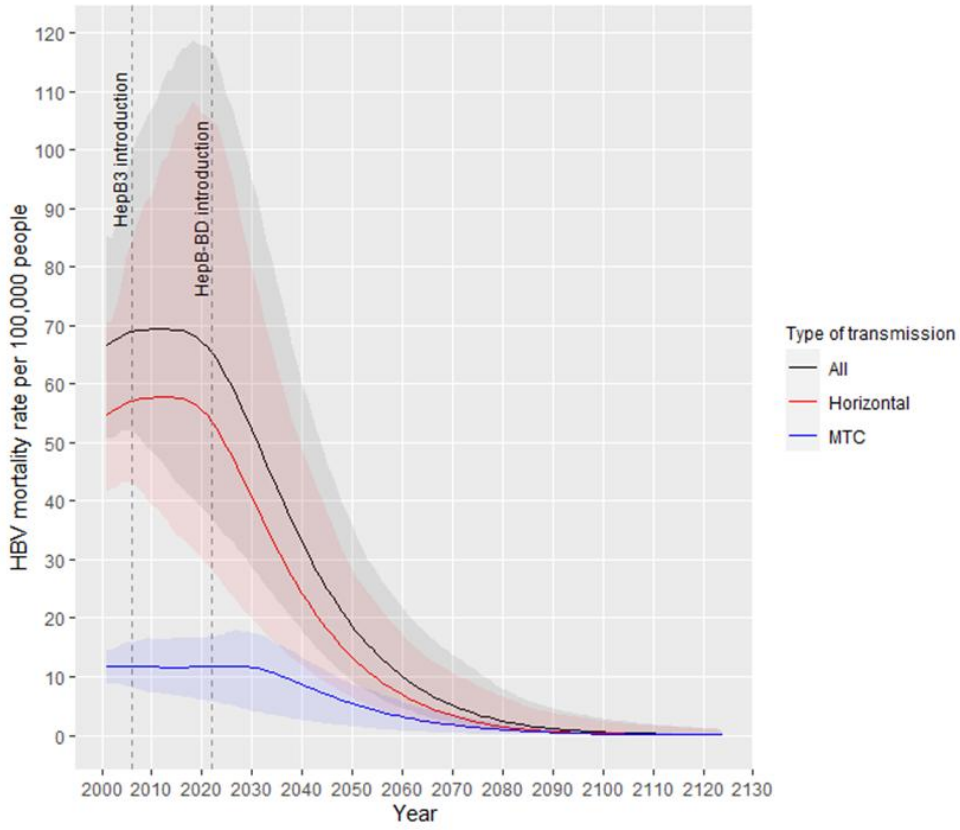


Figure 4.4.4 - Evolution of HBV-related mortality rate overall, and by mode of transmission according to the current situation in Burkina Faso

4.4.3.2. Epidemiological and health outcomes after strategy implementation

After implementation of HBV screening in pregnant women and TDF prophylaxis, the model predicted HBV elimination by 2118 for the HBV DNA, HBeAg and HBcrAg RDT strategies and by 2117 for the Prophylaxis for All strategy. MTCT elimination was estimated to occur by 2039 for the HBV DNA and HBcrAg-RDT strategies, by 2040 for the HBeAg strategy, and by 2034 for the Prophylaxis for All strategy.

Implementation of HBV screening and TDF prophylaxis between 2024 and 2124 showed a reduction in chronic HBV infections of 2.0% [0.5%; 7.3%] in the HBV DNA strategy, 1.8% [0.4%; 5.6%] in the HBeAg strategy, 1.8% [0.5%; 6.4%] in the HBcrAg strategies, and 2.8% [0.6%; 8.1%] in the Prophylaxis for All strategy (Table 4.4.2a and Table 4.4.2b). Similarly, the projected reductions in MTCT-related infections were 8.8% [4.0%; 9.6%], 7.7% [2.8%; 8.5%], 8.0% [3.1%; 9.9%], and 12.1% [4.9%; 13.9%], respectively. This translated into reductions in HBV-related deaths of 2.3% [1.2%; 5.5%], 2.0% [0.9%; 4.4%], 2.1% [1.0%; 4.7%] and 3.1% [1.3%; 6. 7%], and reductions in MTCT-related HBV deaths of 7.3% [4.4%; 8.7%], 6.4% [3.2%; 8.3%], 6.6% [3.5%; 8.7%] and 10.0% [4.1%; 13.2%], respectively (Table 4.4.2a and Table 4.4.2b).

The estimated reductions in DALYs for the above strategies were 3.1%, 2.7%, 2.8% and 4.2%, respectively. In addition, DALYs due to MTCT were projected to decrease by 8.4% [5.6%; 10.9%], 7.3% [4.3%; 9.3%], 7.5% [4.8%; 10.1%], and 11.4% [5.6%; 16.0%], respectively (Table 4.4.2a and Table 4.4.2b). These DALYs were primarily attributable to years of life lost due to premature mortality (YLLs), accounting for about 97% of the total DALYs, while 3% of the DALYs were years of healthy life lost due to disability (YLDs).

Table 4.4.2a: Health outcomes derived from the epidemiological model when strategies are implemented over the period 2024-2124 in Burkina Faso

Strategy	Total number of chronic infections [95%CI]	HBV-related deaths [95%CI]	YLDs [95%CI]	YLLs [95%CI]	DALYs [95%CI]	Number of chronic infections averted (%) [95%CI]	HBV-related deaths averted (%) [95%CI]	DALYs averted (%) [95%CI]
Current situation	40,229,471 [19,494,169; 94,274,400]	461,455 [237,062; 952,050]	448,261 [198,722; 1,102,077]	14,063,855 [6,484,999; 32,382,701]	14,512,116 [6,709,593; 33,370,682]	-	-	-
1. HBV DNA	39,417,092 [19,395,642; 87,406,011]	450,936 [234,217; 899,787]	437,851 [196,161; 1,049,055]	13,630,228 [6,396,663; 30,156,215]	14,068,080 [6,619,424; 31,105,450]	812,379 [98,527; 6,868,389] (-2.0%) [-0.5%; -7.3%]	10,519 [2,846; 52,263] (-2.3%) [-1.2%; -5.5%]	444,037 [90,170; 2,265,233] (-3.1%) [-1.3%; -6.8%]
2. HBeAg+	39,523,378 [19,413,165; 88,963,592]	452,312 [234,881; 910,480]	439,213 [196,673; 1,059,085]	13,686,913 [6,418,614; 30,626,275]	14,126,126 [6,639,545; 31,592,137]	706,093 [81,003; 5,310,808] (-1.8%) [-0.4%; -5.6%]	9,143 [2,181; 41,570] (-2.0%) [-0.9%; -4.4%]	385,991 [70,049; 1,778,546] (-2.7%) [-1.0%; -5.3%]
3. HBcrAg-RDT	39,496,746 [19,401,849; 88,285,681]	451,967 [234,721; 907,205]	438,872 [196,481; 1,053,622]	13,672,709 [6,420,368; 30,356,556]	14,111,581 [6,639,856; 31,311,072]	732,725 [92,320; 5,988,719] (-1.8%) [-0.5%; -6.4%]	9,488 [2,341; 44,845] (-2.1%) [-1.0%; -4.7%]	400,536 [69,738; 2,059,610] (-2.8%) [-1.0%; -6.2%]
4. Prophylaxis for All	39,121,135 [19,373,773; 86,671,570]	447,103 [233,912; 888,016]	434,058 [195,761; 1,034,845]	13,472,446 [6,373,692; 29,688,649]	13,906,504 [6,603,110; 30,639,373]	1,108,336 [120,396; 7,602,830] (-2.8%) [-0.6%; -8.1%]	14,352 [3,150; 64,034] (-3.1%) [-1.3%; -6.7%]	605,613 [106,484; 2,731,309] (-4.2%) [-1.6%; -8.2%]

Table 4.4.2b: Health outcomes due to mother-to-child transmission (MTCT) derived from the epidemiological model when strategies are implemented over the period 2024-2124 in Burkina Faso

Strategy	Total number of chronic infection due to MTCT [95%CI]	HBV-related deaths due to MTCT [95%CI]	YLDs due to MTCT [95%CI]	YLLs due to MTCT [95%CI]	DALYs due to MTCT [95%CI]	Number of chronic infections due to MTCT averted (%) [95%CI]	HBV-related deaths due to MTCT averted (%) [95%CI]	DALYs due to MTCT averted (%) [95%CI]
Current situation	6,966,442 [1,951,872; 15,672,544]	123,636 [35,655; 209,891]	120,684 [31,804; 230,191]	4,553,220 [1,104,387; 8,066,231]	4,673,903 [1,139,201; 8,266,810]	-	-	-
1. HBV DNA	6,350,461 [1,872,935; 14,162,286]	114,556 [34,076; 191,629]	111,710 [30,426; 207,637]	4,171,875 [1,042,377; 7,199,902]	4,283,584 [1,075,688; 7,369,447]	615,980 [78,936; 1,510,258] (-8.8%) [-4.0%; -9.6%]	9,080 [1,579; 18,262] (-7.3%) [-4.4%; -8.7%]	390,319 [63,513; 897,363] (-8.4%) [-5.6%; -10.9%]
2. HBeAg+	6,431,013 [1,896,751; 14,338,616]	115,743 [34,500; 192,489]	112,883 [30,686; 208,694]	4,221,714 [1,056,392; 7,316,540]	4,334,597 [1,090,413; 7,494,891]	535,429 [55,120; 1,333,928] (-7.7%) [-2.8%; -8.5%]	7,893 [1,155; 17,402] (-6.4%) [-3.2%; -8.3%]	339,307 [48,789; 771,919] (-7.3%) [-4.3%; -9.3%]
3. HBcrAg-RDT	6,410,827 [1,892,176; 14,118,069]	115,446 [34,395; 191,735]	112,589 [30,592; 210,099]	4,209,224 [1,050,383; 7,253,337]	4,321,813 [1,083,964; 7,431,679]	555,615 [59,696; 1,554,474] (-8.0%) [-3.1%; -9.9%]	8,190 [1,260; 18,156] (-6.6%) [-3.5%; -8.7%]	352,090 [55,237; 835,131] (-7.5%) [-4.8%; -10.1%]
4. Prophylaxis for All	6,126,426 [1,856,284; 13,495,906]	111,251 [34,199; 182,111]	108,444 [30,613; 200,112]	4,033,259 [1,042,462; 6,764,773]	4,141,703 [1,075,831; 6,946,720]	840,016 [95,587; 2,176,638] (-12.1%) [-4.9%; -13.9%]	12,385 [1,456; 27,780] (-10.0%) [-4.1%; -13.2%]	532,200 [63,370; 1,320,090] (-11.4%) [-5.6%; -16.0%]

4.4.3.3. Cost-effectiveness outcomes

The results of the cost-effectiveness analyses for implementing the strategies in Burkina Faso over the year 2024 are shown in Table 4.4.3.

Compared to the current situation and without discounting, the strategies resulted in the following incremental costs: US$1,876,365 for the HBV DNA strategy, US$413,925 for the HBeAg strategy, and US$101,009 for the HBcrAg strategy. In contrast, the Prophylaxis for All strategy resulted in cost savings of US$1,472,114. These strategies averted 45,301, 39,024, 40,615, and 58,521 DALYs, respectively.

Using a 3% discount rate, the incremental costs of implementing the strategies compared to the current situation were US$4,351,620 in the HBV DNA strategy, US$2,546,194 in the HBeAg strategy, US$2,320,227 in the HBcrAg strategy, and US$1,725,526 in the Prophylaxis for All strategy. The number of DALYs averted was 21,925, 18,887, 19,657, and 28,322, respectively. This resulted in an ICER of US$198.5 per DALY averted for the HBV DNA strategy, US$134.8 per DALY averted for the HBeAg strategy, US$118.0 per DALY averted for the HBcrAg strategy, and US$60.9 per DALY averted for the Prophylaxis for All strategy.

When comparing each individual strategy to the baseline, all the strategies were cost-effective for Burkina Faso, at a willingness-to-pay threshold of US$416.5 per DALY averted. However, when these strategies were compared with each other, the Prophylaxis for All strategy emerged as the dominant strategy and remained the only one on the cost-effectiveness frontier, delivering the highest number of DALYs averted at the lowest cost
(

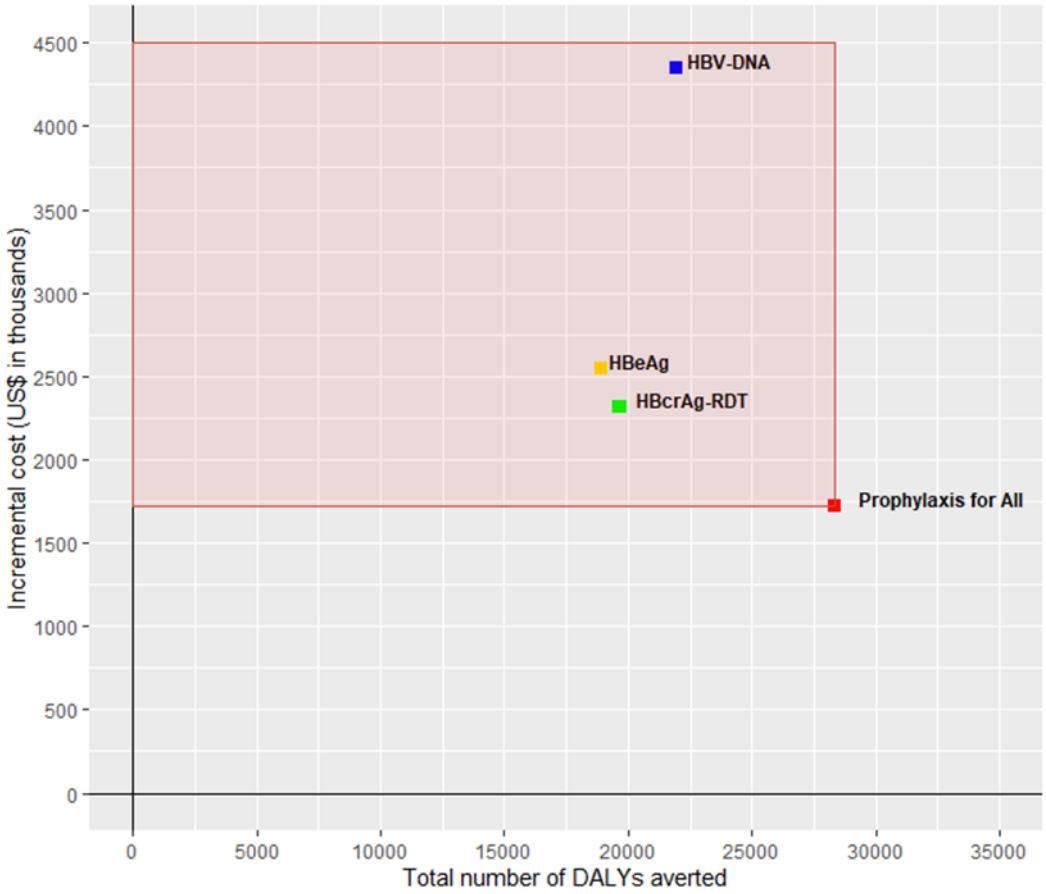
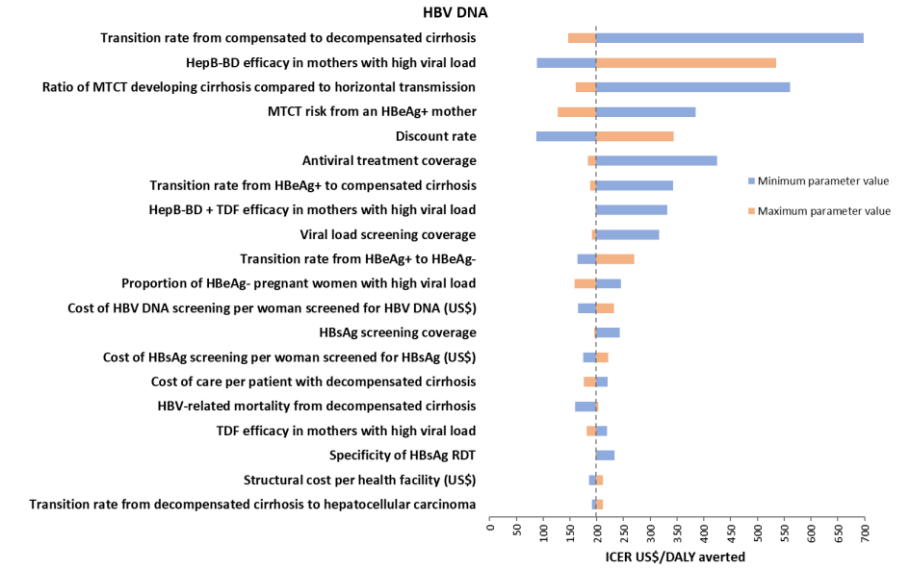
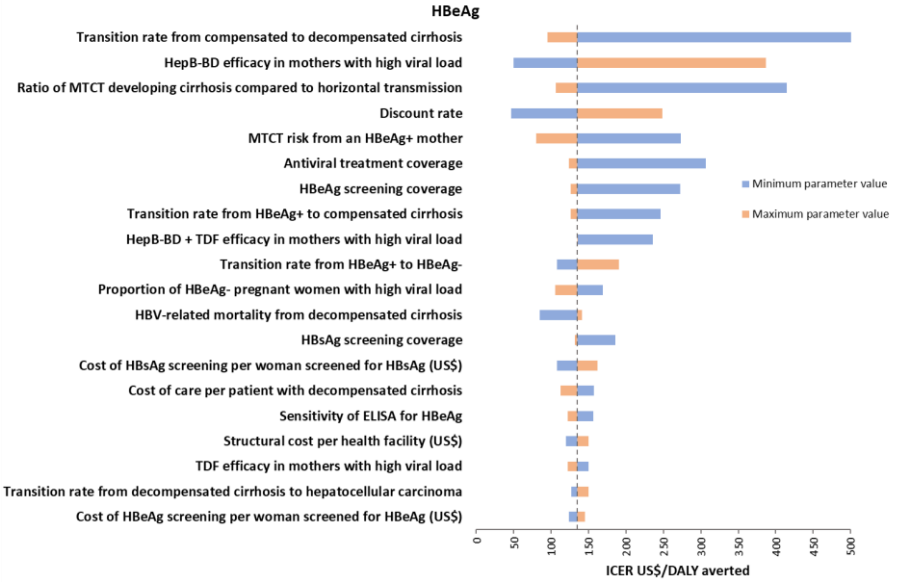
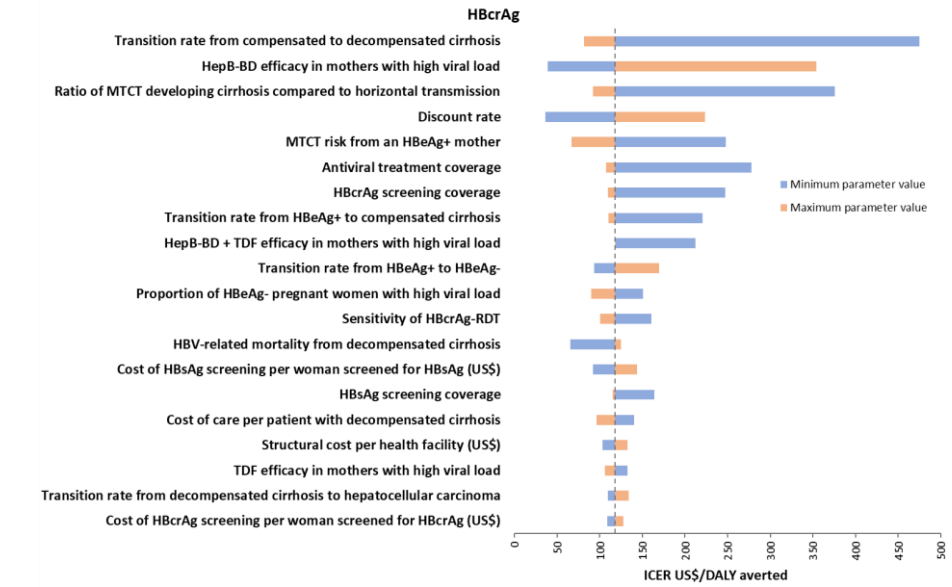


Figure 4.4.5). Even adjusting for the cost of the second screening test would not move other strategies onto the efficiency frontier. To be as low as the HBV DNA strategy in terms of DALYs averted, the potential harm of the Prophylaxis for All strategy in pregnant women with low viral load on TDF prophylaxis should be at least equal to a disability weight of 0.10 per pregnant woman with low viral load on TDF prophylaxis.

Deterministic sensitivity analyses showed greater sensitivity of results to transition rates from compensated to decompensated cirrhosis and to the efficacy of HepB-BD in mothers with high viral load (


HBV DNA
Transition rate from compensated to decompensated cirrhosis
HepB-BD efficacy in mothers with high viral load
Ratio of MTCT developing cirrhosis compared to horizontal transmission
MTCT risk from an HBeAg+ mother
Discount rate
Antiviral treatment coverage
Transition rate from HBeAg+ to compensated cirrhosis
HepB-BD + TDF efficacy in mothers with high viral load
Viral load screening coverage
Transition rate from HBeAg+ to HBeAg-
Proportion of HBeAg- pregnant women with high viral load
Cost of HBV DNA screening per woman screened for HBV DNA (US$)
HBsAg screening coverage
Cost of HBsAg screening per woman screened for HBsAg (US$)
Cost of care per patient with decompensated cirrhosis
HBV-related mortality from decompensated cirrhosis
TDF efficacy in mothers with high viral load
Specificity of HBsAg RDT
Structural cost per health facility (US$)
Transition rate from decompensated cirrhosis to hepatocellular carcinoma
Minimum parameter value
Maximum parameter value
0 50 100 150 200 250 300 350 400 450 500 550 600 650 700
ICER US$/DALY averted


HBeAg
Transition rate from compensated to decompensated cirrhosis
HepB-BD efficacy in mothers with high viral load
Ratio of MTCT developing cirrhosis compared to horizontal transmission
Discount rate
MTCT risk from an HBeAg+ mother
Antiviral treatment coverage
HBeAg screening coverage
Transition rate from HBeAg+ to compensated cirrhosis
HepB-BD + TDF efficacy in mothers with high viral load
Transition rate from HBeAg+ to HBeAg-
Proportion of HBeAg- pregnant women with high viral load
HBV-related mortality from decompensated cirrhosis
HBsAg screening coverage
Cost of HBsAg screening per woman screened for HBsAg (US$)
Cost of care per patient with decompensated cirrhosis
Sensitivity of ELISA for HBeAg
Structural cost per health facility (US$)
TDF efficacy in mothers with high viral load
Transition rate from decompensated cirrhosis to hepatocellular carcinoma
Cost of HBeAg screening per woman screened for HBeAg (US$)
Minimum parameter value
Maximum parameter value
0 50 100 150 200 250 300 350 400 450 500
ICER US$/DALY averted



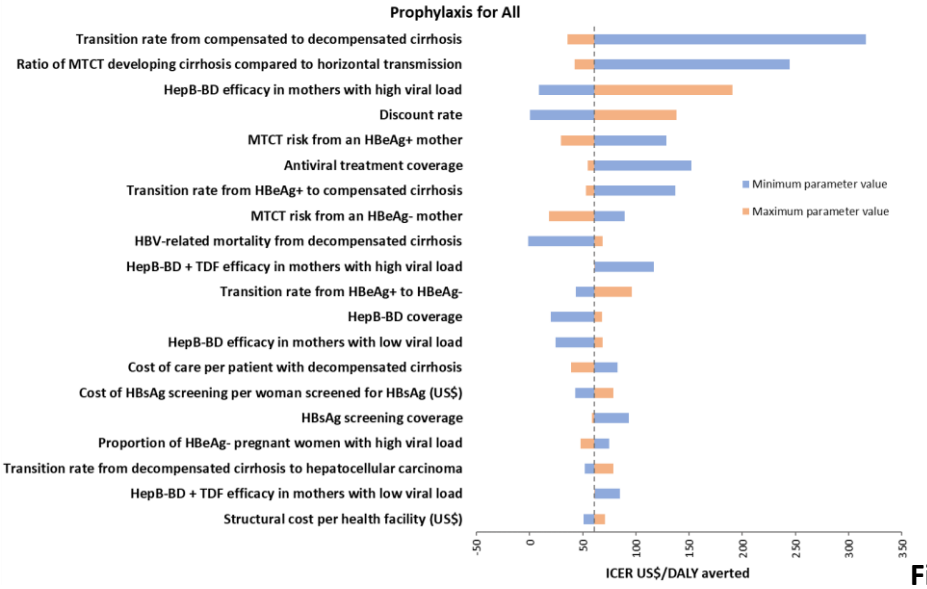


Figure 4.4.6). The lower the rates at which people with compensated cirrhosis progressed to decompensated cirrhosis, the higher the ICER per DALY averted, and the higher the efficacy of HepB-BD in mothers with high viral load, the higher the ICER per DALY averted.

Probabilistic sensitivity analyses showed that the probability that the implementation of HBV screening and TDF prophylaxis would be cost-effective at the US$416.5 threshold, taking into account discounting, was 75.6% for the HBV DNA strategy, 85.8% for the

HBeAg strategy, 86.2% for the HBcrAg strategy, and 91.8% for the Prophylaxis for All strategy (Figure 4.**4.7**).

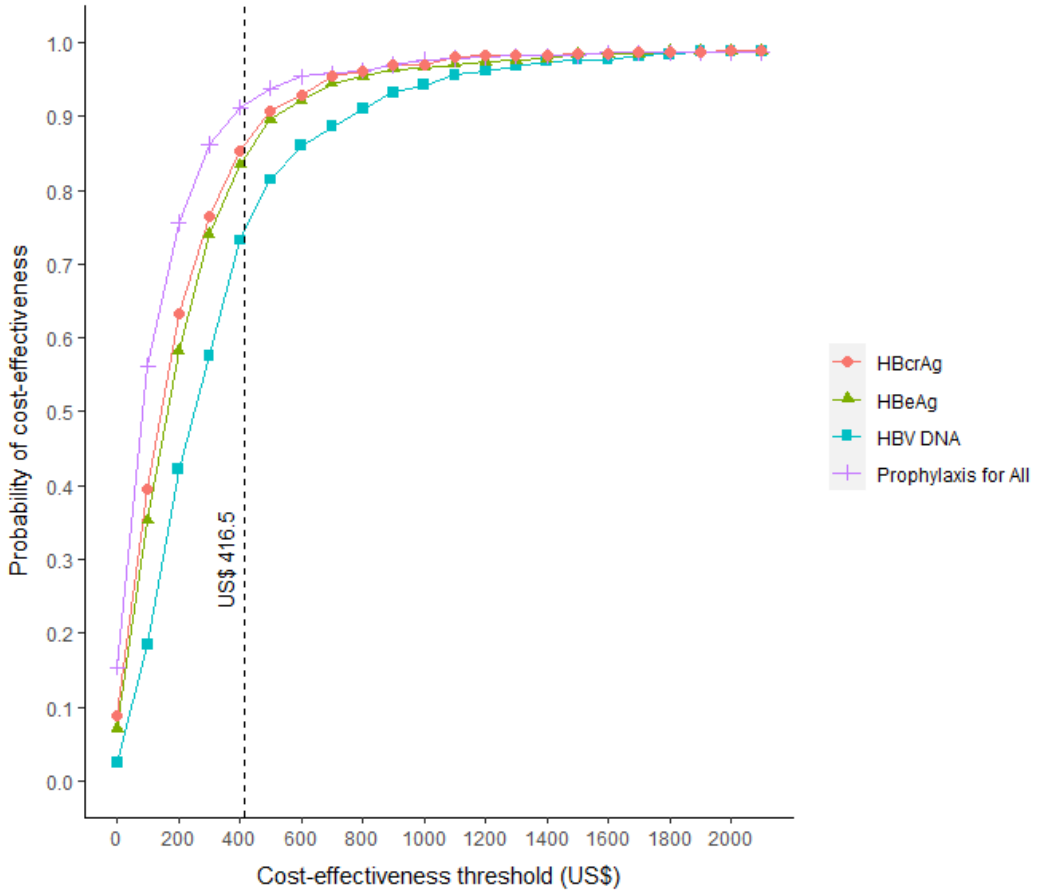


Table 4.4.3: Cost-effectiveness results of the HBV screening and tenofovir prophylaxis strategies in antenatal care in Burkina Faso, compared to the current situation

	Total cost (US$)	Total DALYs	Incremental cost [95%CI], US$	Number of DALYs averted [95%CI]	Cost per DALY averted [95%CI], US$
HepB-BD + HepB3 (current situation)					
Undiscounted	2,255,903,401	14,517,236	-	-	-
Discounted	1,260,063,006	9,546,861	-	-	-
1. HBV DNA					
Undiscounted	2,257,779,766	14,471,935	1,876,365 [-8,570,958; 6,370,197]	45,301 [8,641; 129,352]	**41.4 [Cost-saving; 578.1]**
Discounted	1,264,414,626	9,524,936	4,351,620 [48,070; 7,798,362]	21,925 [3,771; 64,090]	**198.5 [Cost-saving; 1,311.5]**
2. HBeAg+					
Undiscounted	2,256,317,326	14,478,212	413,925 [-8,524,406; 3,768,599]	39,024 [7,606; 106,773]	**10.6 [Cost-saving; 415.2]**
Discounted	1,262,609,200	9,527,974	2,546,194 [-1,370,965; 4,756,972]	18,887 [3,188; 53,529]	**134.8 [Cost-saving; 1,156.6]**
3. HBcrAg-RDT					
Undiscounted	2,256,004,410	14,476,621	101,009 [-8,716,171; 3,552,754]	40,615 [7,215; 108,395]	**2.5 [Cost-saving; 395.7]**
Discounted	1,262,383,233	9,527,204	2,320,227 [-1,551,738; 4,452,467]	19,657 [3,248; 53,219]	**118.0 [Cost-saving; 1,021.2]**
4. Prophylaxis for All					
Undiscounted	2,254,431,287	14,458,715	-1,472,114 [-13,586,175; 3,563,165]	58,521 [8,247; 157,539]	**Cost-saving [Cost-saving; 293.9]**
Discounted	1,261,788,532	9,518,539	1,725,526	28,322	**60.9**

	[-3,913,515; 4,442,448]	[3,961; 76,174]	**[Cost-saving; 868.7]**

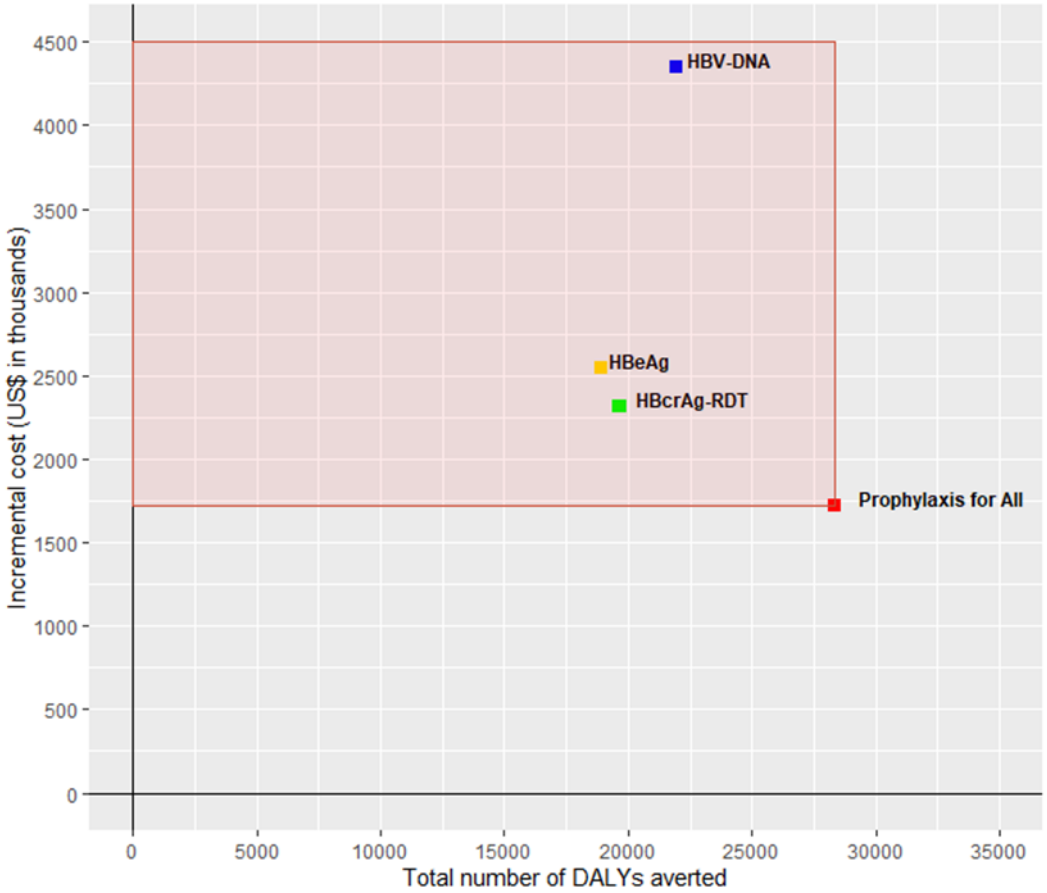


Figure 4.4.5 - Cost effectiveness plan showing discounted incremental costs and DALYs averted at a 3% discount rate, and dominance of the intervention strategies

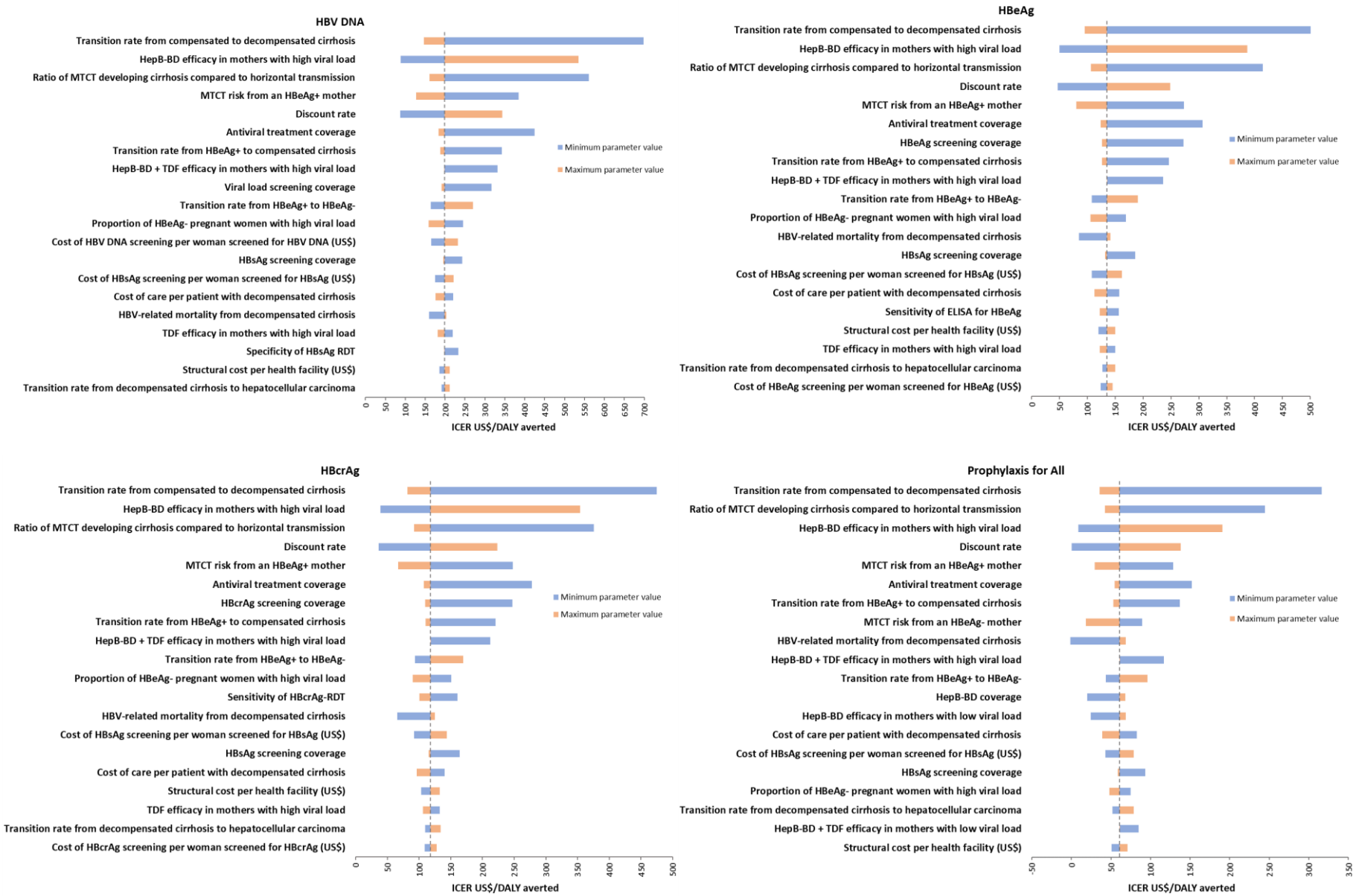


Figure 4.4.6 - Tornado diagram showing results of the one-way deterministic sensitivity analyses for each intervention strategy, considering discounting for costs and DALYs

4.4.4. Discussion

Finding a sustainable antenatal care strategy that provides screening and TDF prophylaxis for pregnant women against HBV MTCT is an important priority in sub-Saharan African countries with a high HBV burden.

Through modelling, we estimated that MTCT currently accounts for 47.7% of CHB incident cases in Burkina Faso and is responsible of 19% of DALYs and HBV-related deaths. As the health benefits of HBV screening and TDF prophylaxis in pregnant women occur over the long term, our cost-effectiveness analysis focused on capturing these benefits by assessing the cost-effectiveness of implementing these strategies over the year 2024 and projecting the impact over a 100-year horizon. When compared individually with the current situation in Burkina Faso, where only HepB-BD is administered, any strategy that includes HBV screening in pregnant women and TDF prophylaxis is considered cost-effective with a cost-effectiveness threshold set at half of Burkina Faso's gross per capita GDP (US$416.5). However, in the comparative analysis between strategies, only the Prophylaxis for All strategy is lying on the cost-effectiveness frontier. Not only did the Prophylaxis for All strategy result in the highest number of DALYs averted, it also had the lowest incremental cost. Even the hypothetical cost-free

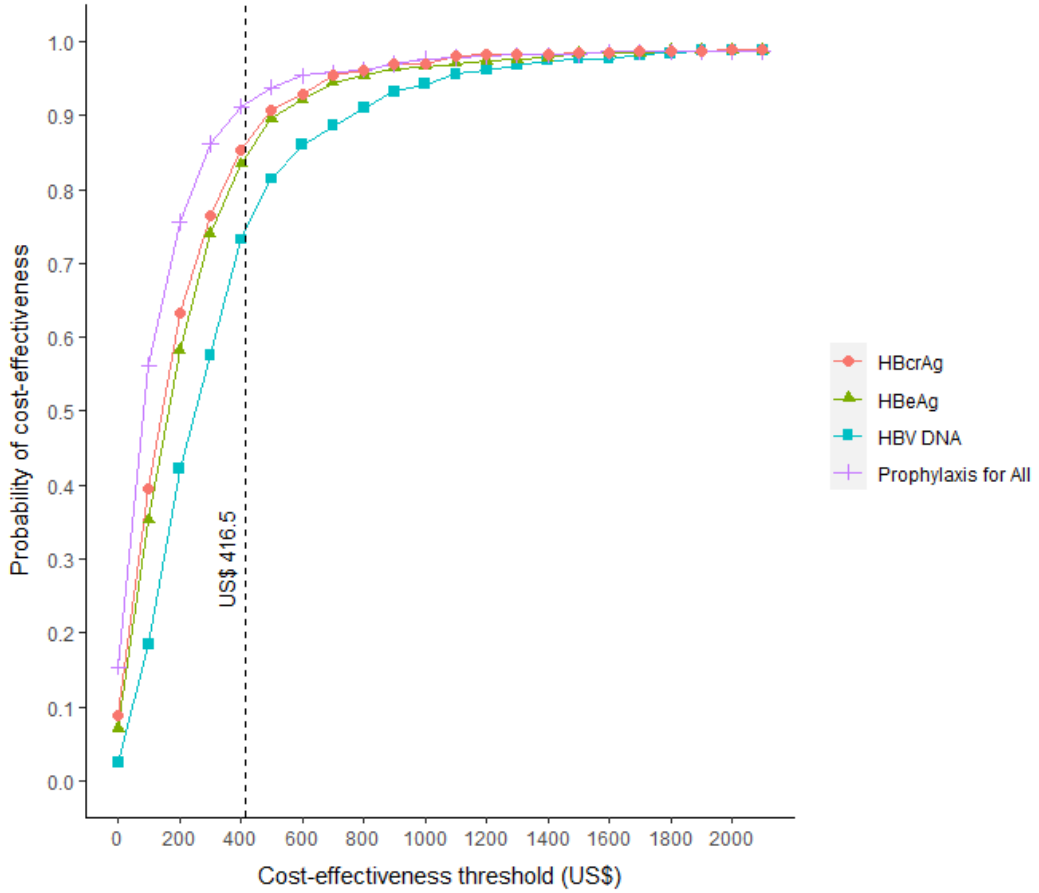


Figure 4.4.7 - Cost-effectiveness acceptability curves comparing each strategy with the current situation in Burkina Faso

addition of the second screening test could not align the HBV DNA, HBeAg, or HBcrAg-RDT strategy on the cost-effectiveness frontier of the Prophylaxis for All strategy. The cost savings derived from treating chronically infected individuals in the advanced stages of the disease was always higher in the Prophylaxis for All strategy. If the risk of MTCT in pregnant women with a low viral load (LVL) is minimal or negligible, the substantially higher number of pregnant women involved, even under minimal risk scenarios, deserves serious attention and consideration as a public health problem. A Prophylaxis for All strategy has never been evaluated in the real world and uncertainties exist regarding the potential adverse effects of TDF prophylaxis in pregnant women with a low viral load. For the Prophylaxis for All strategy to demonstrate an equivalent effectiveness in terms of DALYs averted as the HBV DNA strategy, the second most effective strategy, this potential harm would have to be substantial enough to result in a disability weight of at least 0.10 per low viral load pregnant woman receiving TDF prophylaxis. To put this in perspective, a disability weight of 0.10 could correspond to a health status comparable to untreated stage 4 chronic kidney disease or moderate motor impairment associated with mild intellectual disability (220).

Across all strategies, introducing HBV screening and TDF prophylaxis in pregnant women would have a much important impact on health outcomes due to MTCT than those due to horizontal transmission in Burkina Faso, although indirect effects of such interventions are not negligible. A Prophylaxis for All strategy, when implemented over a 100-year horizon, indicated an important reduction of 12.1% in CHB cases, 10.0% in deaths attributed to MTCT, and 11.4% in DALYs due to MTCT. However, the overall impact on HBV was more limited, with a 2.8% reduction in CHB cases, 3.1% in HBV-related deaths, and 4.2% in DALYs. A Prophylaxis for All strategy could eliminate HBV MTCT by 2034, and all HBV transmission by 2117. Focusing prevention solely on prevention of MTCT and vaccination would not be sufficient to eliminate HBV in the short term, as already shown in a previous global model (44).

Few studies have assessed the cost-effectiveness of adding TDF prophylaxis to HepB-BD in sub-Saharan Africa. A global model (40) found that, in the majority of countries in the WHO African region, the addition of TDF prophylaxis to HepB-BD was not cost-effective in terms of incremental cost per DALY averted. Of the 42 countries evaluated in this region, only seven (17%) found the HBV DNA strategy cost-effective, nine (21%) found the HBeAg strategy cost-effective, and fourteen (33%) found the Prophylaxis for All strategy cost-effective. However, this study did not consider cost variations across world regions or cost savings associated with managing HBV-related liver disease. Another study conducted in South Africa (193) found that compared to no HBsAg screening and no TDF prophylaxis, the Prophylaxis for All strategy was cost-effective, with an incremental cost of US$3,940 per infection averted in newborns. However, this study focused only on screening and treatment costs, ignoring other implementation costs and future savings from avoided treatment costs.

Our study has limitations. First, there exist a high uncertainty regarding the progression of advanced-stage CHB cases in sub-Saharan Africa. The natural history of CHB has specificities in this region (8). While we used data from sub-Saharan Africa to

model CHB progression in this setting, the lack of data on advanced disease stages required us to rely on studies from Asia for this aspect. Although our sensitivity analyses addressed this uncertainty, this point highlights the critical need for more empirical data from African settings. Second, for treatment costs, we only considered the prevailing situation in Burkina Faso, where people seek care only when symptomatic, which corresponds to decompensated cirrhosis or HCC stages. We did not include costs associated with treatment eligibility criteria for people with CHB who are not in the decompensated cirrhosis or HCC stages (163). Including these treatment eligibility criteria would increase the cost of treating CHB cases, making HBV screening and TDF prophylaxis in pregnant women even more cost-effective. Third, we did not consider the impact of HBV screening on identifying pregnant women eligible for post-pregnancy TDF. A structured programme is essential to ensure proper post-pregnancy follow-up of eligible women. Finally, although we considered implementation costs of the strategies at the most decentralised levels of the health system, our study did not take into account the ongoing security crisis in Burkina Faso, which could affect intervention costs.

In conclusion, our study estimated the impact of implementing universal antenatal HBsAg screening and TDF prophylaxis in PHCs in Burkina Faso according to four different strategies and assessed their cost-effectiveness compared with the current practice of administering HepB-BD only. While the HBV-DNA, HBeAg, HBcrAg-RDT, and the Prophylaxis for All strategies are individually cost-effective, the Prophylaxis for All strategy strongly dominates all the other strategies. While these strategies promise substantial reductions in HBV MTCT in the short term, prevention of MTCT has a more limited impact on the global evolution of HBV. To achieve HBV elimination in the short term, additional interventions, particularly treatment of HBV cases, are essential to significantly reduce HBV-related burden.

5. General discussion

Given that those infected as neonates or infants have a very high risk of developing CHB, addressing HBV MTCT in all its components is essential to reduce the burden of HBV in West Africa, a region where the prevalence of CHB infection is particularly high. Identifying optimal strategies to prevent HBV MTCT is essential for their sustainable and effective implementation across West African countries.

My thesis aimed to address several objectives. Initially, the absence of data on the implementation costs and cost-effectiveness of HepB-BD vaccination posed a significant barrier to promoting this prevention policy in West Africa. To address this, I assessed the costs associated with the implementation of HepB-BD, drawing on the Senegalese experience of its implementation in 2016. I also examined the cost-effectiveness of HepB-BD in a context where its efficacy is more limited in pregnant women with high viral loads, compared to other settings, notably Asia. Furthermore, one of the main research hypotheses underlying my thesis was that to eliminate HBV MTCT completely, in addition to providing HepB-BD to newborns, pregnant women need to be targeted during antenatal visits for antiviral prophylaxis. However, determining the optimal eligibility criteria for selecting pregnant women for TDF prophylaxis remained a challenge. Through my thesis, I was able to evaluate the costs of implementing HBV screening and TDF prophylaxis during antenatal care in Burkina Faso, according to different strategies for determining the eligibility of pregnant women. I used mathematical modelling techniques to assess which strategy could achieve the fastest elimination of HBV MTCT, and to identify the optimal strategy through a cost-effectiveness analysis.

This general discussion is structured to summarise and discuss the results of the first two articles, which focus on HepB-BD vaccination, and the last two articles, which focus on TDF prophylaxis and HBV MTCT elimination. It also highlights the strengths and limitations of my thesis work, its potential impact on HBV elimination policies, and future perspectives.

5.1. Results in context

5.1.1. Implementation of HepB-BD

Cost and cost-effectiveness of implementing HepB-BD

In the first article, results showed that the economic cost of implementing HepB-BD in Senegal was US$759,406 in 2016 and US$867,311 in 2017, representing 0.37% and 0.41% of national government health expenditure, respectively. The economic cost of implementing HepB-BD per dose administered in Senegal were quite different from those found in the second article, where the analysis was conducted in the context of the Dafra health district in Burkina Faso. In Senegal, the cost in 2017 was US$1.85 per dose

administered for a 72% HepB-BD coverage, while in Dafra it ranged from US$0.5 to US$0.6 for coverage between 50% and 89.6%. While recognising the limitations of direct comparisons, these differences are worth exploring. Factors contributing to the differences include, firstly, methodological variations. In Senegal, data collection was based on real data, whereas in Burkina Faso, resources were collected hypothetically, based on previous implementation of other vaccines in the EPI. Moreover, certain cost categories, such as EPI management and supervision costs, were not included in Burkina Faso, while these categories accounted for approximately 17% and 11% of total costs in Senegal. Additionally, the data were collected in different years (2016 for Senegal and 2017 for Dafra) and in countries with different living standards. Adjusting for differences in living standards, using the 2016 purchasing power parity (PPP) conversion factor and the 2017 inflation rate to convert Senegal's costs to Burkina Faso's 2017 prices, the cost found in Senegal becomes US$1.6 for Burkina Faso, bringing it much closer.

An earlier study in Senegal evaluated the average annual cost of treating HBV-related cirrhosis and HCC at Dakar's main hospital in 2010 (225) and found an average annual cost of US$2,160 for a person with decompensated cirrhosis and US$1,035 for a person with HCC. Extrapolating these costs to the entire population yielded a total cost of US$28,760,830 for treating decompensated cirrhosis, representing 16% of the Senegalese government health budget in 2010, and US$9,918,284 for treating HCC, representing 5% of the government health budget. Using these total costs as a reference, the total cost of implementing HepB-BD represent 3% of the spending for treating decompensated cirrhosis and 10% of the budget for treating HCC, which seems at first glance to be a good value.

Results of the cost-effectiveness analysis of HepB-BD in the Dafra health district showed that implementation of HepB-BD was cost-effective at the cost-effectiveness threshold of US$335 in 2017. In terms of effectiveness, the results indicated that the implementation of HepB-BD in addition to HepB3 could lead to a reduction of less than 0.1% in DALYs compared to HepB3 administration from 6-8 weeks of age. Although this reduction may be underestimated due to the limitations of the Markov model in accounting for the herd immunity effect, even this modest reduction is significant in terms of preventing HBV-related complications, which would be a major burden on health care budgets, despite the late entry of patients into care. When comparing the effectiveness results with costs, the implementation of HepB-BD resulted in an ICER of US$18 per DALY averted, considering a discount rate of 3%. HepB-BD implementation remained cost-effective as long as the cost per administered dose was below US$1.55.

Generalisation to other West African countries

Regarding the costs of implementing HepB-BD, while the use of PPPs can help account for differences in living standards, it is important to note that differences in health system organisation and priorities across West African countries can also affect the implementation cost of HepB-BD. For instance, countries may prioritise monitoring activities at different degrees. Storage capacities may also differ, affecting transport costs,

with some countries having more storage capacity and requiring less transport expenditure, or vice versa.

In terms of effectiveness, the impact of implementing HepB-BD found in the cost-effectiveness analysis in Dafra are likely to be comparable in other regions of Burkina Faso or in other West African countries. The parameters used in the model to estimate effectiveness were derived from a broader perspective, based primarily on data from Burkina Faso or, where appropriate, other West African or sub-Saharan countries where the former were not available. In the model, adjusting the parameters to account for potential regional differences and varying the inputs to represent different contexts did not affect the cost-effectiveness results.

Another important consideration to consider before generalising the results is the likelihood of different cost-effectiveness thresholds in different countries. This threshold could affect the minimum implementation cost at which a country could afford HepB-BD. Among the 16 West African countries, ranked by GDP per capita from highest to lowest, Burkina Faso stands as the 12th. Using GDP per capita as a benchmark for defining cost-effectiveness threshold, most West African countries are likely to perceive the implementation of universal HepB-BD in their EPI as cost-effective. However, for countries with a lower GDP per capita, such as Niger or Sierra Leone, the likelihood that universal HepB-BD would be cost-effective may be lower.

5.1.2. Implementation of TDF prophylaxis in HBV-infected pregnant women

Cost, cost-effectiveness, and epidemiological impact of implementing HBV screening and TDF prophylaxis in antenatal care

In the third article, results showed that the implementation of HBV screening and TDF prophylaxis in antenatal care in Burkina Faso resulted in different costs according to the strategy evaluated. Strategies with simplified HBV screening procedures, such as HBcrAg-RDT or Prophylaxis for All, had lower implementation costs than HBV DNA or HBeAg strategies. The cost of implementation was US$3,959,689 for the HBcrAg-RDT strategy and US$4,141,206 for the Prophylaxis for All strategy.

Although the HBcrAg-RDT strategy was the least costly, its performance was more limited. In the cost-effectiveness model of the last article, results showed that the HBcrAg-RDT strategy was less optimal than the Prophylaxis for All strategy. With an ICER of US$60.9 per DALY averted, the Prophylaxis for All strategy not only dominated all other strategies, but was also cost-effective at a willingness-to-pay threshold of US$416.5. The Prophylaxis for All strategy resulted in the lowest number of perinatal infections and in the lowest costs due to the costs associated with the complications avoided. The cost-effectiveness results were not strongly influenced by variations in the costs of the screening test or TDF. Sensitivity analyses showed greater sensitivity to the rates of transition from compensated to decompensated cirrhosis, the effectiveness of HepB-BD in mothers with high viral loads, and the risk ratio of developing cirrhosis from MTCT

compared with horizontal transmission. However, in the Prophylaxis for All strategy, varying each parameter individually did not affect the cost-effectiveness of this strategy, and the probability of the Prophylaxis for All strategy being cost-effective was high (91.8%).

Despite current WHO recommendations focusing on high-risk pregnant women, results showed that pregnant women with a low viral load represented a significant proportion (90.3%) of HBV-infected pregnant women and should not be neglected despite their low risk of MTCT. The epidemiological model in the last article projected that implementation of a Prophylaxis for All strategy could accelerate global HBV elimination by 2117 and HBV MTCT by 2034, compared with implementation of HepB-BD alone, which could eliminate HBV by 2120 and HBV-MTCT by 2044 in Burkina Faso. In the epidemiological model, although the Prophylaxis for All strategy had a greater impact on reducing MTCT than on reducing HBV overall, the indirect effect was not negligible. Among all chronic infections averted, 75.8% were due to reduced MTCT, while 24.2% were linked to lower horizontal transmission. Similarly, 86.3% of deaths and 87.9% of DALYs averted were attributed to reduced MTCT, while 13.7% and 12.1%, respectively, were due to reduced horizontal transmission. It's important to note, however, that while a Prophylaxis for All strategy in combination with HepB-BD has been shown to be effective in reducing HBV transmission, it alone is not sufficient to achieve a rapid reduction in the overall HBV burden, as confirmed by an earlier global model (44). To significantly reduce the global burden of HBV, implementing a widespread screening programme and ensuring that all HBV-infected individuals receive appropriate care are critical steps (163).

Generalisation to other West African countries

The cost of implementation of the Prophylaxis for All strategy in antenatal care represented 0.64% of Burkina Faso's national budget. The allocation of health budgets to implement such strategies may differ in other West African countries. In the West African region, Burkina Faso ranks 4th out of 16 countries in terms of government health expenditure per capita (110). For countries like Benin or Togo, with government health expenditure per capita between 4 and 6 times less than Burkina Faso, the budgetary share for implementing these strategies could be higher. Obviously, the cost of implementing such strategies would also depend on countries' health system capacity and management.

In the cost-effectiveness model, given that the uncertainties were mainly due to parameters related to the natural history of HBV and that variations in costs had a minimal impact, results should be similar in other West African countries. Given the low ICER per DALY averted, implementation of the Prophylaxis for All strategy should also be cost-effective in the other West African countries.

In the epidemiological model, findings are compared to a scenario where HepB-BD is already implemented and coverage of HepB-BD, screening and TDF prophylaxis is 90%. If this coverage highlights the urgent need for widespread implementation of these interventions, the generalisability of these results to other West African countries also depends on the feasibility of meeting these conditions.

5.2. Strengths and limitations

5.2.1. Strengths

This work draws on the experiences of Senegal and Burkina Faso, both pioneers in combatting HBV transmission, to assess the costs and effectiveness of implementing HepB-BD, as well as antenatal screening of pregnant women and TDF prophylaxis.

The primary strength lies in the commitment to grounding the entire study in local data. The cost study in Senegal is the first to document costs associated with introducing HepB-BD at the national level in a Sub-Saharan African country using real-world data. This assessment, based on Senegal's actual experience of introducing HepB-BD in its EPI in 2016, effectively accounts for all costs associated with the introduction of HepB-BD beyond the vaccine itself. Data were collected in five regions of Senegal, covering 40% of the population, and capturing demographic, geographic and economic diversity, as well as varying levels of HepB-BD coverage. The large sample included two national-level agencies, five regional health offices, 15 district health offices, and 78 primary care facilities. Additionally, the data could be extrapolated to the national level using inverse probability weighting to account for the size of the regions.

Similarly, the study on the costs of implementing HBV screening and TDF prophylaxis in antenatal care in Burkina Faso is the first to provide comprehensive details on implementation costs. It goes beyond the costs of testing and TDF to include salaries, capital costs and other recurrent costs associated with the various activities involved in implementing such interventions. Costs were calculated nationally, taking into account all levels of the health system, including the central level, 13 regions, 70 health districts and an estimated 2,302 primary health care centres. For strategies requiring blood samples, such as HBV-DNA and HBeAg testing, costs were calculated taking into account the existing capacity in the country. Currently, these tests are only available at the regional level, requiring samples to be transported by courier - a practice already employed in the NeoVac trial and routine screening for diseases such as tuberculosis.

Concerning effectiveness, the study aimed to follow the natural history of HBV in West Africa, which has its own characteristics in this region. The cost-effectiveness study of implementing HepB-BD in Dafra incorporated parameters based on transmission probabilities primarily available in the country, extending to West Africa, sub-Saharan Africa, and Asia when African data were unavailable. The HBV model used to evaluate the effectiveness of TDF prophylaxis at the national level of Burkina Faso went a step further by estimating specific transition probabilities, such as age-specific horizontal transmission rates and rates of transition to compensated cirrhosis for Burkina Faso. This was achieved through a comprehensive calibration process that incorporated prevalence data available in the country, West Africa and sub-Saharan Africa. The HBV model is also the first to estimate MTCT elimination in sub-Saharan Africa, thanks to its stratification by transmission type. The stratification allowed the direct and indirect impacts of TDF

prophylaxis on MTCT and horizontal transmission to be estimated. The study also included sensitivity analyses to account for the range of uncertainty existing in the data, particularly regarding the rate of transition to the advanced disease stages and the effectiveness of HepB-BD in HBV-infected mothers, especially those at high risk of transmission.

5.2.2. Limitations

The primary limitation of this work relates to the generalisability of the estimated costs to other West African countries. Although the study showed that varying the implementation costs of HBV screening in pregnant women and TDF prophylaxis did not significantly affect the cost-effectiveness results, the cost-effectiveness of HepB-BD was more sensitive to variations in implementation costs. This increased sensitivity in the implementation of universal HepB-BD requires some caution in the generalisability of its cost-effectiveness in settings where implementation costs of HepB-BD may be higher and which may be constrained by more limited health budgets.

The second main limitation relates to the methodology used to estimate economic costs for the implementation of HBV screening and TDF prophylaxis. The assumption of technical efficiency in the Burkina Faso health system, with all capital equipment operating at 80% capacity and each primary health care facility meeting the staffing levels recommended by the Ministry of Health, is consistent with WHO guidelines for cost-effectiveness analysis. This assumption of technical efficiency ensure that "observed differences in the cost-effectiveness of interventions are due to the intrinsic characteristics of the intervention rather than to the extent to which capital and labour were used in the setting in which the interventions were evaluated" and to improve the comparability of results (197). However, the actual performance of the health system in Burkina Faso remains unknown, and the study was unable to collect information from a representative sample of primary health care facilities in Burkina Faso. This uncertainty could particularly affect data on midwives' salaries, which were based on national averages and may underestimate true costs, especially as some midwives may receive different bonuses, including a bonus for working in remote areas. In addition, the ongoing security crisis in Burkina Faso since 2015, which has particularly affected six of the 13 regions, introduces additional complexities, such as the closure of health facilities, internal population displacement, disruptions in supply chain management, increased loss to follow-up in antenatal care, and delays in childhood immunisation. These factors, which were not included in the analysis, may result in unanticipated financial costs for the effective implementation of strategies, and require a closer examination of existing health system failures.

A third main limitation is the lack of data on transition rates in the advanced stages of CHB infection in the specific context of West Africa. While mortality rates in people with HCC are known to be very high in sub-Saharan Africa (226), there is uncertainty about transitions to cirrhosis and from cirrhosis to other states. There is limited research on people in the advanced stages of CHB infection in sub-Saharan Africa. This lack of research is compounded by the high costs associated with diagnosis and treatment, along with low

coverage rates. These uncertainties contribute significantly to the overall uncertainty in the cost-effectiveness results, both for the implementation of HepB-BD and the implementation of TDF prophylaxis in HBV-infected pregnant women.

Another limitation is the lack of data on whether screening pregnant women and providing TDF prophylaxis to HBV-positive pregnant women would improve the assessment and uptake of long-term treatment for eligible women. Such improvements could reduce the risk of disease progression to advanced stages of HBV, but this was not accounted for in the model.

A final major limitation is the uncertainty surrounding the cost-effectiveness threshold in sub-Saharan Africa as a whole. While the threshold has been estimated to be half or less of GDP per capita in LMICs (174), this threshold has not been assessed using empirical evidence in the context of African countries. In addition, there is no guarantee that the societal willingness to pay for health improvement is linearly related to GDP per capita (227).

5.3. Public health implications

The findings of this thesis have several important public health implications for controlling HBV transmission and reducing the burden of the disease.

First, regarding the implementation of HepB-BD, if the WHO target is 90% coverage (12), there are still many countries in West Africa that have not yet implemented it, although it is a critical intervention to reduce the risk of MTCT and horizontal transmission during early life. The cost analysis conducted in Senegal showed that the resources needed to implement HepB-BD were largely already available within the health system, reducing the financial burden. This factor may be shared by other countries in West Africa that have implemented HepB-BD, but it is also possible that a similar situation exists in countries that have not yet integrated HepB-BD into their EPI. An assessment of the capacity of each country's health system would allow to verify budgetary feasibility. If in 2016, the government health budget in Senegal was US$14 per capita (101), this amount differs among the countries in West Africa. In comparison, among the West African countries that have implemented HepB-BD in their EPI, half had a higher or equivalent government health budget per capita, while among countries that have not yet implemented HepB-BD, only one in seven (Ghana) had a higher government health budget per capita. It should be noted that while countries may have the financial means to implement HepB-BD, assessing the cost-effectiveness of universal implementation is essential to ensure optimal resource allocation. The opportunity cost of implementing HepB-BD should be weighed against other potentially more cost-effective interventions. GAVI's initiative to fund HepB-BD implementation in financially constrained countries is a critical step, particularly given the severe impact of HBV in West Africa, especially among children. Furthermore, ensuring high HepB-BD coverage is essential to effectively protect newborns and reduce HBV transmission. While Senegal has high HepB-BD coverage and Burkina Faso achieved respectable coverage in its first year of implementation, disparities in coverage, as observed in The Gambia with an estimated

25% coverage within 24 hours of birth, raise concerns about the feasibility of interventions in certain settings. Suggested measures proposed to scale up HepB-BD coverage include implementation of national guidelines for administration of HepB-BD within 24 hours of birth, availability of an administration protocol in all health facilities, increased training of health personnel including community health workers, standardisation of immunisation reporting tools (immunisation cards, immunisation registers and data management systems) to include HepB-BD, administration of HepB-BD at the delivery ward, completion of newborn discharge checklist form, raising awareness among pregnant women and communities, providing home vaccination for pregnant women who cannot or do not want to go to a health facility, or using out-of-chain vaccination (73). Implementing these solutions also requires an efficient overall system in terms of health infrastructure, logistics and transport, availability of health workers, security or political stability. Systematic HBV screening in pregnant women also holds promise for improving HepB-BD coverage in newborns born to HBV-positive mothers, contributing to the overall success of the intervention.

Second, regarding HBV screening in all pregnant women and TDF prophylaxis in HBV-infected pregnant women, the results support a Prophylaxis for All strategy as an optimal, cost-effective approach that could eliminate MTCT in the fastest way, by 2034 for Burkina Faso when implemented in combination with HepB-BD. These results offer valuable insights in light of the 2024 WHO guideline updates, which now recommend extending antiviral prophylaxis to all HBsAg-positive pregnant women in settings where HBV DNA or HBeAg testing is unavailable (19). Although the Prophylaxis for All strategy has not yet been evaluated in real-world settings, its potential benefits require urgent evaluation of its safety and feasibility. While TDF has been shown to be safe in HBV-infected pregnant women with high viral load or co-infected with HIV, more research is needed on those with low viral load and no co-infection (24). However, as assessed in the model, the degree of harm of providing TDF prophylaxis to HBV-infected pregnant women with low viral load should be substantially high enough to make a Prophylaxis for All strategy suboptimal. The robustness of the cost-effectiveness under different intervention costs suggests that the implementation of a Prophylaxis for All strategy would likely be consistent with allocative efficiency in West Africa. In Burkina Faso, the Ministry of Health has already developed a plan for the triple elimination of MTCT of HIV, syphilis and HBV in 2021-2025, which already considers the possibility of treating all HBsAg-positive pregnant women to eliminate HBV transmission in young children. The implementation of such a plan can facilitate the rapid integration of HBV screening and TDF prophylaxis into antenatal care. The development of national guidelines that include these interventions is a critical step in the elimination of HBV MTCT. The implementation of HBV screening and TDF prophylaxis should also strengthen guidelines against HBV MTCT and improve HepB-BD coverage for infants born to HBV-infected mothers (228). The implementation of such strategy plays a crucial role in advancing progress toward the WHO target of achieving 90% coverage in the prevention of HBV MTCT (12). The implementation of a Prophylaxis for All strategy also raises the issue of postpartum follow-up of HBV-infected mothers identified through screening. It is essential that

national guidelines are enforced to ensure continuity of care for these women after childbirth. A small proportion of pregnant women should be eligible for long-term post-pregnancy treatment (24). Despite the incorporation of national recommendations, potential barriers related to accessibility may remain if the financial cost of follow-up is borne by the patient and health facilities qualified to provide care for HBV-infected patients are limited to centralised locations.

The results also highlight that the combined implementation of TDF prophylaxis, HepB-BD and HepB3 alone may not be sufficient to drastically reduce the HBV burden in the short term. In Burkina Faso, a significant proportion of the current HBV cases in the model were prevalent cases from several years ago. Widespread screening of the general population and treatment of eligible HBV-infected individuals are essential to achieve a substantial reduction in the burden of HBV.

Financing the implementation of health interventions is always an important issue, especially in LMICs. If political will is important for the implementation of such strategies, so is the will of external funding organisations, particularly in West Africa, where countries are heavily dependent on external financial support, and where this source of funding represents between 11% and 32% of current health expenditure, depending on the country (110). In the actual unequal balance of power between international funders and beneficiaries, the allocation of funds may not consistently align with local health priorities. To maximise global health gains and achieve greater equity and health systems development, a more efficient allocation of external funds to finance local health priorities is critical (229). HBV has been neglected for too long, despite its endemic status and harmfulness in West Africa. Now that the cost-effectiveness of strategies that could eliminate HBV MTCT in the next few years has been demonstrated, there is an urgent need to mobilise resources for the effective implementation of such strategies.

5.4. Perspectives

The study highlights that effective implementation of HepB-BD and TDF prophylaxis in West Africa has a high potential to be cost-effective in most countries. Although TDF prophylaxis was compared with HepB-BD in this analysis because it is the current practice in Burkina Faso, no one has yet attempted to study the effect of solely implementing HBV screening and TDF prophylaxis in pregnant women in settings that are struggling to effectively implement HepB-BD. Studies evaluating the efficacy of TDF prophylaxis against MTCT in the absence of HepB-BD are lacking. If HepB-BD is the recommended intervention against MTCT, it is important to acknowledge that in some settings, the challenges associated with timely implementation of HepB-BD may hinder the effective prevention of MTCT. Implementing TDF prophylaxis in antenatal care may offer a more flexible and feasible alternative, particularly in a strategy such as Prophylaxis for All, as it removes some of the logistical constraints associated with HepB-BD and is consistent with existing practices of screening and treating pregnant women for HIV during antenatal care, where TDF is also the first-line treatment regimen for HIV. However, real-world data on the acceptability and feasibility of a Prophylaxis for All strategy are lacking,

necessitating a thorough evaluation to ensure its suitability and adaptation to the local context.

There is also a growing desire to focus collective efforts on the triple elimination of MTCT of HBV, HIV, and syphilis in sub-Saharan Africa (12,230). These three diseases can be effectively prevented through appropriate screening and treatment during antenatal care (231). However, it is essential to assess the feasibility of implementing such a combined approach in real-world contexts.

Filling the gaps in understanding the evolution of the natural history of HBV in West Africa in the advanced stages of the disease, and particularly in the transition to and from cirrhosis is also important. Given the importance of these parameters for the effectiveness of all strategies, the availability of such evidence would help to refine estimates.

There is also a lack of evidence on cost-effectiveness thresholds in sub-Saharan Africa. Relying on appropriate thresholds is important to avoid investing in inefficient strategies that would result in net losses in population health. These thresholds should be assessed in the context of other local policy and programme options, with and without the inclusion of external funding sources.

In addition, the debate about the choice between universal and targeted HepB-BD is still ongoing (232). A study in North Korea compared different vaccination strategies, using the current vaccination schedule starting at 4-8 weeks of age, and showed that selective administration of HepB-BD was the most cost-effective option compared with universal administration of HepB-BD (233). However, there appears to be more support for universal HepB-BD in sub-Saharan Africa (188,232,234). The main arguments in favour of universal over selective HepB-BD include the complexity of guidelines if newborns were to be selected, the limited availability of HBV screening for mothers, and the low rate of attendance at four or more antenatal visits, all of which could lead to suboptimal coverage of HepB-BD and new perinatal HBV infections. In São Tomé, a study found that universal rather than selective implementation of HepB-BD is cost-saving, as administering HepB-BD to all infants was less costly than screening all pregnant women (188). In Cameroon, another study found that the incremental cost of universal HepB-BD administration was slightly higher than that of selective HepB-BD administration and was the preferred option as it was still below the Cameroonian cost-effectiveness threshold (235). They also found that a selective strategy was preferable when HepB3 coverage exceeded 80% and HBV prevalence was below 13%. However, all these studies assessed the importance of universal HepB-BD administration in a context where routine HBV screening of pregnant women is not standard practice. The potential introduction of TDF prophylaxis in antenatal care alongside HepB-BD in countries that have not yet included it in their EPI may change the outcome of whether universal or selective HepB-BD would be more cost-effective.

While efforts to prevent HBV MTCT have traditionally focused on mothers with high viral load or HBeAg, the transmission mechanisms in pregnant women with low viral load remain unclear. Investigating the characteristics of pregnant women with low viral load who transmit HBV is important to better tailor strategies for this population. A comprehensive understanding of the transmission mechanisms in these women could

refine interventions and allow more precise targeting of pregnant women at risk of transmission.

Understanding the underlying structural barriers within the health system is crucial for effective and sustainable implementation of preventive interventions for HBV MTCT. Recognising that a sole focus on specific disease interventions may lead to inefficiencies (76,236), a comprehensive approach that takes into account the complexity of the entire health system is imperative. Thinking through the whole system and its complexity could guide the adoption of strategies aimed at strengthening the health system as a whole, which in turn could strengthen the implementation and scale-up of disease-specific interventions. While various frameworks suggest the analysis of health systems through diverse dimensions like service delivery, health workforce, technologies, or governance, it is important to emphasise that the interdependence of these dimensions within a specific system is equally important to consider (76).

Besides, people are more aware of what HBV is and more likely to take HBV-preventive measures if they have a higher level of education and socio-economic status (204,237). In this regard, increased education and health empowerment, not only of pregnant women but also of their relatives, appear as critical factors in the success of HBV prevention and treatment interventions. However, there are very few studies on the impact of empowerment education on such success in the context of sub-Saharan Africa, highlighting the need for more research in this area (238).

Furthermore, the results underscore that relying solely on prevention of HBV MTCT and administration of HepB3 would not be sufficient for a significant short-term reduction in HBV burden. With the release of the 2024 guidelines (19), the assessment of treatment eligibility for people with CHB has been simplified to reduce reliance on multiple clinical examinations, which previously made the process more complex, particularly in LMICs (65). Some have advocated for a Treat All strategy for all individuals with HBV infection. Although simplification of treatment eligibility has been evaluated (239), it has not been evaluated with real-world data. Changes in eligibility criteria may influence the risk of HBV transmission and alter transmission patterns. If this proves to be the case, the cost-effectiveness of the interventions evaluated in this thesis would need to be reassessed.

Finally, research on HBV in West Africa has a long history, dating back to the early development of the HBV vaccine in the late 1970s. While significant progress has been made in controlling HBV transmission, particularly through vaccination efforts, interventions against HBV transmission, starting with the introduction of vaccination, have taken too long to implement. This experience prompts reflection on the role of researchers, and particularly in the context of global health research partnerships that bring together researchers and scientists from LMICs and HICs. Undoubtedly, such collaborations are beneficial, but recognising that challenges exist is crucial for the effective, successful and sustainable implementation of programmes or interventions aimed at improving the health of local populations. Since the beginning of HBV research in West Africa, many advancements have been made in research ethics and related regulations, with funders and ethics committees requiring in particular that research should address local needs. However, power imbalances and inequalities remain when

resources, access to funding and publication opportunities are concentrated in HICs. There are also challenges regarding the sustainability of studies and programmes in resource-limited areas once researchers have left, or problems in the implementation process of the partnership, such as communication barriers, diverging priorities, or differences in research cultures (229,240). Given these challenges, the decolonising global health movement encourages reflection on how current practices need to be changed to eliminate all forms of supremacy in global health practice, within countries, between countries and at a global level (241). There is a body of literature in nursing research that has introduced postcolonial feminist approaches to uncover and deconstruct the effects of dominant ideologies on subjugated knowledge and the processes by which social inequalities are perpetuated within the context of historical legacies from imperial times, intertwined with patriarchy (242). Adopting this approach has allowed for a comprehensive reflection and awareness of the detrimental consequences of unconscious behaviours, beliefs and biases left over from colonial times and patriarchal structure in the way care is provided, health reforms are implemented, or in the attitudes during nursing placements in developing countries (243–245). There are no universal principles for the implementation of decolonisation in global health, especially in research. While measures such as strengthening authorship policies, disseminating results, practicing open science, or facilitating knowledge transfer have been proposed to enhance ethics and equity in programmes or studies conducted in partnerships between HICs and LMICs (246–249), adopting a postcolonial feminist approach would also involve considering knowledge that is marginalised and voicing the viewpoints of those concerned by the interventions or programmes (242,250). The ultimate goal of decolonising global health is to advocate for health as a fundamental human right, both locally and globally, rather than viewing global health as an act of charity or saviourism, while finding solutions inclusively, with respect and humility (241).

5.5. Conclusion

HepB-BD and TDF prophylaxis are recognised as cornerstones in the fight against HBV MTCT, but the effective implementation of these strategies in West Africa remains a challenge, despite the high burden of HBV infection. Senegal and Burkina Faso are two countries that have taken decisive steps to combat HBV transmission. Through the lens of these two countries, I evaluated the implementation of HepB-BD and TDF prophylaxis interventions in terms of cost and effectiveness.

The findings of my thesis underscore several key points. First, the implementation of HepB-BD in Senegal proved to be financially feasible and sustainable, leveraging existing resources within the health system. However, while HepB-BD implementation in Burkina Faso demonstrated cost-effectiveness, its sensitivity to economic costs emphasises the need for evaluation based on each country's capacity to ensure allocative efficiency in their health systems. Universal implementation of HepB-BD may require external financial support from organisations such as GAVI. Furthermore, the use of an RDT such as HBcrAg emerged as a strategy that used fewer resources and was less costly for

identifying pregnant women with high viral load. However, despite the minimal risk of MTCT in pregnant women with low viral load, the significant number of affected women should be recognised as a public health concern that warrants attention. In this regard, a Prophylaxis for All strategy, including universal HBV screening of pregnant women attending antenatal care and TDF prophylaxis for all HBV-infected women, emerged as the dominant and cost-effective strategy in Burkina Faso, with the potential to eliminate HBV MTCT by 2034.

Given the urgency of the consequences of MTCT and the delayed implementation of strategies leading to avoidable HBV burden, these results strongly support the immediate implementation of HepB-BD in countries that have not yet adopted it, with an urgent need to accelerate funding processes by organisations such as GAVI that are committed to supporting HepB-BD implementation in countries facing financial constraints. In addition, an urgent evaluation of a Prophylaxis for All strategy for countries that have and have not implemented HepB-BD is necessary to explore the full range of solutions to achieve rapid elimination of HBV MTCT in West Africa.

Since the discovery of HBV, its severe impact on sub-Saharan Africa, particularly West Africa, has been well documented. If the WHO has made the fight against HBV a priority in its health agenda worldwide, this fight should be an even higher priority in West Africa where HBV is a devastating disease. This thesis has outlined optimal strategies to combat HBV MTCT that have the potential to eliminate it in the next few years. Urgent implementation of these strategies is essential in the context of West Africa to make this region HBV free.

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APPENDICES

A. Appendix to Chapter 5.1

Table A.1: Weighted average economic costs (in USD 2016) per activity and per study site in Senegal.

Activities	Regional Health Office			District Health Office			First-level health facilities			
							Health posts		Health centers	
	2015 (*n* = 5)	2016 (*n* = 5)	2017 (*n* = 5)	2015 (*n* = 15)	2016 (*n* = 15)	2017 (*n* = 15)	2016 (*n* = 66)	2017 (*n* = 69)	2016 (*n* = 9)	2017 (*n* = 9)
Initial training	662.3	0.0	0.0	812.4	0.0	0.0	0.0	0.0	0.0	0.0
Social mobilization	0.0	438.8	0.0	0.0	380.0	4.3	1.1	0.9	6.7	16.0
Vaccine administration (excluding the costs of vaccines and safety supplies)	0.0	0.0	0.0	0.0	53.4	79.1	202.6	259.1	675.7	869.2
Storage	0.0	230.0	227.8	0.0	61.9	74.4	21.9	27.3	54.4	105.5
Supervision	0.0	1051.9	1070.3	0.0	1110.1	1327.6	9.4	13.9	0.0	0.0
Distribution	0.0	168.9	168.9	0.0	24.1	29.7	3.7	5.1	2.8	4.0
Management	0.0	578.0	619.6	0.0	757.8	878.7	4.0	6.8	3.0	20.3
Waste management	0.0	6.7	6.7	0.0	1.6	1.9	0.0	0.0	0.0	0.0
Total	662.3	2474.3	2093.3	812.4	2388.8	2395.7	242.8	313.1	742.6	1015.1

B. Appendices to Chapter 5.2

Appendix B1: Population-based demographic survey of NéoVac study in Burkina Faso

The Neonatal Vaccination against Hepatitis B in Africa study (NéoVac) is a Hepatitis B vaccine birth-dose (HepB-BD) research programme started in 2015 in three African countries (Burkina Faso/Senegal/Madagascar) where the hepatitis B three-dose vaccination series (HepB3) is scheduled at 6, 10, and 14 weeks (Senegal and Madagascar) or 8, 12, and 16 weeks (Burkina Faso). Funded by the Total Foundation, the aim of the programme is to develop and/or evaluate a strategy to implement timely (i.e., within 24 hours of birth, as recommended by the WHO) administration of HepB-BD. It was designed in two successive steps. Step 1, was the formative phase, where epidemiological, anthropological, and economic data were collected from each country to develop a locally adapted, sustainable strategy for timely administration. Step 2 is ongoing and assesses the impact of this strategy on HBV infection reduction in infants.

In Burkina Faso, Step 1 was conducted in 2016-2017 in Dafra, one of the eight districts in the Hauts-Bassins Region. Implementing the Expanded Programme on Immunization (EPI) in Dafra is the responsibility of 16 primary health centres, half of which are located in rural areas. The district covers 337,112 inhabitants, 92% of whom live <5 kilometres from a primary health centre (159). As part of the NéoVac study, in February-June 2017, we conducted a population-based demographic survey in Dafra to estimate both the proportion of institutional deliveries and hepatitis B vaccination coverage. The survey targeted all women 15-50 years old living in areas covered by the district's eight rural health centres. At each health centre, a community sensitization meeting was organized to explain the survey's objectives. With the support of community health workers, a group of fieldworkers then visited all the households in 45 villages in the study zone. After obtaining informed consent, a trained fieldworker interviewed eligible women using a standardized questionnaire to collect information about their experience of pregnancy and child delivery, as well as the vaccination status of their children. The survey included 8,647 women. A detailed report of the population-based demographic survey is currently under preparation.

Appendix B2: Details about the risk of perinatal infection

We defined our model parameters and (primarily) used pooled African estimates from a systematic review conducted by Keane et al. (6), which summarized pooled risks of MTCT, stratified by maternal HBeAg status and provision of HepB-BD. Model parameters were as follows: the risk of MTCT in infants receiving HepB-BD whose mothers were HBsAg-positive and HBeAg-positive was 32.4% (95% CI: 10.2-58.3), based on three studies, and the risk in infants not receiving HepB-BD whose mothers were HBsAg-positive HBeAg-negative was 4.8% (95% CI: 0.1-13.3), based on five studies. However, we did not use the systematic review's pooled risk in children not receiving HepB-BD whose mothers were HBsAg-positive HBeAg-positive (36.6%, 95% CI: 8.3-69.9, based on three studies), as there was evidence for between-study heterogeneity (I^2=60.76%, p=0.08). Instead, we used an estimate from the only intervention study in sub-Saharan Africa (SSA) to date which assessed the effectiveness of starting hepatitis B vaccination at birth, compared with starting it at 6 weeks after birth (58.8%, 95% CI: 36.0-78.0[a]) (167). Neither did we use the Keane et al. systematic review's pooled estimate for the risk in neonates receiving HepB-BD whose mothers were HBsAg-positive and HBeAg-negative (all three studies identified in Keane et al.'s systematic review provided a 0% risk but the total number of study participants in this pooled estimate was too small (n=162) to precisely estimate such a low risk). We therefore used an estimate from another systematic review by Machaira M. et al., which was based on three Asian and one European study with a total of 1,992 participants (0.7%, 95% CI: 0.0-2.1%) (23).

[a] The 95% confidence interval was not reported in the original article by Ekra et al. We therefore used the interval estimated in the systematic review by Keane et al. based on the point estimate reported by Ekra.

Appendix B3: Details about the transition probabilities to simulate the natural history of CHB

- **Transition probabilities from 'susceptible to HBV infection' to 'horizontally-acquired HBV infection' health states**

We estimated the annual risk of horizontal transmission in children susceptible to HBV infection (i.e., who were not perinatally infected and who did not complete HepB3 schedule) using the prevalence of anti-hepatitis B core antibodies (anti-HBc) estimated by Peto et al. in a cross-sectional survey of Gambian adults aged 17 to 22 years who did not receive any hepatitis B vaccination (178). That study found an anti-HBc prevalence of 56.0% in these adults, indicating that 56.0% were exposed to HBV either perinatally or horizontally. In our study, we considered that among neonates positive for anti-HBc, 16 and 84% of cases were attributable, respectively, to mother-to-child transmission (MTCT) and horizontal transmission (43). Assuming that the annual risk of horizontal transmission remained the same from the age of 1 year to 20 years, we estimated the annual risk of horizontal transmission in those susceptible using the following formula:

$$1 - (1 - p_{anti-HBc} * 0.84)^{1/20}$$

- **Probabilities of transition between health states i) from 'new HBV infection' to 'Chronic HBV infection (CHB)' and ii) from 'CHB' to 'resolved infection'**

Age-specific transition probabilities from perinatally- or horizontally-acquired infections to chronic HBV infection (CHB) were taken from Edmunds et al. (7) The age-specific probability of seroconversion from positive HBsAg to negative HBsAg in people with CHB was taken from a study of the natural history of CHB in Gambia (43).

- **Probabilities of transition between health states: from 'CHB without advanced liver disease' i) to 'decompensated cirrhosis' or ii) 'hepatocellular carcinoma'**

Since the natural history of CHB differs according to the disease's mode of transmission, we estimated the transition probabilities from CHB to decompensated cirrhosis (DC), and from CHB to hepatocellular carcinoma (HCC) separately, for those who developed CHB through perinatal transmission and those who developed CHB through horizontal transmission. In order to obtain the estimate for the former, we first computed the numerator, which is the number of incident HBV-related DC (or HCC) cases due to MTCT in a given age group. We then estimated the denominator, which is the number of people who developed CHB through MTCT in a given age group. Finally, we divided the numerator by the denominator. This was repeated for those who developed CHB through horizontal transmission.

Numerator

First, we obtained the age-specific incidence rates of decompensated cirrhosis (DC) from any cause in Burkina Faso, provided by the Institute for Health Metrics and Evaluation (IHME) (180). Similarly, we obtained the age-specific incidence rates of liver cancer

from any cause in Burkina Faso, provided by the GLOBOCAN database (181). We then estimated the incidence rates of HBV-related DC and HBV-related HCC by applying the proportion attributable to HBV infection in SSA, which is 38% for cirrhosis (251) and 57% for primary liver cancer (252), respectively, to the age-specific incidence rates from any cause described above. Among the incident cases of HBV-related HCC, we considered that 62% developed HCC following cirrhosis and 38% developed it without cirrhosis (185). We then estimated the number of HBV-related DC and HBV-related HCC cases due to MTCT by applying the population attributable fractions (PAFs). The PAFs were calculated for the effects of maternal HBV serostatus (which is a proxy marker of MTCT) on HBV-related DC and HCC in people living with CHB using the following formula:

$$\frac{p\ (OR-1)}{p\ (OR-1)+1}$$

Where:

- p = proportion of CHB due to MTCT, which was estimated in a study in Gambia (0.16) (43) based on the prevalence of HBsAg and HBeAg among pregnant women, the risk of MTCT from HBeAg-positive mothers, the risk of MTCT from HBeAg-negative mothers, the coverage rate of HepB-BD, and the prevalence of chronic HBV infection in Burkina Faso. In our main analysis, p was 0.07.
- *OR* = odds ratio for the association between maternal HBsAg sero-positivity - which is a marker of MTCT - and the occurrence of cirrhosis or HCC in people with CHB. In our main analysis, OR was defined as being equal to 16 for cirrhosis cases and 13 for HCC cases (135).

Denominator

Using a HBsAg prevalence rate of 9% in Burkina Faso (158) and the proportion of CHB cases attributable to MTCT - estimated at 16% in SSA (43) - we obtained the number of people who developed CHB in Dafra through MTCT, and the number of people who developed CHB through horizontal transmission.

Transition rates

The age-specific transition rates from the CHB to cirrhosis or HCC health states were calculated separately for those who developed CHB through MTCT and for those who developed it through horizontal transmission, by dividing the number of HBV-related cirrhosis or HCC incident cases due to MTCT or horizontal transmission in a given age group, by the number of HBV prevalent cases due to MTCT or horizontal transmission in the same age group, respectively.

- **Probabilities of transition between health states: i) from 'decompensated cirrhosis (DC)' to 'HCC', ii) from 'DC' to 'death', and iii) from 'HCC' to 'death'**

Transition probabilities from DC to HCC and to death were taken from Peng et al. (30) who took into account the effect of antiviral treatment on the reduction of the risk of HCC and mortality. The annual probability of death in people who progressed to HCC

was estimated from survival data in patients with HCC who did not receive specific treatment for liver cancer in a multi-country observational study conducted in SSA by Yang et al. (183)

Appendix B4: Details about the costs of HBV immunization

The costs of HBV immunization were estimated separately for HepB-BD and for HepB3 using data from a micro-costing study conducted in May-June 2017 as part of the NéoVac project. The study documented vaccination-related organisation and resources use (with their corresponding related-activities, quantities and costs) over the period 2016-2017 to implement the Expanded Programme on Immunization (EPI) in the Dafra district. In addition, the study sites included i) the regional health office (Hauts Bassins) (which supervises the EPI and delivers vaccines to the Dafra district) and ii) the national level (specifically the National Medical Supplies Agency, which is in charge of vaccines storage before being dispatched to regional offices). Data were collected using standardized data collection tools, field-based observation in study sites, and semi-structured interviews with EPI officers at the four levels of the healthcare system (national, regional, district, and primary health facilities).

Activities involved in implementing HBV immunization and their respective costs were identified using the methods proposed by the WHO and the Bill & Melinda Gates Foundation (141,142). Specifically, resources were classified into the following activities: i) vaccine administration (including both vaccines and injection supplies and human resources), ii) vaccine storage, iii) vaccine distribution, iv) waste management, v) advanced vaccination strategies for boosting HepB-BD coverage (considered only in the base-case analysis and in the sensitivity analysis where the HepB-BD coverage rate was 95%).

For each activity, we distinguished between recurrent and capital costs and considered the following cost items:

- Vaccine administration: vaccines, injection supplies, and labour time
- Vaccine storage: cold chain equipment, and operating costs including energy consumption, cold chain maintenance, and labour time
- Vaccine distribution: vehicles, fuel for transportation, maintenance of vehicles, labour time, per diems, and transport allowances
- Waste management: incinerators and operating costs including energy consumption, incinerator maintenance, and labour time
- Advanced vaccination strategies for boosting HepB-BD coverage: per diems and transport allowances.

The total costs dedicated to the activities specifically related to HepB-BD and to HepB3 immunization were estimated using an economic approach which considered that each resource used for HBV immunization had an opportunity cost as it was no longer available for an alternative use. This was especially the case for costs related to human resources involved in vaccine administration, as well as for costs related to vaccine distribution and storage. The economic cost of human resources involved in vaccine administration was calculated as the amount of time allocated to the administration of HepB-BD or HepB3 multiplied by the mean hourly wage. The economic cost of HBV

vaccine distribution and storage costs were estimated by allocating a share of the total annualized cost of transportation and storage to HepB-BD or HepB3 using an allocation criterion based on their volume.

In the base-case analysis, we used an HepB3 coverage rate of 86.3%, based on the estimation obtained in the 2017 population-based demographic survey conducted in Dafra as part of the Néovac project. Additionally, we hypothesized an HepB-BD coverage of 89.6%, based on the rate of childbirths in health facilities in Dafra (assuming that every child born in a health facility was vaccinated at birth).

All capital costs included in the analysis were annualized by taking into account a 3% discount rate. Their purchasing cost was divided by an annualizing factor given by:

$$\frac{(1\ -discount\ factor)}{0.03}$$

where the $discount\ factor\ = \frac{1}{(1+r)^n}$ and n = expected lifetime of the equipment.

We computed the total cost for HepB-BD and HepB3 immunization in the district of Dafra by adding the respective costs of each activity (vaccine administration, vaccine distribution and storage, waste management and advanced vaccination strategies for boosting HepB-BD coverage (considered in the base-case analysis and in the sensitivity analysis where the HepB-BD coverage rate was 95%).

The total cost for HepB-BD and HepB3 was then divided by the estimated number of vaccinated neonates in 2017 (10,270 for the HepB-BD and 9,892 for HepB3 in the base-case analysis) in the district of Dafra, in order to obtain the HepB-BD and HepB3 unit cost per vaccinated child.

Methods for calculating the costs of each activity are presented in detail below.

a) Vaccine administration

- *Vaccines*

The number of vaccine doses supplied for one year was multiplied by the unit price per dose of vaccine to estimate the annual cost of vaccines. The unit price per dose of vaccine was provided by the UNICEF Supply and Logistics Division (2017). A rate of 30% was added to the unit price of vaccine to take into account freight expenses. The number of vaccine doses, n, was determined using the WHO guidelines (14):

$$n = i * b * d * (\frac{1}{1-w})$$

Where:
i = immunization coverage rate (in the main analysis: 89.6% for HepB-BD and 86.3% for HepB3)
b = birth cohort

d = number of doses per fully immunized child (one dose for HepB-BD, and three doses for HepB3)
w = wastage rate which was equal to 1% for single-dose vials, and 5% for 10-dose vials (format used for HepB3 vaccination)

- *Syringes*

The annual cost of syringes was estimated by multiplying the annual number of syringes needed for the birth cohort by the price per syringe (including freight expenses). The annual number of syringes, *s*, was estimated as follows:

$$s = n * \left(\frac{1}{1 - w}\right)$$

Where:
n = number of injections administered per year, which was equal to the number of vaccine doses supplied,
w = wastage rate, which was equal to 10% according to the WHO guidelines.

- *Safety boxes*

The annual cost of safety boxes was estimated by multiplying the annual number of safety boxes needed by the unit price of safety box (including freight expenses). The annual number of safety boxes needed for the birth cohort was estimated based on the annual number of syringes. Safety boxes each had a capacity of 100 syringes. A wastage rate of 50% was considered based on the WHO guidelines. The number of safety boxes needed, *sb*, was therefore estimated as follows:

$$sb = \frac{s}{100} * \left(\frac{1}{1 - w}\right)$$

- *Human resources*

Using observations of the time spent by healthcare workers to administer the BCG vaccine during immunization sessions in Dafra's health facilities, we estimated the time required to administer one BCG vaccine dose to be five minutes. From the number of hours worked per year (2,080 hours per year according to Burkina Faso law), we estimated the hourly wage of the staff in charge of immunization at 1,020 CFA franc. Hence, the economic cost of human resources, *l*, was estimated as follows:

$$l = \frac{5}{60} * n * hw$$

Where:
n = number of injections administered per year
hw = hourly wage of the personnel in charge of immunization

b) Vaccine distribution and storage

The system of vaccine distribution and storage in Burkina Faso involves all four levels of the healthcare as follows: the National Medical Supplies Agency stores vaccines before distributing them to Regional Health Offices, which in turn, distributes to Health Districts, the latter finally distributing them to primary health facilities (called Health and Social Promotion Centres).

- *Vaccine storage*

The economic cost of the HepB-BD (HepB3) cold storage for the Dafra district was calculated as follows: volume required for the HepB-BD (HepB3) vaccine divided by the volume (in litres) required for all EPI vaccines at the time of the study, multiplied by the annualized cost of the EPI vaccines cold storage for the Dafra district.
The volume (in litres) required for all EPI vaccines was calculated using i) the total number of doses required per year (equal to the vaccine coverage rate in the target population multiplied by the number of doses required per individual, the wastage rate, and a reserve stock of 25%), ii) the volume (in litres) used by each vaccine, iii) the number of vaccine doses supplied per year (which differs according to vaccine).
Similarly, the volume required for HepB-BD (HepB3) was calculated using i) the total number of doses required per year, ii) the volume (in litres) of one packaged vaccine dose (i.e. 2.8 cm^3 per dose/1000 litres for 10-dose vials of HepB-BD, 14.4 cm^3 per dose/1000 liters for single-dose vials of HepB-BD, and 2.75 cm^3 per dose /1000 liters for 10-doses vials of HepB3), iii) the number of vaccine doses supplied per year (i.e., six deliveries of supplies at each level).
We estimated that the additional volume required for the HepB-BD cold storage would be lower than the total volume currently available in the EPI cold chain (without the HepB-BD) and consequently, we considered that no additional equipment would be required for the HepB-BD storage.
The annualized cost of cold storage for all EPI vaccines included the following capital and recurrent costs: annualized costs of the cold storage equipment, cold storage maintenance and energy consumption (electricity, fuel, etc.), and salary costs of personnel in charge of the cold storage. First, the annualized cost of cold storage was estimated for each level involved in vaccine storage (i.e., the national, regional and district levels, as well as primary health facilities). Second, a share[b] of the annualized costs at the national and regional levels was allocated to the Dafra district. Third, the total HepB-BD (HepB3) cost of cold storage for the Dafra district was calculated as being equal to the costs of storage at the Dafra district + the cost of storage in each primary health facility in the Dafra district + the share of the annualized costs of storage at the central and regional levels.

- *Vaccine distribution*

[b] The share of the annualized costs of storage at the national and regional levels which was allocated to the Dafra district was calculated by dividing the volume used for the HepB-BD (HepB3) vaccines of the Dafra district by the total volume required for all EPI vaccines at each of these two levels.

The economic cost of the HepB-BD (HepB3) distribution for the Dafra district was calculated as follows: volume required for the HepB-BD (HepB3) vaccine divided by the volume (in litres) required for all EPI vaccines at the time of the study, multiplied by the annualized cost of the EPI vaccines' distribution for the Dafra district.
The volume required for the HepB-BD (HepB3) and that required for all EPI vaccines were calculated in the same way as for the cold storage (see above), except that we did not take into account a reserve stock of 25% for the distribution costs.
The annualized cost of distribution included the following capital and recurrent costs: annualized costs of vehicles, cold boxes and vaccine carriers, as well as annual costs related to vehicle maintenance, per diems, fuel, and salary costs of drivers. We used the same approach as that for storage costs to compute the distribution costs for the Dafra district. First, the annualized cost of distribution was estimated for each level involved in vaccine distribution (i.e., the national, regional and district levels). Second, a share[c] of the annualized costs at the national and regional levels was allocated to the Dafra district. Third, the total HepB-BD (HepB3) cost of distribution for the Dafra district was calculated as being equal to the costs of distribution at the Dafra district + the share of the annualized costs of distribution at the central and regional levels.

c) Waste management

As the Dafra district is not equipped with an operational incinerator, we estimated the economic cost involved for waste management as recommended in guidelines[16,17]. The annualized cost of waste management included the economic cost of an incinerator, considering an expected lifetime of 10 years and a discount rate of 3%, as well as annual costs related to incinerator maintenance (5% of the incinerator cost), energy consumption, and salary costs of personnel in charge of the waste management (considering that 30% of labour time was spent on incineration of EPI waste). The economic cost for the waste management of HepB-BD (HepB3) for the Dafra district was calculated as being equal to the volume required for the HepB-BD (HepB3) vaccine divided by the volume (in litres) required for all EPI vaccines at the time of the study, multiplied by the annualized cost of the EPI waste management for the Dafra district.

d) Advanced vaccination strategies for boosting HepB-BD coverage

Based on WHO guidelines (253), we assumed that advanced vaccination strategies for boosting HepB-BD coverage are needed to achieve a high HepB-BD coverage. To reach a coverage rate of 89.6% (base-case analysis), we considered community mobilization activities and reinforced communication. To reach a coverage rate of 95% (sensitivity analysis), in addition of community mobilization activities and reinforced communication, we considered notification of births.

[c] The share of the annualized costs of distribution at the national and regional levels which was allocated to the Dafra district was calculated by dividing the volume used for the HepB-BD (HepB3) vaccines of the Dafra district by the total volume required for all EPI vaccines at each of these two levels.

Methods for calculating the costs of each of this activity are presented in detail below.

- *Strengthening community mobilization and reinforced communication among pregnant women*

We collected information on the social mobilization activities already in place using interviews with nurses in charge of primary health centres. These activities included communicating the importance of antenatal care to pregnant women, providing child delivery services in primary health centres, and vaccination of young children. Missing from these declared listed activities was HepB-BD awareness raising for pregnant women and caregivers. Accordingly, we considered that such an activity would last half a day in each of the 32 vaccination sites covered by the 16 primary health centres in Dafra. In addition, in rural area, we considered a five-day period during which town criers would go around the district's villages to inform and mobilize communities before the awareness raising activity.
Resources considered for this activity included fuel for transportation and per diem payments for health workers and town criers.

- *Notification of births to health workers*

To achieve a 95% coverage rate of HepB-BD we considered that a system for notifying home births would be required to promote HepB-BD within 24 hours. Data to estimate the resources needed for this activity and their associated cost were collected from nurses in charge of primary health centres providing similar pregnancy monitoring activities. Community health workers play a central role to ensure high levels of pregnancy monitoring in their communities, and ensure post-natal check-ups for new-borns and mothers. Accordingly, we hypothesized that homebirth notification by community health workers could help administer HepB-BD within 24 hours. More specifically, we considered that home birth notification by community health workers would require the following:

- They would already be familiar to pregnant women in their community, and provide advice and information on the importance of pregnancy monitoring to the latter.
- They would be informed immediately after a home birth and would visit mothers.
- They would inform the primary health centre by SMS or another mobile phone service.
- They would encourage mothers to go to a primary health centre for a post-natal consultation and to vaccinate their babies.
- The mother and her new-born would be taken to the primary health centre at her expense or at her family's expense.

Resources considered for estimating the cost included per diem payments to community health workers for each home birth.

Appendix B5: Details about the costs of care for HBV-related decompensated cirrhosis and HBV-related HCC

To estimate the cost of care and treatment associated with DC and HCC, the types and quantities of resources used to treat patients with DC and HCC, as well as related unit costs were obtained from expert interviews at the Yalgado Ouédraogo University Hospital in Ouagadougou. Organisation of DC and HCC care in the Yalgado Ouédraogo University Hospital were representative of the current clinical practices in Burkina Faso as this University Hospital was both the main training centre of gastroenterologists and hepatologists in Burkina Faso and the main place to treat advanced liver diseases. Clinical practices follow WHO guidelines (65). The following cost items were included to estimate the costs of care for HBV-related DC and HBV-related HCC: diagnosis and pre-therapeutic clinical staging, hospitalizations, treatment and follow-up visits. We considered that people with CHB benefited from antiviral treatment only when they progressed to the DC health state and that those who directly developed HCC without passing through DC received only pain killers for a three-month duration, corresponding to the median survival time for HCC in SSA (183). No cost was associated with: i) CHB health state without advanced liver disease (as we assumed that people would not be diagnosed while asymptomatic), or ii) acute HBV infection (as people rarely seek modern medical care in West Africa when they develop a combination of fever and acute jaundice (254)).

Table B1 : One-way sensitivity analyses of the cost-effectiveness of implementing HepB-BD+HepB3 compared with HepB3 alone in the estimated birth cohort of Dafra, Burkina Faso (N=11,462)

Parameter	Low value of the range			High value of the range		
	Incremental cost	DALYs averted	ICER	Incremental cost	DALYs averted	ICER
Epidemiological parameters						
HBsAg prevalence in pregnant women	1666	25	67	-557	37	Cost-saving
HBeAg prevalence in HBsAg+ pregnant women	1361	26	52	-252	35	Cost-saving
Perinatal infection risk in mothers HBeAg-positive and with HepB-BD (%)	-1876	44	Cost-saving	3390	15	225
Perinatal infection risk in mothers HBeAg-positive and no HepB-BD (%)	3051	17	179	-1548	42	Cost-saving
Perinatal infection risk in mothers HBeAg-negative and with HepB-BD (%)	120	33	4	1423	26	55
Perinatal infection risk in mothers HBeAg-negative and no HepB-BD (%)	3036	17	178	-5650	65	Cost-saving
Susceptible to horizontally acquired infection (up to 20 years of age)	550	31	18	558	31	18
Annual heath state transition probabilities						
Acquired infection to chronic infection	1714	24	71	-162	35	Cost-saving
Acquired infection to death (fulminant hepatitis)	554	31	18	554	43	13
Chronic HBV infection to resolved infection (HBsAg seroconversion)	-845	36	Cost-saving	1587	26	61
Chronic HBV infection to decompensated cirrhosis	3140	20	157	-1697	40	Cost-saving
Chronic HBV infection to HCC	572	27	21	527	36	15

Decompensated cirrhosis to HCC	-783	30	Cost-saving	2105	32	65
Decompensated cirrhosis to death	-2458	28	Cost-saving	3551	34	105
HCC to death	332	30	11	584	31	19
Disability weights						
Symptomatic acute infection	554	31	18	554	31	18
Decompensated cirrhosis	554	31	18	554	31	18
HCC	554	31	18	554	31	18
HepB-BD coverage rate and costs						
HepB-BD coverage rate and total HepB-BD cost per administrated dose - 10-dose vial [a]	-238	17	Cost-saving	4624	33	152
HepB-BD coverage rate and total HepB-BD cost per administrated dose - Single-dose vial [a]	3116	17	182	12017	33	367
Persons at advanced stage of disease (DC and HCC) receiving care (%)	3333	31	108	554	31	18

[a] the total HepB-BD cost per administrated dose depended on HepB-BD coverage, therefore the two variables varied simultaneously.

C. Appendices to Chapter 5.4

Appendix C1: further information on the HBV model structure for Burkina Faso

1. Parameters

1.1. Demographic data

Demographic data used in the HBV model were from the United Nations (UN) (211). The initial population size of the model was derived from Burkina Faso's 1950 population statistics, stratified by age and sex. Population growth within the model was calculated based on variations in births, deaths and net migration at each time step. Age-, sex- and time-specific fertility rates for women aged 15-49 and mortality rates were available for a 5-year period. We used a linear interpolation to estimate values according to the time step of the model (6 months). Age-, sex- and time-specific migration rates were estimated from the survival ratio method defined by the UN (255).

1.2. Data used for calibration of the model

Table C1 presents data obtained from literature for the calibration of the model. We conducted a literature search on Pubmed, with a primary focus on Burkina Faso. We performed the search using the keywords "HBV prevalence Burkina Faso". Studies conducted only in blood donors and people living with HIV (PLHIV) were excluded. HBV prevalence data were classified into the following groups: general population, adult women (aged ≥15), including pregnant women, adult men, and children (aged <15). Among the retained studies, we also searched for age-specific data on HBeAg prevalence, anti-HBc prevalence, and proportion of HBV-positive pregnant women with high viral load. We supplemented the age-specific HBeAg prevalence with results from a study conducted in The Gambia for comparison (43). Given the limited data available on anti-HBc prevalence in Burkina Faso, we performed an additional literature search on Pubmed using the keywords "anti-HBc prevalence Africa". Studies limited to blood donors, PLHIV, and pregnant women were excluded, while studies from West Africa reporting age-specific anti-HBc prevalence were retained. Data on HBV-related mortality in West Africa were very scarce. Therefore, we used all-cause mortality in people with chronic HBV infection (CHB) estimated in a study in The Gambia (43), and HBV mortality projections from the Global Burden Disease (GBD) (13).

Table C1: Sources and types of data used for the calibration of the model

Author	Data collection year	Study population	Country	Prevalence (%)	Reference
HBV prevalence					
General population					
Lingani (2018)	1996 – 2001 2002 – 2006 2007 – 2011	General (Systematic review)	Burkina Faso	12.8 11.8 11.1	(158)

	2012 – 2017			11.1	
Diarra (2017)	2016	General	Burkina Faso	9.8	(256)
Diarra (2018)	2017	General	Burkina Faso	10.4	(257)
Kania (2013)	2011	General	Burkina Faso	11.5	(258)
Mulders (2004)	2002	General	Burkina Faso	21.3	(259)
Tao (2014)	2014	General	Burkina Faso	14.5	(260)
Adult women (≥15y)					
Diarra (2017)	2016	All adult women	Burkina Faso	8.16	(256)
Diarra (2018)	2017	All adult women	Burkina Faso	7.80	(257)
Tao (2014)	2014?	All adult women	Burkina Faso	11.60	(260)
Meda (2018)	2010	All adult women	Burkina Faso	7.80	(194)
Simpore (2006)	2003	Pregnant women	Burkina Faso	9.30	(261)
Sangaré (2009)	2005	Pregnant women	Burkina Faso	11.40	(262)
Ilboudo (2002)	1999	Pregnant women	Burkina Faso	12.04	(176)
Andernach (2014)	2007	Pregnant women	Burkina Faso	14.50	(263)
Nacro (2000)	1998	Pregnant women	Burkina Faso	10.70	(264)
Simpore (2006)	2004	Pregnant women	Burkina Faso	9.80	(261)
Yelemkoure (2018)	2014	Pregnant women	Burkina Faso	9.30	(265)
Adult men (≥15y)					
Diarra (2017)	2016	All adult men	Burkina Faso	11.96	(256)
Diarra (2018)	2017	All adult men	Burkina Faso	13.40	(257)
Tao (2014)	2014	All adult men	Burkina Faso	18.60	(260)
Meda (2018)	2010	All adult men	Burkina Faso	10.50	(194)
Children					
Andernach (2014)	2001	2-6y	Burkina Faso	12.2	(263)
Age-specific HBV prevalence in children					
Sanou (2018)	2015	1-9y	Burkina Faso		(266)
Lingani (2020)	2018	1-9y	Burkina Faso		(267)
Age-specific HBeAg prevalence					
Diarra (2017)	2016	General	Burkina Faso		(256)
Shimakawa (2016)	1974, 1980	General	Gambia		(43)
Anti-HBc prevalence					
Kania (2013)	2011	General	Burkina Faso	64.2	(258)
Age-specific anti-HBc prevalence					
Edmunds (1996)	1984, 1989	General	Gambia		(154)
Martinson (1996)	1993	6-18y	Ghana		(268)
Proportion of HBV-positive pregnant women with high viral load					
Guingané (2022)	2014–2019	Pregnant women	Burkina Faso	9.5	(204)

HBV mortality rate (per 100,000)					
GBD 2019 Hepatitis B Collaborators (2022)	1990 2015 2019	General	Burkina Faso	13.6 7.3 6.2	(13)
All-cause mortality in people with CHB (per 100,000)					
Shimakawa (2016)	2012-2013	General	Gambia	397.6	(43)

1.3. Model Parameters

Risk to rate conversion

Parameters presented as risks (or proportions) were considered as a cumulative proportion of persons for whom an event has incurred after one year. These risks were derived as a mean annual rate using the following relationship (131):

$$risk = 1 - e^{-rate}$$

$$\text{or} \quad rate = -\ln(1 - risk)$$

Transition rate from acute infection to HBeAg+

The average age-specific risks of developing chronic HBV infection within six months were described as follows (7):

$$\sigma(a) = \begin{cases} \exp(-0.645a^{0.455}), 6 \text{ months} < a < 100 \text{ years} \\ 0.885, a \leq 6 \text{ months} \end{cases}$$

To account for the higher risk of being HBeAg+ in males than in females (269), the sex-specific risk of becoming HBeAg+ after acute infection was estimated. Assuming equal proportions of men and women in the acute state, the risk of developing chronic HBV infection was distributed by sex as follows:

$$\sigma(a) = (\sigma_{g=m}(a) + \sigma_{g=f}(a))/2$$

The female-to-male ratio for the risk of developing chronic HBV infection was defined as follows:

$$\tau_{HBeAg+} = \frac{\sigma_{g=f}(a)}{\sigma_{g=m}(a)}$$

Thus, the sex-specific risk of becoming HBeAg+ in the six months following acute infection was then calculated as follows:

$$\sigma_{g=m}(a) = \frac{2\sigma(a)}{1+\tau_{HBeAg+}}$$

$$\sigma_{g=f}(a) = \tau_{HBeAg+} * \sigma_{g=m}(a)$$

Then, the annual sex- and age-specific rate from acute to HBeAg+, $f_g^{A\to EP}$, was obtained using the risk to rate conversion equation:

$$f_g^{A\to EP}(a) = -\ln(1 - \sigma_g(a))/0.5$$

Transition rate from acute infection to seroconversion/immune

People in the acute infection state who did not progress to the HBeAg+ state or die of fulminant hepatitis within six months were assumed to progress to the seroconversion/immune state. In a deterministic model, the number of people remaining in a health state can never be zero. Therefore, a 99.9% boundary was used as the proportion of people leaving the acute infection state within six months, and the annual transition rate from acute infection to seroconversion/immune state, $f_{g,z}^{A\to R}$, was calculated using the risk to rate conversion equation:

$f_{g,z}^{A\to R}(a) = -\log\left(1 - (0.999 - \sigma_g(a) - (1 - e^{-\mu_z^A}))/0.5\right.$

Transition rate from HBeAg+ to compensated cirrhosis

Transition rate from HBeAg+ to compensated cirrhosis was assumed to differ by age, mode of transmission, and sex (135,270,271), and was defined using the following function:

$$l(a) = \begin{cases} \theta_{a<10}\,\tau_{\text{cirrhosis}}\,\omega_{cirrhosis}\,a^{\gamma_{a<10}}, & a < 10 \text{ years} \\ \theta_{a\geq 10}\tau_{\text{cirrhosis}}\,\omega_{cirrhosis}\,a^{\gamma_{a\geq 10}}, & 10 \text{ years} \leq a < 100 \text{ years} \end{cases}$$

With $\theta_{a<10}, \theta_{a\geq 10}, \gamma_{a<10}, \gamma_{a\geq 10}$ being parameters calibrated.

Transition rate from HBeAg- to compensated cirrhosis

Transition rate from HBeAg- to compensated cirrhosis was assumed to differ by age, mode of transmission, and sex (135,270,271), and was defined from the following function:

$$m(a) = \begin{cases} \alpha_{cirrhosis,a<10}\tau_{\text{cirrhosis}}\,\omega_{cirrhosis}\,a^{\gamma_{a<10}}, & a < 10 \text{ years} \\ \alpha_{cirrhosis,a\geq 10}\tau_{\text{cirrhosis}}\,\omega_{cirrhosis}a^{\gamma_{a\geq 10}}, & 10 \text{ years} \leq a < 100 \text{ years} \end{cases}$$

With $\alpha_{cirrhosis,a<10}, \alpha_{cirrhosis,a\geq 10}, \gamma_{a<10}, \gamma_{a\geq 10}$ being parameters calibrated.

2. Differential equations

Table C2: Definition of health state labels used in the differential equations

Health state labels	Definition
S	Susceptible
A	Acute infection
EP	HBeAg+
EN	HBeAg-
C	Compensated cirrhosis
D	Decompensated cirrhosis
H	Hepatocellular carcinoma
R	Seroconversion/Immune

$$\frac{\partial S(a,t)}{\partial t} + \frac{\partial S(a,t)}{\partial a} = S(0,t) - \lambda(a,t)\,S(a,t) - v(a,t)\,S(a,t) - (m_g(a,t)\,S(a,t) - \mu_z^A A_z(a,t) - \mu_z^D D_z(a,t) - \mu_z^H H_z(a,t)) + n_g(a,t)\,S(a,t)$$

$$\frac{\partial A(a,t)}{\partial t}+\frac{\partial A(a,t)}{\partial a} = A_{inf}(a,t) \; - \; f_g^{A\to EP}(a)\,A(a,t) - f_{g,z}^{A\to R}(a)\,A(a,t) - \mu_z^A A(a,t) - m_g(a,t)\,A(a,t) + n_g(a,t)\,A(a,t)$$

$$\frac{\partial EP(a,t)}{\partial t}+\frac{\partial EP(a,t)}{\partial a} = f_g^{A\to EP}(a)\,A(a,t) - f^{EP\to EN}(a)\,EP(a,t) - \; f_z^{EP\to C}\,EP(a,t) - m_g(a,t)\,EP(a,t) + n_g(a,t)\,EP(a,t)$$

$$\frac{\partial EN(a,t)}{\partial t}+\frac{\partial EN(a,t)}{\partial a} = f^{EP\to EN}(a)\,EP(a,t) - f_z^{EN\to C}\,EN(a,t) - f^{EN\to R}(a)\,EN(a,t) - m_g(a,t)\,EN(a,t) + n_g(a,t)\,EN(a,t)$$

$$\frac{\partial C(a,t)}{\partial t}+\frac{\partial C(a,t)}{\partial a} = f_z^{EP\to C}\,EP(a,t) + f_z^{EN\to C}(a)\,EN(a,t) - f^{C\to D}C(a,t) - m_g(a,t)\,C(a,t) + n_g(a,t)\,C(a,t)$$

$$\frac{\partial D(a,t)}{\partial t}+\frac{\partial D(a,t)}{\partial a} = f^{C\to D}\,C(a,t) - f^{D\to H}\,D(a,t) - \mu^D\,D(a,t) - m_g(a,t)\,D(a,t) + n_g(a,t)\,D(a,t)$$

$$\frac{\partial H(a,t)}{\partial t}+\frac{\partial H(a,t)}{\partial a} = f^{D\to H}\,C(a,t) - \mu^H\,H(a,t) - m_g(a,t)\,H(a,t) + n_g(a,t)\,H(a,t)$$

$$\frac{\partial R(a,t)}{\partial t}+\frac{\partial R(a,t)}{\partial a} = v(a,t)\,S(a,t) + f_{g,z}^{A\to R}(a)\,A(a,t) + f^{EN\to R}(a)\,EN(a,t) - m_g(a,t)\,R(a,t) + n_g(a,t)\,R(a,t)$$

Where:

$$A_{inf}(a,t) = \begin{cases} A(0,t), & \text{z = MTCT} \\ \lambda(a,t)\,S(a,t), & \text{z = horizontal transmission} \end{cases}$$

3. HBV transmission

People could be infected with HBV through horizontal transmission or mother-to-child transmission (MTCT).

3.1. Horizontal transmission

Force of infection λ(a,t) was age- and time-dependent, and was expressed as follows:

$$\lambda(a,t) = B \times I(a,t)$$

Where:

B is the who acquires infection from whom (WAIFW) matrix, where contact rates were defined by age and assumed to be constant within the following age subgroups [0-2[, [2-15[, [15-100[(Table C3).

I(a,t) is the age- and time-specific proportion of infectious person in the population where:

$$I(a,t) = \frac{\int_0^{100} A(a,t) + \alpha EP(a,t) + EN(a,t) + C(a,t) + D(a,t) + H(a,t)\, da}{\int_0^{100} N(a,t)\, da}$$

Table C3: Structure of the WAIFW matrix used in the HBV model

		Age range of the infectious person (years)		
		[0-2[	[2-15[	[15-100[
Age range of the susceptible person (years)	[0-2[	β_1	β_4	β_5
	[2-15[	β_4	β_2	β_5
	[15-100[	β_5	β_5	β_3

Where:
β_i are the rates at which a specific susceptible person and a specific infectious person come into effective contact.

3.2. Mother-to-child transmission and number of newborns

MTCT was assumed to be perinatal. Babies were born either susceptible or infectious.

3.2.1. Mother-to-child transmission risks according to viral status of the mothers

In the model, MTCT risks were modelled in terms of viral load status, irrespective of HBeAg status. MTCT risks of mothers with high viral load (HVL) (δ_{HV}) and mothers with low viral load (LVL) (δ_{LV}) were defined as follows:

$$\delta_{EP} = \delta_{HV} \times p_{HV_EP} + \delta_{LV} \times (1 - p_{HV_EP})$$

and

$$\delta_{EN} = \delta_{HV} \times p_{HV_EN} + \delta_{LV} \times (1 - p_{HV_EN})$$

where δ_{EP} and δ_{EN} are the risks of MTCT in the absence of intervention if the mother is HBeAg positive and HBeAg negative, respectively. δ_{EP} and δ_{EN} are weighted averages of δ_{HV} and δ_{LV} with p_{HV_EP} and p_{HV_EN} serving as the weights. By substituting δ_{EP}, δ_{EN}, p_{HV_EP}, and p_{HV_EN} with the values of the base-case analysis, MTCT risks of HVL and LVL mothers in the base-case analysis were equal to:
δ_{HV} = 0.6736 and δ_{LV} = 0.0347

3.2.2. HBsAg screening in HBV-infected pregnant women in intervention strategies

Number of HBeAg+ and HBeAg- pregnant women screened for HBsAg:

$$EP_{testedHBsAg}(a,t) = test_cov_{HBsAg} \times EP_{g=f}(a,t)$$

$$EN_{testedHBsAg}(a,t) = test_cov_{HBsAg} \times (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t))$$

Number of HBeAg+ and HBeAg- pregnant women not screened for HBsAg:

$$EP_{notestedHBsAg}(a,t) = (1 - test_cov_{HBsAg}) \times EP_{g=f}(a,t)$$

$$EN_{notestedHBsAg}(a,t) = (1 - test_cov_{HBsAg}) \times (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t))$$

Number of HBeAg+ and HBeAg- pregnant women correctly diagnosed as HBsAg+:

$$EP_{testedHBsAg_pos}(a,t) = EP_{testedHBsAg}(a,t) \times sens_{HBsAg}$$

$$EN_{testedHBsAg_pos}(a,t) = EN_{testedHBsAg}(a,t) \times sens_{HBsAg}$$

Number of HBeAg+ and HBeAg- pregnant women falsely diagnosed as HBsAg-:

$$EP_{testedHBsAg_neg}(a,t) = EP_{testedHBsAg}(a,t) \times (1 - sens_{HBsAg})$$

$$EN_{testedHBsAg_neg}(a,t) = EN_{testedHBsAg}(a,t) \times (1 - sens_{HBsAg})$$

3.2.3. Assessment of eligibility for tenofovir prophylaxis in pregnant women diagnosed as HBsAg-positive in intervention strategies

- **HBV DNA, HBeAg, HBcrAg-RDT strategies: antiviral treatment in pregnant women at high risk of transmission**

The number of diagnosed pregnant women eligible for antiviral treatment is determined according to the sensitivity and specificity of the different tests.

Number of pregnant women with a high viral load diagnosed eligible for antiviral treatment:

$$elig_TDF_{HVL}(a,t) = sens_i \times test_cov_i \times (EP_{testedHBsAg_pos}(a,t) \times p_{HV_EP} + EN_{testedHBsAg_pos}(a,t) \times p_{HV_EN}))$$

Number of pregnant women with a low viral load diagnosed eligible for antiviral treatment:

$$elig_TDF_{LVL}(a,t) = (1 - spec_i) \times test_cov_i \times (EP_{testedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{testedHBsAg}(a,t) \times (1 - p_{HV_EN})))$$

Number of pregnant women with a high viral load not diagnosed eligible for antiviral treatment:

$$noelig_TDF_{HVL}(a,t) = (1 - sens_i) \times test_cov_i \times (EP_{testedHBsAg}(a,t) \times p_{HV_EP} + EN_{testedHBsAg}(a,t) \times p_{HV_EN}))$$

$$+ (1 - test_cov_i) \times (EP_{testedHBsAg}(a,t) \times p_{HV_EP} + EN_{testedHBsAg}(a,t) \times p_{HV_EN}) + EP_{notestedHBsAg}(a,t) \times p_{HV_EP} + EN_{notestedHBsAg}(a,t) \times p_{HV_EN}$$

Number of pregnant women with a low viral load not diagnosed eligible for antiviral treatment:

$$noelig_TDF_{LVL}(a,t) = spec_i \times test_cov_i \times (EP_{testedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{testedHBsAg}(a,t) \times (1 - p_{HV_EN})) + (1 - test_cov_i) \times (EP_{testedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{testedHBsAg}(a,t) \times (1 - p_{HV_EN})) + EP_{notestedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{notestedHBsAg}(a,t) \times (1 - p_{HV_EN})$$

With *i ∈{HBV DNA; HBeAg; HBcrAg}*

- **Prophylaxis for All strategy: antiviral treatment in all HBsAg+ pregnant women**

Number of pregnant women with a high viral load diagnosed eligible for antiviral treatment:

$$elig_TDF_{HVL}(a,t) = EP_{testedHBsAg}(a,t) \times p_{HV_EP} + EN_{testedHBsAg}(a,t) \times p_{HV_EN}$$

Number of pregnant women with a low viral load diagnosed eligible for antiviral treatment:

$$elig_TDF_{LVL}(a,t) = EP_{testedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{testedHBsAg}(a,t) \times (1 - p_{HV_EN})$$

Number of pregnant women with a high viral load not diagnosed eligible for antiviral treatment:

$$noelig_TDF_{HVL}(a,t) = EP_{notestedHBsAg}(a,t) \times p_{HV_EP} + EN_{notestedHBsAg}(a,t) \times p_{HV_EN}$$

Number of pregnant women with a low viral load not diagnosed eligible for antiviral treatment:

$$noelig_TDF_{LVL}(a,t) = EP_{notestedHBsAg}(a,t) \times (1 - p_{HV_EP}) + EN_{notestedHBsAg}(a,t) \times (1 - p_{HV_EN})$$

3.2.4. Number of newborns infected by mother-to-child transmission or susceptible

- **In the baseline scenario (HepB-BD and HepB3 only)**

Total number of babies born in the acute state:

$$A(0,t) = \int_{15}^{50} f(a,t) \times$$

$$[HepBBD_{cov} \times [(1 - eff_{HV_BD}) \times \delta_{HV} \times (EP_{g=f}(a,t) \times p_{HV_EP} + (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t)) \times p_{HV_EN})) + (1 - eff_{LV_BD}) \times \delta_{LV} \times (EP_{g=f}(a,t) \times (1 - p_{HV_EP}) + (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t)) \times (1 - p_{HV_EN})))] + (1 - HepBBD_{cov}) \times [\delta_{HV} \times (EP_{g=f}(a,t) \times p_{HV_EP} + (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t)) \times p_{HV_EN})) + \delta_{LV} \times (EP_{g=f}(a,t) \times (1 - p_{HV_EP}) + (A_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t)) \times (1 - p_{HV_EN})))]] da$$

- **In the intervention scenarios**

Total number of babies born in the acute state:

$$A(0,t) = \int_{15}^{50} f(a,t) \times [HepBBD_{cov} \times [TDF_{cov} \times [(1 - eff_{HV_BD_TDF}) \times \delta_{HV} \times elig_TDF_{HVL}(a,t) + (1 - eff_{LV_BD_TDF}) \times \delta_{LV} \times elig_TDF_{LVL}(a,t)]] + [(1 - TDF_{cov}) \times [(1 - eff_{HV_BD}) \times \delta_{HV} \times elig_TDF_{HVL}(a,t) + (1 - eff_{LV_BD}) \times \delta_{LV} \times elig_TDF_{LVL}(a,t)]] + (1 - eff_{HV_BD}) \times \delta_{HV} \times noelig_TDF_{HVL}(a,t) + (1 - eff_{LV_BD}) \times \delta_{LV} \times noelig_TDF_{LVL}(a,t)] + [(1 - HepBBD_{cov}) \times [TDF_{cov} \times [(1 - eff_{HV_TDF}) \times \delta_{HV} \times elig_TDF_{HVL}(a,t) + (1 - eff_{LV_TDF}) \times \delta_{LV} \times elig_TDF_{LVL}(a,t)]] + (1 - TDF_{cov}) \times (\delta_{HV} \times elig_TDF_{HVL}(a,t) + \delta_{LV} \times elig_TDF_{LVL}(a,t)) + \delta_{HV} \times noelig_TDF_{HVL}(a,t) + \delta_{LV} \times noelig_TDF_{LVL}(a,t)]$$

- **In all scenarios**

Number of babies born in the acute infection state by sex:

$$A_{g=f}(0,t) = A(0,t)/(\tau_{births} + 1)$$
$$A_{g=m}(0,t) = A(0,t) - A_{g=f}(0,t)$$

Babies born in the susceptible state:

$$S(0,t) = \int_{15}^{50} f(a,t) \times \Big(S_{g=f}(a,t) + A_{g=f}(a,t) + EP_{g=f}(a,t) + EN_{g=f}(a,t) + C_{g=f}(a,t) + D_{g=f}(a,t) + H_{g=f}(a,t) + R_{g=f}(a,t)\Big) - A(0,t)\, da$$

Number of babies born in the susceptible state by sex:

$$S_{g=f}(0,t) = S(0,t)/(\tau_{births} + 1)$$
$$S_{g=m}(0,t) = S(0,t) - S_{g=f}(0,t)$$

4. Calibration

4.1. Calibrated parameters

Table C4 provides an overview of the model parameters obtained through calibration, showing their estimated values derived from the best-fitting model. The calibration process involved a manual approach in which model estimates were visually compared with data of Table C1. Parameter values were iteratively adjusted by hand until fitting the model as closely as possible to the data. Starting parameter values were set arbitrarily to initiate the calibration process. Contact rates were calibrated assuming that $\beta_1 \geq \beta_2 \geq \beta_3$ and that $\beta_1 \geq \{\beta_4; \beta_5\}$. This assumption implied that children had higher effective contact rates, while adults had comparatively fewer effective contacts. In addition, the annual transition risk from acute infection to HBeAg+ was assumed to be lower in females than in males, with τ_{HBeAg+} assumed to be lower or equal to one. Transition parameters associated with the progression to cirrhosis were adjusted, ensuring that transition rates for individuals aged < 10 were lower than for those aged ≥10.

Table C4: Model parameters calibrated to data

Parameter	Description	Estimated value	Range for sensitivity analysis	Distribution
β_1	Contact rates	4.15×10^{-3}	$3.6 \times 10^{-3} – 4.4 \times 10^{-3}$	Beta(427.3, 1.0×10^5)
β_2	Contact rates	4.15×10^{-3}	$3.6 \times 10^{-3} – 4.4 \times 10^{-3}$	Beta(427.3, 1.0×10^5)
β_3	Contact rates	2.3×10^{-3}	$2.1 \times 10^{-3} – 2.5 \times 10^{-3}$	Beta(507.6, 2.2×10^5)
β_4	Contact rates	1.0×10^{-4}	$0.9 \times 10^{-5} – 1.1 \times 10^{-4}$	Beta(384.9, 3.8×10^6)
β_5	Contact rates	1.0×10^{-5}	$0.9 \times 10^{-6} – 1.1 \times 10^{-5}$	Beta(384.9, 3.8×10^6)
τ_{HBeAg+}	Female-to-male ratio of the annual transition risk from acute infection to HBeAg+ state	0.87	0.8 – 1.0	Beta(47.8, 7.1)
$\theta_{a<10}$	Factor of the rate at which HBeAg+ people aged <10 transit to compensated cirrhosis	0.004	0.001 – 0.008	Beta(5.1, 1272.6)
$\theta_{a\geq10}$	Factor of the rate at which HBeAg+ people aged ≥10 transit to compensated cirrhosis	0.01	0.005 – 0.015	Beta(15.9, 1575.6)
$\alpha_{c,a<10}$	Factor of the rate at which HBeAg- people aged <10 transit to compensated cirrhosis	0.0001	$1.0 \times 10^{-5} – 1.0 \times 10^{-3}$	Beta(0.1, 929.0)
$\alpha_{c,a\geq10}$	Factor of the rate at which HBeAg- people aged ≥10 transit to compensated cirrhosis	0.0001	$1.0 \times 10^{-5} – 1.0 \times 10^{-3}$	Beta(0.1, 929.0)
$\gamma_{a<10}$	Exponential factor of age for transitions to compensated cirrhosis when age <10	0.2	0.1 – 0.3	Beta(12.4, 49.5)
$\gamma_{a\geq10}$	Exponential factor of age for transitions to compensated cirrhosis when age ≥10	0.9	0.5 – 1	Beta(3.4, 0.4)

4.2. Graphical representation of the best-fitted model

4.2.1. Model fit to age-specific anti-HBc prevalence

Age-specific anti-HBc prevalence was particularly influenced by contact rates and pattern of the WAIFW matrix.

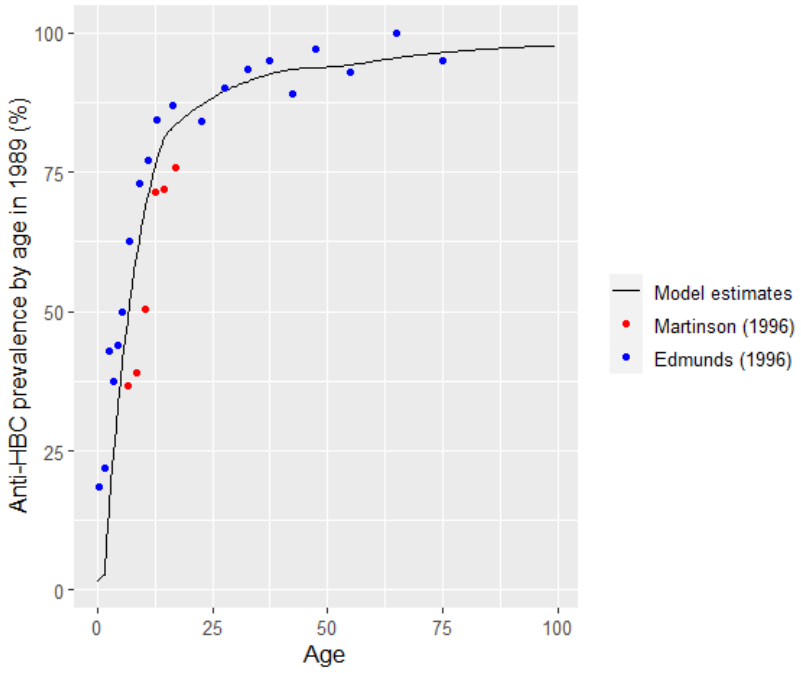

Figure C1 - Model fit to age-specific anti-HBc prevalence

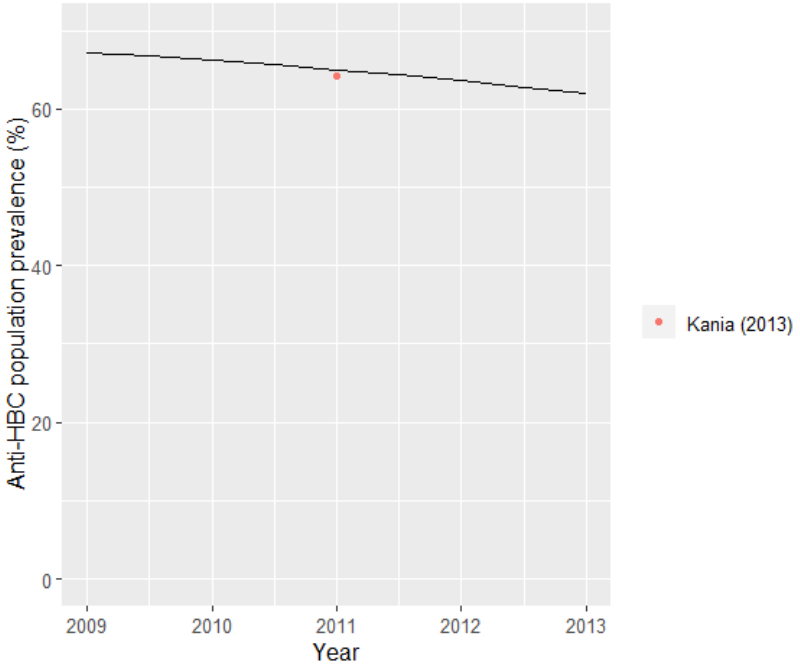

Figure C2 : Model fit to anti-HBc prevalence in the general population

4.2.2. Model fit to HBV prevalence

HBV prevalence was particularly influenced by contact rates and transition rates from HBeAg+ state. Adult prevalence was mainly determined by past childhood infection, contacts with infectious children (β_5) and HBV-related mortality.

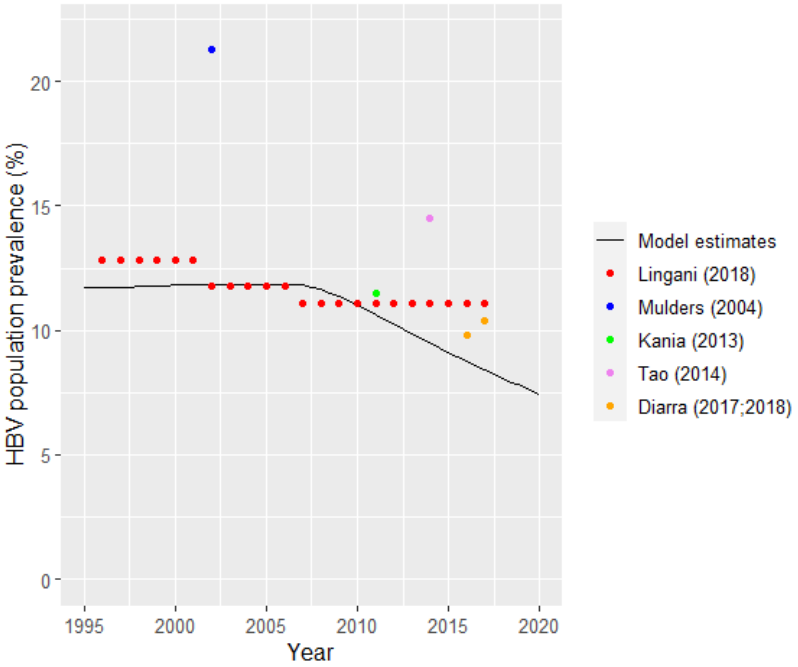

Figure C3: Model fit to HBV prevalence in the general population

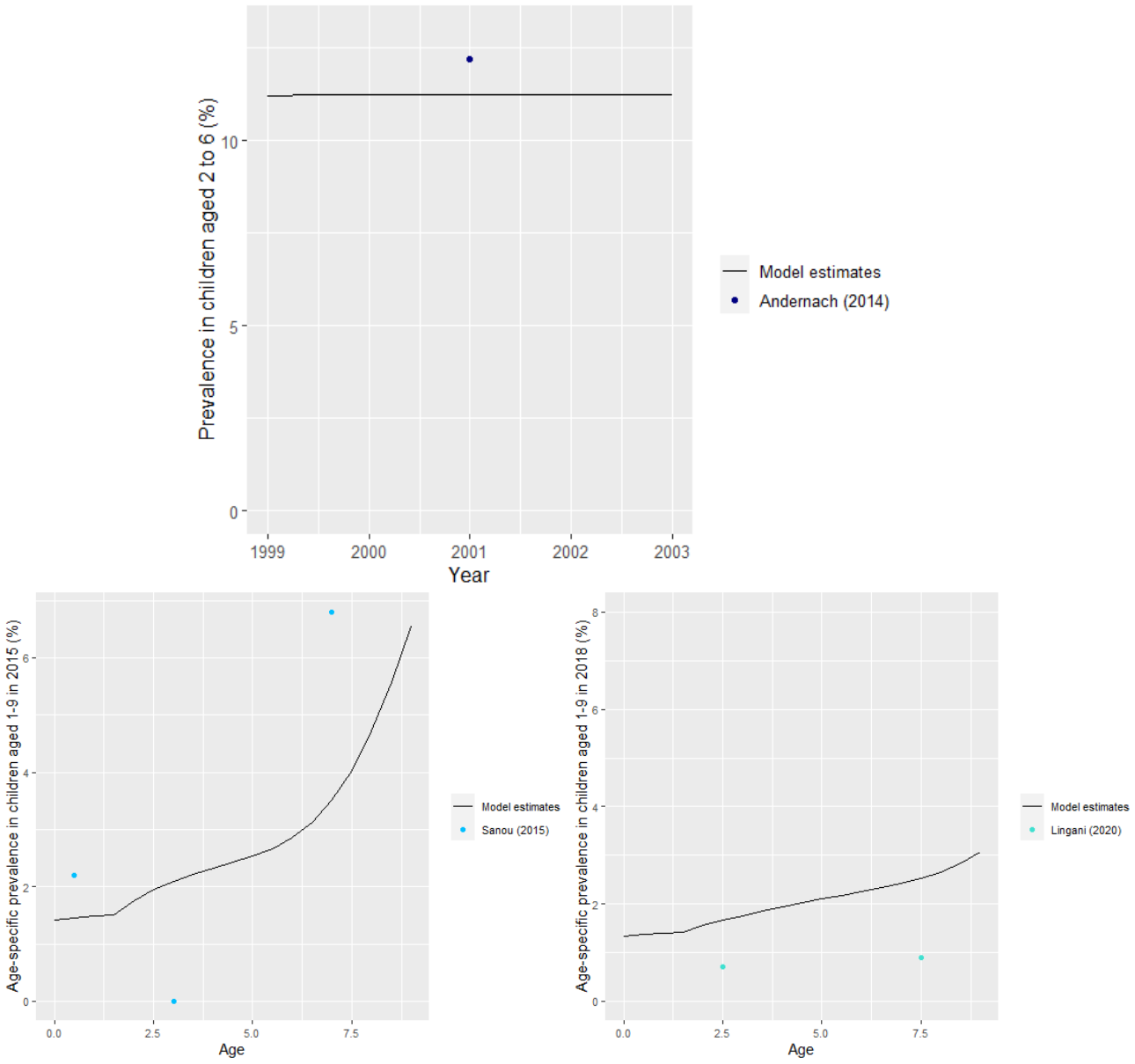

Figure C4 : Model fit to HBV prevalence among children

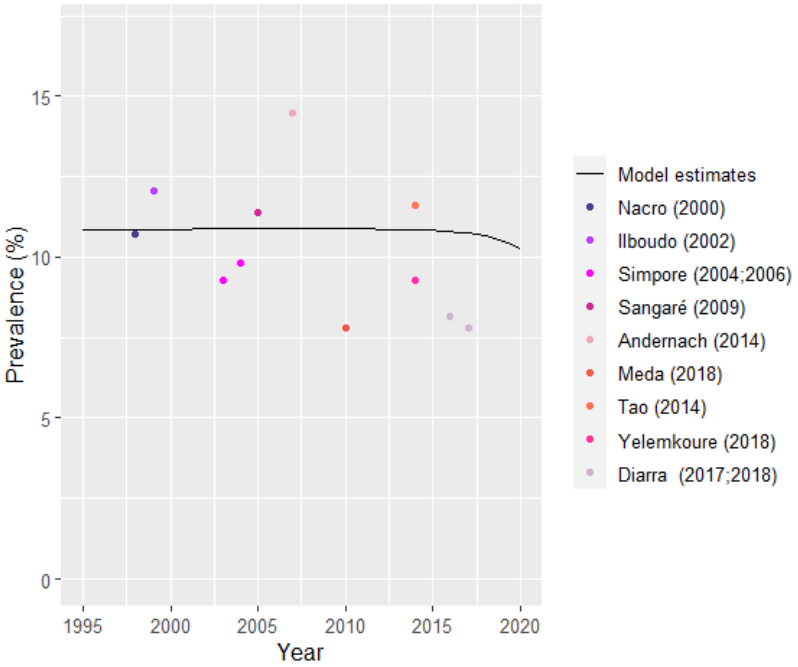

Figure C6: Model fit to HBV prevalence among adult women (aged ≥15)

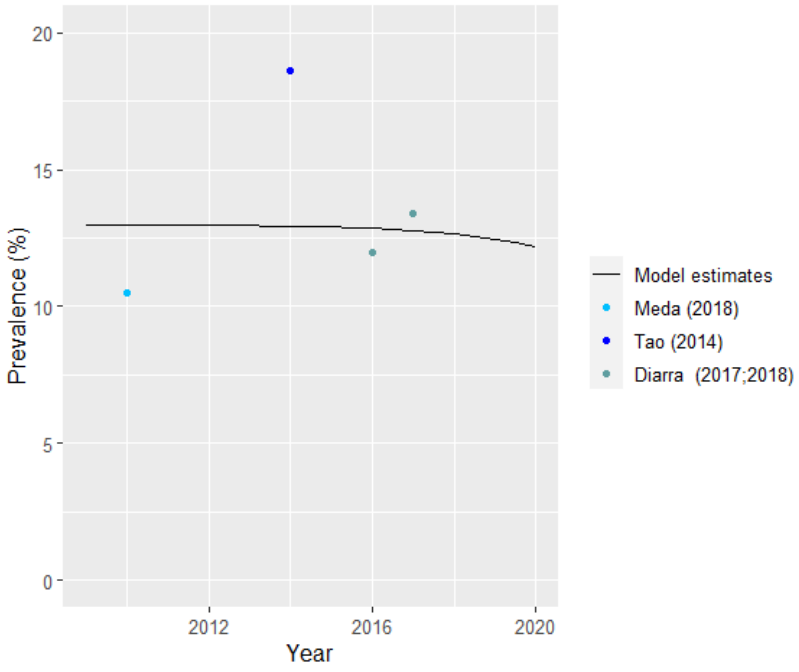

Figure C5: Model fit to HBV prevalence among adult men (aged ≥15)

4.2.3. Model fit to age-specific HBeAg prevalence among HBV infected individuals

Age-specific HBeAg prevalence was strongly influenced by changes in the rate from HBeAg+ to compensated cirrhosis.

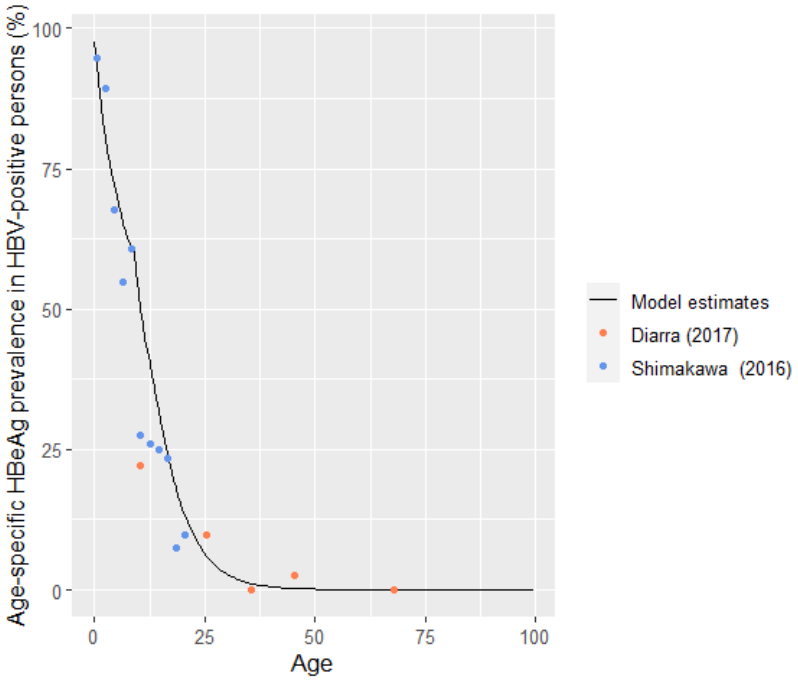

Figure C7: Model fit to age-specific HBeAg prevalence among HBV infected individuals

4.2.4. Model fit to age-specific proportion of HBV-positive pregnant women with high viral load

As with age-specific HBeAg prevalence, the age-specific proportion of HBV-positive pregnant women with a high viral load was strongly influenced by changes in the rate from HBeAg+ to compensated cirrhosis.

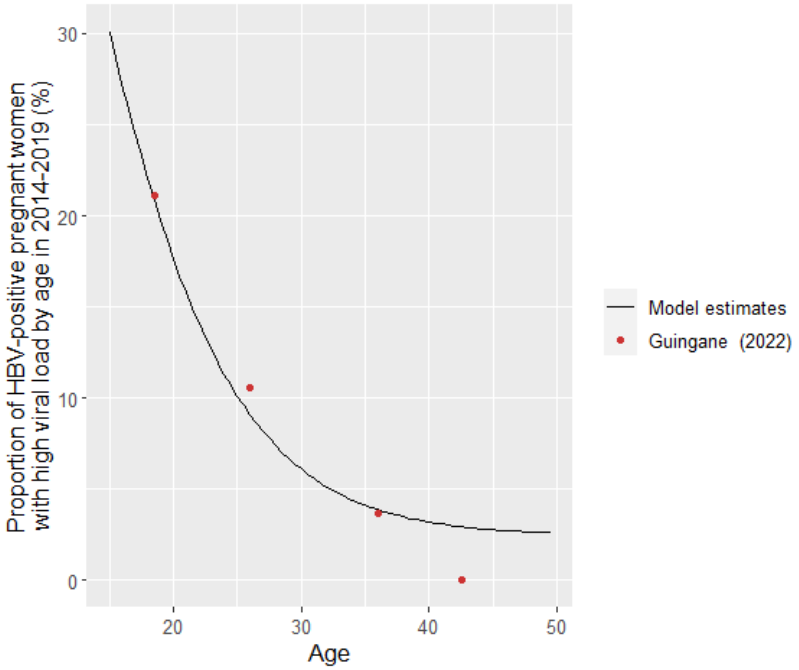

Figure C8 : Model fit to the age-specific proportion of HBV-positive pregnant women with high viral load

4.2.5. Model fit to HBV mortality

HBV mortality was mainly influenced by transition rates from HBeAg+ or HBeAg- to compensated cirrhosis.

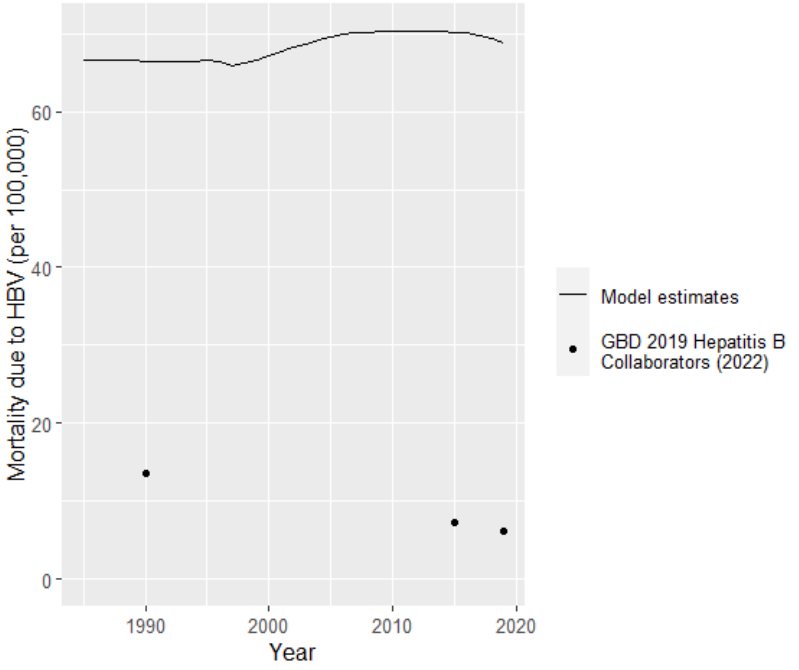

Figure C9: Model fit to HBV mortality rate (per 100,000)

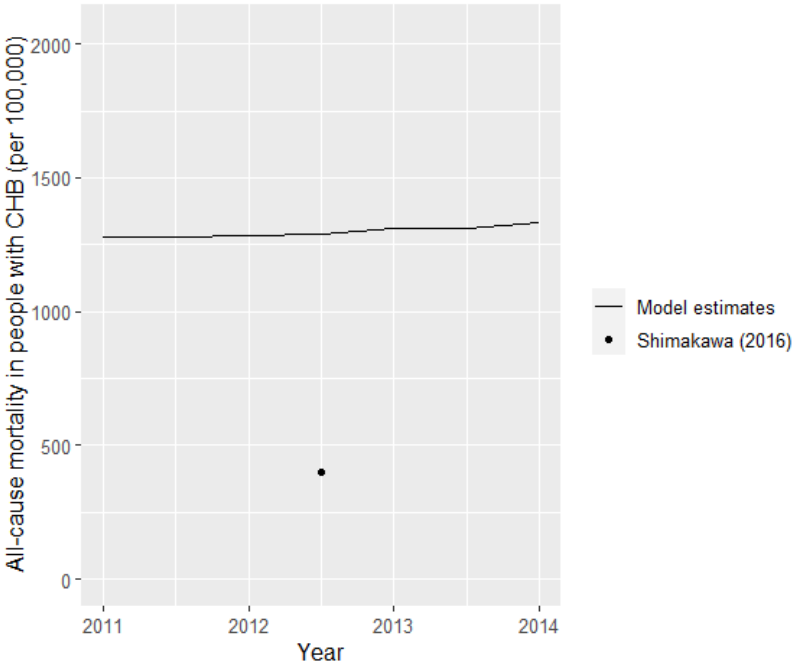

Figure C10: Model fit to all-cause mortality in people with chronic HBV infection (CHB) (per 100,000)