

**Complex interventions in complex health systems: Hepatitis B birth-dose  
vaccination programs in the African region**



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## Abstract

**Background:** Of the 296 million chronic carriers of hepatitis B virus (HBV) infection worldwide, the majority are found in the African and Western Pacific regions. Neonates who acquire the infection from their mothers (mother-to-child transmission or MTCT) carry a 90% risk of chronicity. To prevent serious liver complications such as liver cancer, cirrhosis, and premature death, the World Health Organization (WHO) recommends hepatitis B vaccination at birth, followed by vaccination during infancy. Despite the longstanding implementation of universal hepatitis B infant vaccination programs, the African region maintains the highest prevalence (2.5%) of chronic HBV infection among children  $\leq 5$  years of age. While optimal coverage of the hepatitis B birth-dose vaccine could avert further infections in this region, weak implementation and poor program performance have raised global concern. This study provides a comprehensive update on the status of HBV MTCT in Africa and explores how complex interactions between intervention and the health system may influence the performance of hepatitis B birth-dose vaccination programs in the region.

**Methods:** This qualitative systematic review study was conducted in two phases where phase 1 involved a scoping review and phase 2 the systematic review. The scoping review mapped current evidence on HBV MTCT and hepatitis B birth-dose vaccination programs in Africa. In addition, the scoping phase informed the development of an adapted systems-based logic model for assessing complexity in the design or causal pathway of hepatitis B birth-dose vaccination programs. For the qualitative systematic review, a Boolean search strategy was utilized to retrieve relevant peer-reviewed literature published between 2009–2022 indexed in PubMed, EBSCOhost databases, Scopus, and Web of Science, with supplementary searches conducted to identify any missed articles. No language restrictions were applied. Data extraction, synthesis and analysis were guided by the systems-based logic model tailored to systematic reviews of complex interventions.

**Results:** Findings from the scoping review provided compelling evidence on the risk of HBV MTCT in Africa, spurred by the considerable burden of HIV co-infections in the region. Despite this, only 15 WHO African member states have so far adopted hepatitis B birth-dose vaccination programs, with noteworthy inconsistencies in performance. Previous scoping reviews exploring the determinants of program success have been limited by the scanty representation of evidence from the African region. Furthermore, these reviews have failed to adequately address the complexities within the intervention or the multiple interactions across the intervention, the health systems and contexts which deliver them. Our systematic review search yielded 672 published records. Of these, 28 were judged to be eligible for inclusion. Among the 12 African states represented, the origin of evidence weighted highest in Nigeria ( $n=12$ ) and Senegal ( $n=5$ ). The performance of hepatitis B birth-dose vaccination programs across African states highlighted underlying complexities across multiple themes. The findings further emphasized the need for improved compliance with global recommendations when formulating national vaccine policies and guidelines; limitations of current vaccine supply chain systems; the need for renewed commitment towards intensified domestic investments complemented by donor support; ensuring capable and skilled cadres of health care workers, accurate and appropriate data collection and usage; expanded immunization services with outreach programs, and developments in maternal education and socio-economic status.

**Conclusion:** We highlight the complex interactions between hepatitis B birth-dose vaccination programs and the health systems that deliver them. We further demonstrate how these complex interactions contribute to the sub-optimal performance of hepatitis B birth-dose vaccination programs in the African region. By identifying sources of complexity at the intersection of hepatitis B birth-dose vaccination programs and health systems in Africa, we can better inform the design of immunization programs responsive to the contexts they are embedded in. Ultimately, the performance of hepatitis B birth-dose vaccination programs in Africa extends beyond vaccine supply and is further driven by a multiplicity of program-specific, system-wide determinants that should be considered if the region is to progress towards improved control of HBV MTCT.

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## Acronyms

HIV	Human Immunodeficiency Virus
HBV	Hepatitis B virus
UNICEF	United Nations International Children’s Fund
WHO	World Health Organization
WHO AFRO	World Health Organization African Region
MTCT	Mother-to-child-transmission
PMTCT	Prevention of MTCT
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBV DNA	Hepatitis B virus deoxyribonucleic acid
OR	Odds ratio
AOR	Adjusted odds ratio
COR	Crude odds ratio
UI/CI	Uncertainty interval/ Confidence interval
GHSS	Global Health Sector Strategy
SAGE	Strategic Advisory Group of Experts
EPI	Expanded Programme of Immunizations
BCG	Bacillus Calmette-Guérin
OPV	Oral Poliovirus Vaccine
LMIC	Low-and-middle-income-countries
Gavi/GAVI	Global Alliance for Vaccines and Immunization, the Vaccine Alliance
JBI	Joanna Briggs Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-ScR	PRISMA extension for Scoping Reviews
CASP	Critical Appraisal Skills Programme
MMAT	Mixed Methods Appraisal Tool
HCWs	Health care workers
TBAs	Traditional birth attendants
MoH	Ministry of Health
LBW	Low birth weight
VLBW	Very low birth weight
ANC	Antenatal care
MCH	Maternal child health
COVID-19	Coronavirus 2019

## Glossary

Mother-to-child-transmission	Transmission of disease-causing pathogen during the perinatal period (before, during or after birth). Common routes of infection include intra-uterine / transplacental, exposure during the birth process or breastfeeding. Mother-to-child-transmission (MTCT) is also frequently referred to as vertical transmission
Horizontal transmission	Transmission of disease-causing pathogen through direct exposure (e.g., infected blood) or indirect exposure (e.g., inhalation of infective materials) between individuals, and outside of the mother-child relationship in the peri-natal period
Hepatitis B surface antigen	The surface protein of HBV; its presence indicates chronic infection and risk of infectiousness
Hepatitis B e antigen	The e protein of HBV. This serological marker is a qualitative marker of HBV replication and relative infectivity.
HBV DNA levels	Levels of the viral genome that can be detected and quantified in serum. It remains the most important predictor of HBV MTCT but requires greater laboratory support. The HBeAg serves as a more accessible marker of infectivity in resource restricted settings.
Hepatitis B immune globulin	Human immunoglobulin containing high content of antibodies to HBsAg administered within 24 hours of life after exposure in order to provide passive immunity against infection
Universal vaccination	Universal vaccination refers to the strategy of administering the vaccine regardless of the risk of exposure
Selective or targeted vaccination	The exclusive administration of a vaccine only to those considered at high risk of acquiring the infection
Health systems	A network of organizations, people and actions with the foremost intent to promote, restore and maintain health <sup>1</sup>
Systems thinking	The attempt at acquiring an in-depth understanding of the linkages, relationships, interactions, and behaviors among elements that encompass the entire system <sup>2</sup>
System thinking lens	Using a systems thinking approach or perspective <sup>2</sup>
Complex interventions	An intervention likely comprising of multiple interacting components, following a non-linear causal pathway and may have different forms in different contexts <sup>3</sup>
System level building blocks	Key functions and components recognized as important determinants of health system performance <sup>1</sup>
System-wide effects	The full range of effects and potential synergies across multiple system level building blocks <sup>1</sup>
System-level intervention	Target one or multiple system level building blocks directly as opposed to an intervention targeting a health problem specifically. It is likely to affect all other building blocks in the system <sup>2</sup>

<sup>1</sup> World Health Organization. *Everybody's business: strengthening health systems to improve health outcomes: WHO's framework for action*. Geneva: World Health Organization (2007).

<sup>2</sup> de Savigny D, Adam T eds. *Systems thinking for health systems strengthening*. Alliance for Health Policy and Systems Research. Geneva: World Health Organization (2009).

<sup>3</sup> Petticrew M. When are complex interventions 'complex'? When are simple interventions 'simple'? *Eur J Public Health* (2011) 21:397–398.

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## PART A: REVIEW PROTOCOL

### Assessing complex interventions in complex health systems: Hepatitis B birth-dose vaccination programs in Africa

#### 1. Introduction<sup>1</sup>

Viral hepatitis mortality is ranked among the leading causes of global mortality, surpassing the global total number of deaths caused by malaria, tuberculosis and Human Immunodeficiency Virus (HIV) infection in 2015 (1). The five distinct types of viral hepatitis are A, B, C, D and E; predominantly hepatitis B and C are responsible for 95% of hepatitis related sickness and untimely deaths (2). Globally, majority of the disease burden is experienced by chronic hepatitis B sufferers (296 million) compared to those infected with chronic hepatitis C virus (58 million) (3). Epidemics associated with hepatitis B virus (HBV) are more prevalent in the World Health Organization Africa (WHO AFRO) and Western Pacific regions (1,3). Chronic infection with HBV is associated with serious liver complications including cirrhosis, end stage liver disease and liver cancer or hepatocellular carcinoma, which makes it a significant public health threat in endemic regions like Africa (1).

Chronic infection with HBV poses a 15–25% lifetime risk of acquiring liver cirrhosis or hepatocellular carcinoma, however the age of exposure is inversely proportional to the development of chronic infection (1,4). About 90% of babies born to mothers positive for hepatitis B surface (HBsAg) or e antigen (HBeAg), will become chronically infected (1). In contrast, exposure in adulthood through direct contact with infected blood or bodily fluids only carries a 5–10% chance of chronic HBV infection (1). Debates on the leading route of transmission driving the epidemic in Africa have previously favored horizontal transmission (5,6). However, a growing body of evidence now suggests an epidemiological shift towards HBV mother-to-child-transmission (MTCT) with increased prevalence found among pregnant women in several African states (4,7–18). This cannot be addressed outside of the disproportionate HIV epidemic within the region as Africa is home to 66% (25 million) of the global total of people living with HIV (3). Co-infection with HBV and HIV is common and associated with higher likelihood of HBV MTCT compared to HBV mono-infection (19).

Currently, while the Western Pacific region has more chronic HBV carriers (115 million or 5.9% [95% Uncertainty Interval (UI) 4.9–7.3] vs 82 million or 7.5% [95% UI 5.7–10.5] of the population in the WHO AFRO), the highest proportion of children younger than 5 years of age living with HBV are in Africa, estimated at 2.5% and surpassing the global prevalence of 0.9% [95% UI 0.7–1.6] (3). This suggests the region is on course to having one of the highest prevalence of chronic HBV carriers compared to any other region without urgent and intensive public health intervention. Several strategies for the prevention of HBV MTCT and early childhood acquisition of HBV are available globally (1) but the most widely practiced intervention in Africa has been the universal hepatitis B infant vaccination (4), maintaining relatively good coverage (71% in 2021) (20). However, the rising prevalence of HBV among children younger than 5 years of age could be an indication of ongoing missed opportunities for controlling HBV MTCT.

Universal hepatitis B birth-dose vaccination has been recommended as feasible and appropriate in low-and-middle-income countries (LMICs) in preventing HBV MTCT (1,21,22). This has been endorsed by the WHO for all member states since 2009 (23). It forms an integral part of the World Health Assembly's Global Health

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<sup>1</sup> The protocol presented in Part A has been reviewed and approved through the university systems. It is placed here to contextualize the journal-ready manuscript that follows in Part B.

Sector Strategy (GHSS) on viral hepatitis 2016–2021, aimed at elimination of viral hepatitis as a global public health threat by 2030 (24). Globally, 111 of 194 WHO member states have adopted universal hepatitis B birth-dose vaccination (25,26) with coverage rates reaching 42% in 2021 (20). Despite the commitment of the WHO Africa regional office to the GHSS goal (27), the uptake of hepatitis B birth-dose vaccination is slow with only 15 of 47 member states adopting it to date (28,29). This highlights possible challenges in meeting key global and regional targets. Furthermore, current coverage rates of hepatitis B birth-dose vaccine in the African region (17% in 2021) indicate poor program performance and raises questions on compliance to the timely administration required for effective prevention of HBV MTCT (20).

Identifying barriers to implementation and performance of hepatitis B birth-dose vaccination alone, though helpful, might be unlikely to provide a sustainable solution. It has been suggested that instead, attention should be given to the health systems delivering these services (30,31). Complexity can be viewed as a property of systems as they adapt to changes in local environments and is made up of other complex systems (human beings) (32). Acknowledging the influence of the complexity of health systems, may assist in optimizing its capabilities in supporting immunization programs. Interventions themselves have also been described as complex when possessing certain characteristics such as multiple interacting components and non-linear causal pathways (30,33). Some argue that instead the focus should shift to the complex interaction between the intervention and context (32,34) as well as noting how the researchers' pragmatic perspective in classifying an intervention as 'simple' or 'complex' could influence the research approach, in seeking either a simple or complex explanation (35).

To enhance our understanding of the concepts presented here, it will be important to scope the evidence base on the status of prevention of HBV MTCT and the suboptimal performance of the hepatitis B birth-dose vaccination program in the African region<sup>2</sup>. We posit that a systems perspective can uncover more complex explanations of the current performance of the vaccination program within the African context (35,36). Though previous reviews applied systems thinking in their evidence synthesis methods, both at a global (37) and regional (38) level, their findings possess limited representation of evidence from Africa, rendering generalizability problematic. Additionally, these previous evaluations have not fully appreciated the complexity of the intervention and system, or the diverse contextual underpinnings. This is likely to limit regional efforts to develop evidence-based, context specific public health interventions aimed at encouraging further adoption of universal hepatitis B birth-dose vaccination, and improvements in the performance of existing programs across Africa. Leaving this critical gap in the research evidence unaddressed could derail further progress towards achieving viral hepatitis elimination in Africa.

## 2. Literature review

A scoping review was conducted examining grey and peer-reviewed literature for relevant publications over the last two decades (*see Methods section*). Scoping reviews are appropriate for mapping what is known (and unknown) and set the foundation for informing systematic review studies (39).

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<sup>2</sup> For the purpose of this study, due to the WHO AFRO regional office commitment towards viral hepatitis elimination, we are operationalizing 'the African region/Africa' as the WHO does for WHO AFRO, comprised of 47 member states which excludes Egypt, Djibouti, Libya, Morocco, Somalia, Sudan and Tunisia which fall under the WHO Eastern Mediterranean region.

## 2.1 Status of MTCT of HBV infection in Africa

Areas of high endemicity are defined as having an HBsAg prevalence of  $\geq 8\%$ , moderate endemicity between 2–7% and low endemicity  $< 2\%$  in the general population (4,8). In Africa, an estimated HBsAg prevalence of 7.5% is recorded and it is considered home to approximately 28% of the world's 296 million chronic carriers (3). Historically, horizontal transmission was observed as driving the epidemic in the region (5), an assumption largely based on studies done in the 1980s (6). In recent decades a shift towards vertical transmission has been observed and is cited to be influenced by the HIV epidemic (5,19). Despite this influence and the change in HBV epidemiology in the region, strategies employed to control HBV infections depend almost solely on the 1992 WHO recommendation of universal hepatitis B infant vaccinations commencing at 4 or 6 weeks of life (7). In the absence of strategies targeting the interruption of vertical transmission, the cycle of chronic infection continues to fuel the morbidity and mortality caused by HBV-related cirrhosis and hepatocellular carcinoma (4,18). The *immaturity*<sup>3</sup> of the neonatal immune system increases the risk of viral replication and is suggested as the reason for delayed clearance of HBeAg (40), whereas acute infections in immunocompetent adults are likely to be cleared (18). In a meta-analysis of HBV infection among women in sub-Saharan Africa, HBeAg positivity was shown to increase the risk of vertical transmission to 38.3% compared to 4.8% in HBeAg negative women (41). Therefore, assessing the prevalence of HBV MTCT, the influence of HIV on the epidemiology of MTCT, and the strategies available for effective prevention of HBV MTCT in Africa is essential.

## 2.2 Growing prevalence of HBV MTCT in Africa

It is established that HBV MTCT depends on the presence of increased maternal infectiousness, correlating with HBeAg positivity (1). Historically, women of child-bearing age in Africa are considered to have relatively low prevalence of HBeAg (0.5%–3.5%) compared to that in South and South-East Asia (78%) (7,8,42). Growing evidence on the risk of HBV MTCT in the African region now suggests moderate to high endemicity of HBV infection among pregnant women and women of child-bearing age (4,7,8). A recent review by Breakwell *et al.*, identified 75 studies across 18 countries in Africa which report HBeAg positivity rate among pregnant women ranging from 3.3% in Zimbabwe to 28.5% in Nigeria (4). Studies assessing perinatal transmission in mother-child pairs by testing HBsAg and HBeAg prevalence in mothers and their offspring, have also found high rates of paired positivity (4,7,8), more so in those mothers positive for HBeAg or with high HBV DNA levels (4,7,8). It is worth noting that the risk of vertical transmission was found to remain present but reduced in 2-10% of HBeAg negative pregnant women within the region (7).

In a 2016 situational report compiled by the WHO Africa regional office, scarcity of evidence on chronic HBV infections and the risk of perinatal transmission in Africa were identified by 6 countries as one of the barriers to hepatitis B birth-dose introduction (43). Since then, the knowledgebase has developed and consistently points to a growing risk of vertical transmission within the region (9–18) as presented in **Table 1**. All studies report moderate to high HBV prevalence amongst pregnant women or women of child-bearing age. This is demonstrated by the high HBsAg prevalence among pregnant women in countries like Ethiopia (6.9%), Cameroon (7.7%), The Gambia (9.2%), South Sudan (11%) and Uganda (11.8%) (9–13). In comparison, moderate HBsAg prevalence rates have been reported among pregnant women in countries like the Republic of Congo (2.7%), Tanzania (3.9%), South Africa (4.5%) and Burkina Faso (4.8%) (14–16,18). There are evidently substantial variations in the burden of disease across countries, with the highest HBsAg prevalence rates noted in the Central and West African regions (7,44).

<sup>3</sup> Neonatal immune systems are adapted to the intra-uterine environment and thus considered immature when compared to that of an adult's immune system adapted to multiple microbial exposure in the external world

### 2.3 HIV-HBV co-infection and the risk of HBV MTCT in Africa

Accompanying the high burden of HBV infections in the region is the simultaneous burden of HIV infection. It is estimated that 18 million HIV positive women reside in Africa, of whom the majority are of child-bearing age (1). Given that those who are co-infected with HIV have a greater prevalence of HBeAg positivity, higher HBV DNA levels, and are subject to frequent reactivation of latent HBV infections, the risk of HBV MTCT in HIV co-infected pregnant women is increased compared to that in their HBV mono-infected counterparts (19). A global review of HIV-HBV co-infections cited a 4.6% midpoint prevalence of HBsAg from 23 studies involving pregnant women (45). Several studies in Africa have demonstrated the significant risk of vertical transmission of HBV in both HIV seropositive and negative populations (19,22,46). It is estimated that around 10% of HBV infected pregnant women are HBeAg positive regardless of HIV serostatus, although significant disparities exist in the risk of HBV MTCT within the region (47). This has been demonstrated by the high HBeAg positivity rates among HBsAg positive pregnant women across the region like the Democratic Republic of Congo (10%), Burkina Faso (11.5%), Uganda (14.9%), South Africa (16.6%) and Cameroon (26.1%) (9,12,15,16,18). In two South African studies comparing HBsAg positive pregnant women stratified by HIV status, no significant difference in HBeAg positivity between either group was found (19,22). The widespread availability of HBV-active antiviral therapy for those living with HIV in Africa, offers a plausible explanation for the similarities in prevalence of HBeAg positivity between HIV positive and negative pregnant women (1). Studies in Senegal, Zambia, Uganda, and Cameroon have demonstrated the protective effect of HBV-active antiviral therapy in preventing HBV MTCT (9,17,46,48). These available antiviral therapies like lamivudine, telbivudine, tenofovir, and entecavir have largely been proven effective and safe in reducing HBV viral loads in pregnant women (1). Unfortunately, access and procurement of these medications have been limited to HIV positive populations leaving HBV mono-infected pregnant women at greater risk for vertical transmission (1,6). This is further detailed in the section on strategies for prevention of HBV MTCT.

**Table 1.** Growing evidence on the risk of hepatitis B virus MTCT in Africa (Source: Author)

No.	Author, year	Setting	Study design	Population	Summary of key findings
1	Rashid <i>et al.</i> , 2007 (14)	Tanzania	Cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>Of 310 pregnant women, 3.9% tested HBsAg positive</li> <li>Of these none tested positive for HBeAg</li> <li>9.7% (30/310) tested positive for HIV with 25% of these women co-infected with HBV</li> <li>All HBsAg positive women tested negative for markers of acute infection suggesting chronic carriage</li> </ul>
2	Bayo <i>et al.</i> , 2014 (12)	Uganda	Cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>11.8% (47/397) tested positive for HBsAg</li> <li>Of these 14.9% (7/47) tested HBeAg positive</li> <li>An HIV positivity rate of 9.3% was found among pregnant women but no significant association between HIV and HBV seropositivity</li> <li>Those ≤20-year-old were 2.5 times more likely to test positive for HBsAg</li> </ul>
3	Howell <i>et al.</i> , 2014 (7)	Sub-Saharan Africa	Literature Review	Pregnant women and women of childbearing age	<ul style="list-style-type: none"> <li>Regional HBsAg prevalence ranges from 2.4%–25%</li> <li>Regional HBeAg prevalence ranges from 1–35%</li> <li>HBsAg prevalence within this population is highest in West Africa</li> </ul>
				Mother-child pairs	<ul style="list-style-type: none"> <li><b>Burkina Faso:</b> 37% of unvaccinated infants born to HBsAg positive mothers tested HBsAg positive. Among these 53.3% were from HBeAg positive mother's vs 27% from HBeAg negative mothers</li> <li><b>Ghana:</b> 8% of unvaccinated infants born to 219 HBsAg positive mothers tested HBsAg positive. 3% (6/219) of the HBsAg positive mothers transmitted HBV despite being HBeAg negative</li> <li><b>Tanzania:</b> 8% of unvaccinated infants born to HBsAg positive/HBeAg positive mothers tested HBsAg positive compared to 2% of infants born to HBsAg positive/HBeAg negative mothers at 8 months of age</li> <li><b>Nigeria:</b> 72% of unvaccinated infants born to HBsAg positive mothers had detectable HBV DNA in infant cord blood but only 24% of these tested HBsAg positive</li> <li><b>Cote d'Ivoire:</b> 32.5% of hepatitis B birth-dose vaccinated infants born to HBsAg positive mothers tested HBsAg positive on cord blood. 66.7% of these infants were born to HBeAg positive mothers and 26.9% were born to HBeAg negative mothers. No follow-up for vaccine effectiveness performed</li> <li><b>Malawi:</b> among vaccinated infants born to HIV-HBV co-infected mothers, 9.8% of infants tested HBsAg positive</li> </ul>
4	Sadoh <i>et al.</i> , 2014 (8)	Nigeria	Literature Review	Pregnant women and women of childbearing age	<ul style="list-style-type: none"> <li>Prevalence of HBsAg ranges from 8.3%–12.8%</li> <li>Prevalence of HBeAg ranges from 7.9%–62.5%</li> </ul>
				Mother-child pairs	<ul style="list-style-type: none"> <li>Two studies expressed a MTCT rate of 42.86% and 53.3% respectively</li> <li>In a third study, an HBsAg positivity rate of 13.2% correlated with a 6.9% HBsAg positivity rate among children. Further, 85% of seropositive children were born to HBsAg positive mothers while 77.7% HBeAg positive mothers had seropositive children</li> <li>In a fourth study, 29.4% of infants who presented for their hepatitis B birth-dose vaccination were HBsAg positive</li> <li>Most infants did not receive their vaccine within 24hrs post-birth</li> </ul>
5	Umare <i>et al.</i> , 2016 (11)	Ethiopia	Cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>Overall HBsAg positivity rate was 6.9%</li> <li>HBsAg prevalence was 8% in age group 20–24 years old</li> <li>The highest HBsAg prevalence rate (37.5%) was recorded among pregnant women who were health care workers</li> </ul>
6	Breakwell <i>et al.</i> , 2017 (4)	WHO AFRO	Literature review	Pregnant women	<ul style="list-style-type: none"> <li>Median prevalence of HBsAg ranging from 1.9% in Madagascar to 16.2% in Niger</li> <li>Median prevalence of HBeAg ranging from 3.3% in Zimbabwe to 28.5% in Nigeria</li> </ul>
				Mother-child pairs	<ul style="list-style-type: none"> <li><b>Cote d'Ivoire:</b> 38% of infants born to HBsAg positive/HBeAg positive mothers tested HBsAg positive at 6 weeks of life compared to 0% of infants born to HBsAg positive/HBeAg negative mothers</li> <li><b>Ghana:</b> 5.2% infants born to HBsAg positive mothers tested HBV DNA positive at 2 weeks of life</li> <li><b>Burkina Faso:</b> 32% of infants born to HBsAg positive/HBeAg negative mothers tested HBsAg positive within 24hrs of birth, compared to 29% of infants born to HBsAg positive/HBeAg positive mothers</li> </ul>




7	Chotun <i>et al.</i> , 2017 (18)	South Africa	Prospective cohort	Pregnant women	<ul style="list-style-type: none"> <li>• 4.5% (6/134) tested positive for HBsAg</li> <li>• Of those HBsAg positive, 16.6% (1/6) tested HBeAg positive</li> <li>• 33.3% (2/6) the HBsAg positive women had elevated HBV DNA levels, and were initiated on antivirals</li> <li>• All women tested negative for markers of acute infection, suggesting chronic infection</li> </ul>
				Infants	<ul style="list-style-type: none"> <li>• 100% of all infants tested (n = 4) had undetectable HBV DNA at mean age of 97 days of life</li> <li>• All infants had undetectable HBV DNA when followed up at mean age of 328 days of life/7 months</li> </ul>
8	Kirbak <i>et al.</i> , 2017 (13)	South Sudan	Cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>• 11% (31/280) tested positive for HBsAg</li> <li>• 28% of pregnant women had natural immunity, 2% immunity due to vaccination, 36% were indeterminate and 23% susceptible to infection</li> </ul>
9	Seremba <i>et al.</i> , 2017 (17)	Uganda	Cross-sectional	Mothers	<ul style="list-style-type: none"> <li>• Of 612, 8.7% (n = 53) tested positive for HBsAg</li> <li>• Of these women 18.9% (n = 10) also tested positive for HBeAg</li> <li>• 11.5% (9/80) of HIV infected individuals were co-infected with HBV</li> <li>• 55.6% of HIV/HBV co-infected pregnant women were on HBV-active antivirals</li> <li>• In total, 81.3% (65/80) of HIV positive mothers were on HBV-active antivirals</li> </ul>
				Infants	<ul style="list-style-type: none"> <li>• No HBsAg positive results at 6 weeks of life, on presentation for the first vaccinations</li> <li>• HBV MTCT was deemed to not make a substantial contribution to the burden of disease in Uganda</li> </ul>
10	Sone <i>et al.</i> , 2017 (9)	Cameroon	Prospective cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>• 7.7% (23/298) of pregnant women were carriers of HBV markers of infection</li> <li>• 26.1% (6/23) tested HBsAg positive/HBeAg positive</li> <li>• 1% (3/298) HIV/HBV co-infected and on antiviral therapy</li> </ul>
				Infants	<ul style="list-style-type: none"> <li>• 40% (8/20) of infants born to HBsAg positive mothers tested positive for HBsAg</li> <li>• Of these, 75% (6/8) were HBsAg positive/HBeAg positive</li> <li>• 14.3% (2/14) born to HBsAg positive/HBeAg negative mothers tested positive for HBsAg</li> <li>• 100% of infants born to HIV/HBV co-infected mothers on antivirals tested HBsAg negative</li> <li>• 50% (10/20) tested negative for HBsAg with the presence of HBe-antibodies</li> </ul>
11	Bittaye <i>et al.</i> , 2019 (10)	The Gambia	Cross-sectional	Pregnant women	<ul style="list-style-type: none"> <li>• Prevalence of HBsAg was 9.2% (39/424)</li> <li>• Among pregnant women who were likely to be vaccinated, HBsAg prevalence was 2.3% vs 13.7% among those likely unvaccinated</li> </ul>
12	Guingané <i>et al.</i> , 2020 (15)	Burkina Faso	Prospective cohort	Pregnant women	<ul style="list-style-type: none"> <li>• 4.8% (75/1580) tested HBsAg positive</li> <li>• 11.5% (7/61) of HBsAg positive tested HBeAg positive</li> <li>• 7.5% (4/53) of HBsAg positive samples had elevated HBV DNA levels and initiated antiviral treatment</li> </ul>
				Infants	<ul style="list-style-type: none"> <li>• Infants received hepatitis B birth-dose vaccination and subsequent hepatitis B infant vaccinations according to recommended schedule</li> <li>• Of the infants available for follow up (n = 40), 100% tested negative for HBsAg at 7 months of age</li> </ul>
13	Thompson <i>et al.</i> , 2021 (16)	Democratic Republic of Congo	Cohort	Pregnant women	<ul style="list-style-type: none"> <li>• Of 4016 pregnant women, 2.7% (n = 109) tested positive for HBsAg</li> <li>• 11% of available samples (n = 90) were identified as high risk for MTCT. Of these 90% were HBeAg positive and 50% had elevated HBV DNA levels</li> <li>• 90% of these high-risk pregnant women received antiviral therapy</li> <li>• Only 1% (n = 1) was co-infected with HIV</li> </ul>
				Infants	<ul style="list-style-type: none"> <li>• 68% (60/88) of infants received hepatitis birth-dose vaccination</li> <li>• Of the available sample (n = 53) who presented at 24 weeks for follow up testing, 100% tested negative for HBsAg</li> </ul>

**Note:** HBV - hepatitis B virus; MTCT- mother to child transmission; HBsAg - hepatitis B surface antigen (indication of HBV infection); HBeAg - hepatitis B e antigen (marker of increased infectivity); HBV DNA - hepatitis B deoxyribonucleic acid (genetic matter and marker of increased infectivity); HBV-active antivirals – therapy used to suppress elevated viral loads; antibodies to HBeAg - marker of recovery from HBV infection

## 2.4 Strategies for prevention of MTCT of HBV in Africa

Safe and effective strategies are available for prevention of HBV transmission to neonates and infants from as early as the *in utero* stage, see **Table 2**. Antenatal screening has the advantage of identifying those at risk for HBV MTCT who can then be timely linked to appropriate care such as HBV-active antiviral prophylaxis. During antenatal visits, pregnant women should also be provided with information on HBV infection, the lifetime risk for chronic liver disease associated with HBV MTCT, and the prevention strategies available to them and their babies including hepatitis B birth-dose vaccination (22,47). Unfortunately, for some African countries, antenatal screening for HBV infection can be expensive and impractical if laboratory facilities are not situated close to the antenatal clinics (22,47). Despite this, feasibility for antenatal screening for HBV infection has been proven in South Africa (18), and cost-effectiveness demonstrated in Namibia as part of their prevention of HBV MTCT package (5). Feasibility is considered more achievable if HBV antenatal screening is integrated with existing HIV and syphilis point-of-care testing infrastructure (18,49).

**Table 2.** Prevention strategies for MTCT of HBV per key population groups (Source: Author)(4,6,7,21)

Prevention of mother-to-child transmission of hepatitis B virus infection			
Target population	 Pregnant women	 Neonates	 Infants
HBV MTCT prevention strategies	<ul style="list-style-type: none"> <li>• <b>Antenatal screening</b> for markers of infection (e.g., HBsAg, HBeAg, HBV DNA)</li> <li>• <b>HBV-active antiviral prophylaxis</b> administered between 28–32 weeks gestation to women at high risk for MTCT</li> <li>• <b>Education</b> on HBV infection, risk of MTCT &amp; chronic liver disease, and prevention strategies including birth-dose vaccination</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Universal or selective hepatitis B birth-dose vaccination</b> within 24 hours of life</li> <li>• <b>HBIG</b> administered to HBV exposed infants within 24 hours of life</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Universal hepatitis B infant vaccination</b> at *6, 10, and 14 weeks of life</li> </ul>
<p><b>Note:</b> HBV- hepatitis B virus; MTCT- mother to child transmission; HBsAg- hepatitis B surface antigen (marker of infection); HBeAg- hepatitis B e antigen (marker of infectivity); HBV DNA- hepatitis B deoxyribonucleic acid (genetic matter to quantify high viral load); HBIG- hepatitis B immunoglobulin (providing passive immunity); *Most widely used schedule in the WHO AFRO (4,50)</p>			

Antiviral prophylaxis offered in the third trimester to at-risk pregnant women has been proven to suppress maternal viral loads and decrease the likelihood of HBV MTCT (6,18,51). The HBV-active antiviral prophylaxis is safe, effective, and readily available in Africa (47,51). Despite this, access for HBV mono-infected pregnant women in the region appears limited given that there are no subsidized HBV-active antiviral programs (47,51). To the contrary, HBV-HIV co-infected pregnant women have access to lifesaving prophylaxis through established HIV treatment programs (47,51). The fixed combination dosage of HBV-active antivirals prescribed for the treatment of HIV is subsidized, leaving resource-constrained settings having to pay higher prices for treatment for HBV mono-infection (51). This calls for further interventions at the policy level to improve access

to low-cost antiviral prophylaxis for HBV mono-infected pregnant women as part of HBV MTCT prevention strategies (47).

For neonates born to HBV infected women, hepatitis B immunoglobulin (HBIG) offers further benefit in preventing HBV MTCT by providing passive immunization to HBV exposed neonates particularly when administered within 24 hours of birth (5). According to the international guidelines from key special interest groups like the American, and the European Association for the Study of Liver Disease, HBV exposed infants should receive both HBIG and a birth-dose of the hepatitis B vaccine (52,53). In high income countries the standard of care includes both interventions (49,51). In low resource settings, the high cost and the logistics of cold storage and administration of HBIG limit its acceptability as an HBV MTCT prevention strategy (5,6,18,47,49,51).

Although all strategies have shown effectiveness (22,54), universal hepatitis B birth-dose vaccination has demonstrated both high cost-effectiveness (1,21) and suitability for the African context (22). Unlike HBIG, the hepatitis B birth-dose vaccine is stable outside of the cold chain (55), and therefore improves accessibility in LMICs (56). It also presents a feasible opportunity for integration into existing infrastructure like the Expanded Programme of Immunizations (EPI) and prevention of HIV MTCT packages (16). Hence universal hepatitis B birth-dose vaccination offers an equitable solution to accelerating regional progress towards achieving global elimination of hepatitis B by 2030. Between 75–95% of vertical transmissions can be prevented by vaccinations alone if the hepatitis B birth-dose is followed by completion of at least 3 doses of the hepatitis B vaccine in infancy (21). The global coverage of hepatitis B birth-dose vaccination has steadily improved from 5% in 2000 to 42% in 2021 (20), although this is well below the GHSS 2030 target of 90% (24). Among all 6 WHO regions, the coverage rate of the hepatitis B birth-dose in Africa is significantly dismal at 17%, compared to 78% in the Western Pacific; 59% in the Americas; 51% in South-East Asian; 43% in European; and 33% in the Eastern Mediterranean regions (20). This suboptimal coverage is independent of the number of African states who have adopted the universal hepatitis B birth-dose vaccination (28,29,57). Currently only 15 member states offer the intervention: Algeria, Angola, Botswana, Cabo Verde, The Gambia, Mauritania, Namibia, Nigeria, São Tomé and Príncipe, Senegal, Cote d'Ivoire, Benin, Equatorial Guinea, and Ethiopia all have universal hepatitis B birth-dose policies in place, whereas Mauritius currently provides selective hepatitis B birth-dose vaccinations to HBV exposed neonates (4,28), *see Figure 1*. It is important to note that while other African states have not adopted a national universal hepatitis B birth-dose vaccination policy (28), they may provide targeted hepatitis B birth-dose vaccination to infants born to HBeAg positive mothers in certain sub-regions or health facilities, as per national guidelines for prevention of MTCT or as part of research studies conducted in order to motivate for national implementation (16,18). This could lead to an underestimation of the true hepatitis B birth-dose vaccination coverage in Africa in comparison to what is officially reported to the WHO (20,58). Without universal and optimal HBV screening programs to identify all at-risk pregnant women, these targeted approaches may encounter significant challenges. Nevertheless, the low implementation of universal hepatitis B birth-dose vaccination within Africa is concerning given the growing risk of HBV MTCT in this region.

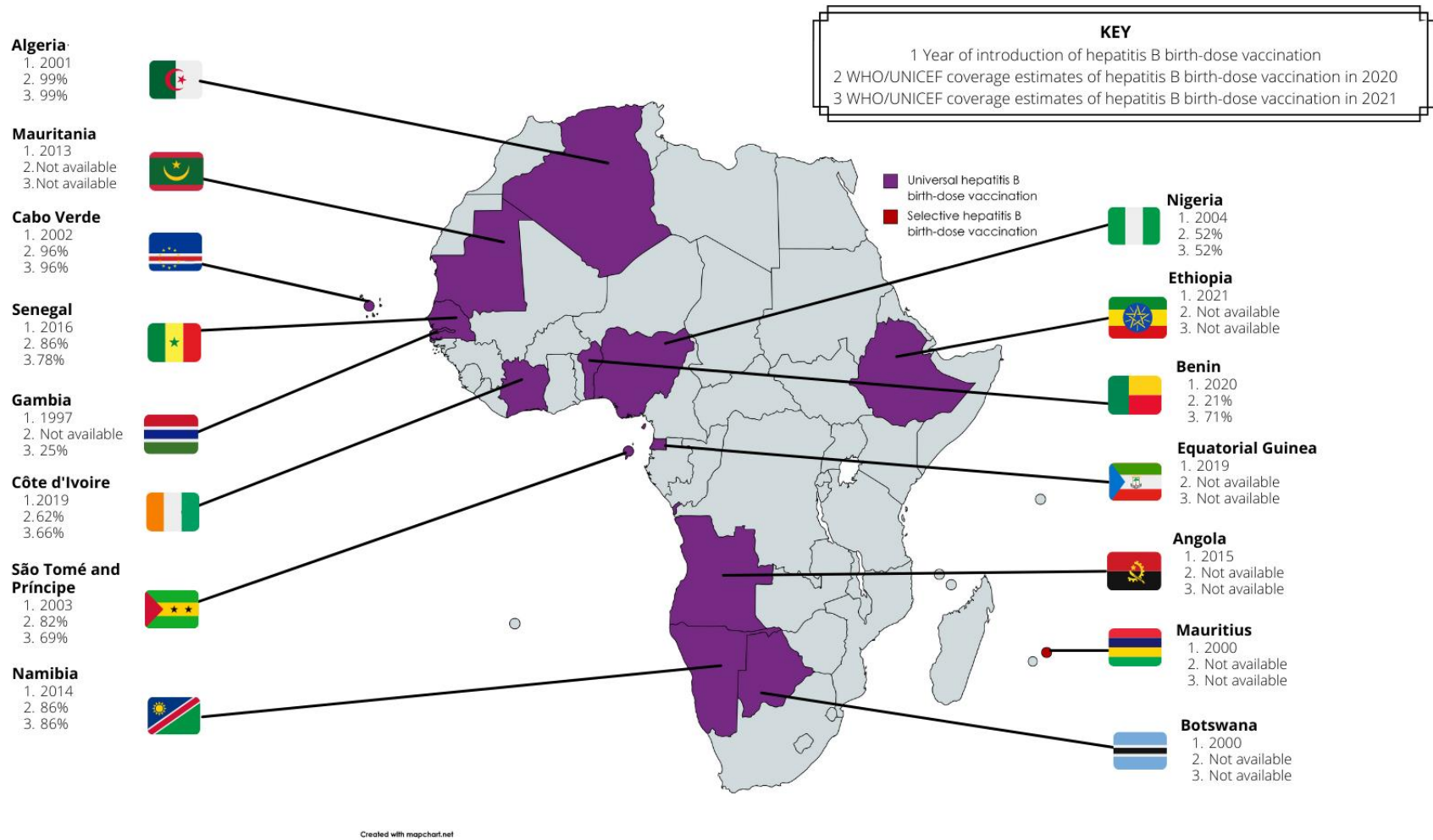


Figure 1. Introduction and coverage of hepatitis B birth-dose vaccination in WHO AFRO member states (Source: Author; drawing on data from WHO/UNICEF) (20,28,29,58)

Despite the lack of region-wide adoption of hepatitis B birth-dose vaccination, universal hepatitis B infant vaccination programs have been successful at reducing the incidence of horizontally transmitted HBV infection in under 5-year-olds, leading to a significant reduction in the burden of the disease worldwide (23). The WHO Africa regional office reports that all 47 member states have introduced routine childhood hepatitis B vaccination with the majority (94%) using the pentavalent vaccine (a combination vaccine for diphtheria, tetanus, hepatitis B, pertussis, and Haemophilus influenzae type B), administered in a 3-dose schedule at 6, 10 and 14 weeks of life (4). However, various studies have demonstrated ongoing HBV infection in children despite the receipt of all 3 childhood doses (6,59–62), suggesting susceptibility to infection from exposure early on at birth (19). It is therefore clear that the current strategy is insufficient at interrupting HBV MTCT which carries a higher likelihood of life-long infection and fatal outcomes.

## **2.5 Barriers to adopting universal hepatitis B birth-dose vaccination in Africa**

The evidence presented so far argues for a growing risk of HBV MTCT in Africa. The 2017 Global Hepatitis Report emphasizes the fact that hepatitis B birth-dose vaccination remains the cornerstone of prevention of vertical transmission (23) due to its cost-effectiveness and far-reaching lifesaving benefits (5). It is therefore considered a non-negotiable component in the HBV MTCT prevention package for the region (5). Cost-effectiveness of hepatitis B birth-dose vaccination in particular has been researched widely across Africa, and proven beneficial in countries within west, east, south and central Africa (5,21,63–68). Despite this, as mentioned above, only 15 African member states have adopted the vaccine as part of their national immunization programs at the time this review was compiled.

Key barriers to the adoption of hepatitis B birth-dose vaccination in countries within the region are cited in the 2016 WHO African Region situational report (43). As identified by countries in the region, these include (i) lack of financial support from Gavi, the vaccine alliance (10 countries), (ii) the need for further evidence on the burden of chronic HBV infection and the risk of perinatal transmission in Africa (6 countries), (iii) insufficient cold chain storage (3 countries), (iv) a high proportion of home births (2 countries), and (v) the lack of trained health care workers (HCWs) in attending to birth or conducting post-natal visits (2 countries) (43). Tamandjou Tchuem *et al.*, further cite a lack of political willingness, poor service delivery arrangements, and inadequate cold-chain systems as reasons for the delay in introducing universal hepatitis B birth-dose vaccination in Africa (47). These findings suggest the need for further high-level political commitment and system-wide approaches to mitigate these barriers and strengthen prevention of HBV MTCT in Africa (47).

## **2.6 Challenges faced by hepatitis B birth-dose vaccination programs in Africa**

In countries that have universal hepatitis B birth-dose vaccination programs in place, coverage estimates reported by the WHO and United Nations International Children's Fund (UNICEF), consistently show sub-optimal and disparate uptake of the hepatitis B birth-dose vaccine. For example, in 2021 WHO estimates indicated that the coverage of hepatitis B birth-dose vaccine ranged from 25% in The Gambia, 52% in Nigeria to 96% in Algeria (20,47) (*see Appendix A*). These disparate coverage rates do not provide information on the timeliness of vaccination. In addition, they suggest persistent programmatic challenges in those countries that have adopted the hepatitis B birth-dose vaccine as part of their national immunization programs. Following the suboptimal uptake of the hepatitis B birth-dose vaccine in Africa, several studies have investigated the current programmatic barriers, using both quantitative and qualitative research approaches. Some of the barriers reported across the literature include: the lack of relevant policies at both national and health facility levels (50,68), lack of funding or out-of-pocket payment requirements (69), poor monitoring and evaluation of

systems (50,68), lack of integration with the maternal and child health package (16,50), lack of awareness about HBV infection and hepatitis B birth-dose vaccination among pregnant women (69,70), geographical inaccessibility of immunization clinics (69,71), inaccessibility due to allotted vaccination days (50,69), frequent stock outs (69), home births (72,73), lack of outreach services (50), mistrust of HCWs handling newborns (70), birth-dose administered on discharge only (50), lack of staff knowledge on contraindications and the absence of delineated staff (50). Access consistently emerges as a common thread across these reported barriers, whether it be the inability of national governments to secure necessary, sustainable financing mechanisms to procure hepatitis B birth-dose vaccines, limited access to information on birth-dose vaccination, geographical access barriers including limited access to immunization clinics, and frequently mentioned, access to the birth-dose vaccine for home births. In relation to the challenges associated with home births, expert opinions have reiterated the importance of encouraging institutional delivery, as the coverage of hepatitis B birth-dose vaccination is correlated with the rate of skilled birth attendance and institutional delivery globally (74). In a previous systematic review addressing Nigeria's position on vertical transmission of hepatitis B, the rate of institutional delivery was reported to be only 35% and those attending antenatal care 58% (8). Consequently, hepatitis B birth-dose vaccine coverage in Nigeria remains sub-optimal (52%) despite integration with the national immunization schedule (20,73,75). Despite the calls for improved institutional delivery (1,4,74), it remains important that national health systems become more responsive to cultural contexts where home births and isolation periods post-birth are concerned (4,70,71). This may require tailored approaches to expanding the reach of the hepatitis B birth-dose within the African setting. Other suggestions for improving uptake of hepatitis B birth-dose vaccination include conducting community outreach and linkage to vaccination services and increasing community awareness through maternal education on HBV and hepatitis B birth-dose vaccination (4,8,71). At the governance and policy level, there is a need to strengthen commitment and prioritization of global HBV elimination targets among national governments (1,72,74,76).

## **2.7 Poor adherence to timely hepatitis B birth-dose vaccination in Africa**

A priority concern facing hepatitis B birth-dose vaccination programs in Africa is the poor adherence to the recommended time of administration (4). The Strategic Advisory Group of Experts (SAGE) recommend administering the hepatitis B birth-dose within the first 24 hours of life, although it remains effective against perinatal infection if administered within 7 days (4), and still beneficial in preventing early horizontal transmission if administered after 7 days (77). Yet national policies in the region recommend a range of what is considered acceptable timely administration of hepatitis B birth-dose vaccination, from 24 hours to as long as 2 weeks in countries like Namibia (4). A study in Senegal found that only 54.5% of infants were vaccinated within 24 hours and in total 58% within 7 days (72). The situation is even more concerning in São Tomé and Príncipe where only 1.1% of infants have been reported to have received their hepatitis B birth-dose vaccination within 24 hours of life (78). In The Gambia, a review of 10 years of coverage data in a district found that only 1% of infants were vaccinated with hepatitis B birth-dose within 24 hours, 5% within 7 days and 58% within 28 days of life (4). Similarly, in Nigeria, among children admitted to an emergency room, the mean age at hepatitis B birth-dose vaccination was 28 days (4). Delayed uptake of the hepatitis B birth-dose could lead to the program being judged as ineffective at interrupting MTCT as neonates who do not receive the vaccine on time will have increased susceptibility to HBV infection. Furthermore, this inconsistency in the timing negatively impacts the potential for greater uptake and adoption of hepatitis B birth-dose in other parts of the region.

The observation of other birth-dose vaccinations in the region could offer further insight into the performance of vaccinations with the same overall specification. In Africa, coverage of all three recommended birth-dose vaccines, namely, BCG, OPV<sup>4</sup> and hepatitis B birth-dose vaccine, are estimated by the WHO/UNICEF as 75%, 70% and 17% in 2021, respectively (20). While coverage data clearly shows poorer uptake of the hepatitis B birth-dose vaccine compared to BCG and OPV, it does not provide an indication of the timeliness of uptake of the vaccine. A systematic review by Bassoum *et al.*, (57) sought to investigate the timeliness of birth-dose vaccinations in sub-Saharan Africa and found that most neonates received their birth-dose vaccines within the first month of life, with coverage at this timepoint as follows; BCG at 71.7%; OPV at 76.1%; hepatitis B birth-dose at 60.8%. In comparison, coverage rates followed a downward trend on day 7 (BCG at 48.7%, OPV at 53.8%, and hepatitis B at 21.5%) and on day 0–1 (BCG at 14.2% and hepatitis B birth-dose at 1.3%) (57). Coverage of OPV for days 0–1 time point was not recorded by any of the included studies (57). Overall, it is evident that in Africa, hepatitis B birth-dose vaccination programs achieve the lowest coverage rates and timeliness despite the explicit requirement of administration within 24 hours (57). It is possible that the coverage and timeliness of BCG and OPV birth-dose vaccinations can be attributed to their near-universal adoption (both vaccines have been included in the national immunization programs of 45 and 39 WHO AFRO member states, respectively) and longstanding programs within Africa (57). In comparison, universal hepatitis B birth-dose vaccination is only available in a limited number (15 countries) of member states (57). Nevertheless, greater efforts are required to ensure timely administration of the hepatitis B birth-dose vaccine. Such efforts will have to be guided by context specific evidence on the barriers to timely administration and uptake of the hepatitis B birth-dose vaccine. Without timely intervention, the combination of low vaccine coverage and the non-adherence to the recommended time of administration may hamper the pursuit of achieving viral hepatitis elimination as a public health threat in the African region.

With the use of evidence synthesis approaches, efforts have been made to better understand the barriers to: the adoption of universal hepatitis B birth-dose vaccination, optimal vaccine coverage, and overall performance of the program across Africa. In 2017, Breakwell *et al.*, published a MEDLINE literature review citing (i) timely administration, (ii) high prevalence of home births, (iii) the lack of services available to reach infants born at home, (iv) and unreliable vaccine supply, as challenges limiting improved progress and coverage (4). Whereas Dionne-Odom *et al.*, undertook a PUBMED literature review which further categorized four barriers to improved performance of hepatitis B birth-dose vaccination in the region, and these included: (i) limited awareness of HBV prevalence and preventative measures, (ii) vaccine availability, (iii) out of facility deliveries and (iv) cold chain storage requirements (1). Furthermore, a WHO systematic review on the global compliance with timely hepatitis B birth-dose vaccination reported a paucity of research evidence from the WHO AFRO compared to the other regions, with only 4 publications representing 4 African countries meeting the inclusion criteria of this review (43). Of the four, only one publication (71) described programmatic barriers which suggested that living in rural areas was the most weighted risk factor limiting access to the hepatitis B birth-dose vaccine post-delivery.

## 2.8 State of health systems and hepatitis B birth-dose vaccination programs in Africa

Global agencies have recognized well-functioning health systems as crucial to the optimal performance of so-called vertical health programs, and in attaining global health targets (31,79). Despite effective and affordable interventions as well as access to international donor funding, fragile and fragmented health systems in some

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<sup>4</sup> OPV coverage estimates are not recorded separately by WHO/UNICEF but included in the full 3-dose polio vaccination regimen

LMICs, are often incapable of delivering key health services of adequate volume and quality (30,31). Identifying programmatic barriers, though essential, is likely only an indication of the weaknesses that exist in the broader health systems in Africa. According to the WHO, a health system encompasses “all organizations, people and actions whose primary intent it is to promote, restore and maintain health” (80). This definition extends beyond just the delivery of health services and includes the acknowledgment of a complex people-centered system requiring the exploration and collaboration of multiple sectors for the attainment of health (80). To promote the common understanding of a health system, the WHO provides a health systems framework consisting of six dimensions (service delivery; health workforce; information; medical products, vaccines, and technologies; financing; leadership and governance) commonly referred to as building blocks and their overall goals or outcomes (30,80).

### **2.8.1 Conceptual models for the assessment of health systems capacity in Africa**

Even though the WHO framework is effective in clarifying essential functions of the health system it has been criticized for depicting the six dimensions in silos (30,80). Realistically it is the interdependence between the dimensions or building blocks that is recognized as paramount to addressing country challenges (80). The interpretation of this model by de Savigny and Adam better explores the interaction between the dimensions in a non-linear relationship centered around the people within the health system (81). The multiple relationships and interactions between the dimensions therefore result in the creation of a system (81). Van Olmen *et al.*, further emphasize the broader context in which a health system is embedded, the influence of its principles and values, and includes the population as part of the system (82). Taken together, these conceptual models (80–82) emphasize the fact that health systems are complex systems (81). Complex systems “are dynamic, with interacting components, at various geographical levels, that lead to adaptation and emergence of new dynamics” (30).

The broader country context has a considerable influence on the capabilities of a country’s health system to effectively support the performance of health programs. Accordingly, barriers to the adoption and performance of universal hepatitis B birth-dose vaccination programs in Africa may be unique to the health systems that deliver them. For example, it has been previously suggested that countries with prolonged civil unrest and unstable governance, as observed previously in Uganda and South Sudan, experience negative implications in the functioning of their health programs such as hepatitis B birth-dose vaccination (13). Furthermore, while countries like Nigeria contribute the largest amount of research on HBV MTCT in the region, the evidence generated has so far not translated into optimal coverage rates of the hepatitis B birth-dose vaccine (4,20), and The Gambia, with more than 10 years of access to universal hepatitis B birth-dose vaccination continues to experience inconsistencies with coverage rates (4,20). This may point to the influence of contextual health systems issues in these settings. These unique settings require a “deeper understanding of the linkages, relationships, interactions and behaviors among elements that make up the entire system” that delivers the program (81). This approach is better referred to as ‘systems thinking’ (81), and as health systems are inherently complex (33), a more ‘complex systems thinking’ approach could be adopted. Using this approach allows for the anticipation of system-wide effects as well as undesired synergies, which can then better inform mitigation strategies or interventions (81). In doing so, system-level interventions can therefore be modified as well as more comprehensive evaluations designed for better monitoring of effects (81).

### **2.8.2 Complexity of hepatitis B birth-dose vaccination in Africa**

Though it is established that not all interventions will benefit from a systems-thinking approach, complex interventions are likely to have profound effects across the system, more so in weak health systems (81).

Among all three birth-dose vaccinations (BCG, OPV, hepatitis B birth-dose) endorsed by the WHO, universal hepatitis B birth-dose vaccination programs in Africa have performed the poorest, a fact likely attributed to the complexity of the intervention and the limited degree of flexibility such as the requirement of administration within 24 hours of life (36,57). This has raised concerns on task shifting, cold storage, data capturing and policy change, proving the complexity of the intervention across most, if not all, the health systems building blocks (16,50,68). It stands to reason that other sources of complexity associated with the intervention, or the health system could provide further explanations for the underperformance of hepatitis B birth-dose vaccination programs in the Africa region. A study by Petticrew *et al.*, offering a pragmatic approach to complex interventions in systematic reviews, provides a comprehensive list of characteristics used to identify complexity and its source from either the intervention itself or from the intervention's causal pathway (36), see **Table 3**. Using the principles of complex systems thinking and applying a systems lens in assessing existing hepatitis B birth-dose programs could facilitate a richer understanding of the aforementioned barriers experienced and inform interventions aimed at scaling up the delivery of the program. Findings from such assessments could potentially guide reforms to current hepatitis B birth-dose vaccination programs, aiding in better odds for attaining global viral hepatitis elimination targets.

**Table 3.** Characteristics of sources of complexity adapted from Petticrew *et al.*, (36)

<b>Examples of characteristics of complexity</b>	
<b><u>Characteristics of the intervention itself</u></b>	<b><u>Characteristics of the intervention's causal pathway</u></b>
Multiple components (made up of various interconnecting parts)	Nonlinear relationships (cannot be arranged along a simple input output line); phase changes
Number of groups or organizational levels targeted by the intervention	Multiple mediators and moderators of effect such as the background characteristics and environment of the patient
Degree of flexibility or tailoring of the intervention permitted	Feedback loops, (e.g., where changes in behavior create the conditions for behavior to change further and where uptake in cycling results in more cyclists, which means that cycling becomes the norm, encouraging more people to take up cycling)
Self-organization, adaptivity, and evolution over time	Synergy between components, and does the program have symbolic value over and above its operational components?
	Number and variability of outcomes; emergent novel outcomes
	Connectivity, where individual components of an intervention are linked together in a system, so they influence each other
	Interaction with context and the capability created from this interaction; very susceptible to effect of different contexts (e.g., policy timing, organizational culture and leadership, resource allocation, staffing levels and capabilities, interpersonal relationships)

### **2.8.3 Health systems approach to assessing the performance of hepatitis B birth-dose vaccination programs**

To date, two previous scoping reviews applied systems-thinking in identifying practices to improve the implementation of hepatitis B birth-dose vaccination (37,38). In 2012 the WHO Immunization, Vaccines and Biologicals department, summarized and appraised implementation evidence of 65 studies using the WHO health system framework to categorize barriers and facilitators (37). Recommendations emerging from the review ranged across all building blocks, some of which included: encouraging governments to adopting a central policy on universal hepatitis B birth-dose vaccination as well as setting clear guidelines on the definition of 'timely administration'; the meticulous tracking of pregnancies and birth by community health workers to improve the hepatitis B birth-dose vaccine coverage; and the usage of single dose vials to discourage the

practice of delaying hepatitis B birth-dose vaccination due to the perception of waste from multi-dose vials (37). Although the review sought to provide guidance for LMICs in implementing universal hepatitis B birth-dose vaccination programs, none of the included studies were from Africa or focused on the complexity of the intervention or system. More recently in 2022, Boisson *et al.*, sought to identify literature focused on introducing hepatitis B birth-dose vaccination programs and barriers to uptake in sub-Saharan Africa (38). This review summarized and categorized 39 relevant reports based on determinants of implementation at a policy, facility, and community level (38). Findings ranged from policy advocacy, facility supply and stockouts, to community HCW involvement, among other factors (38). Overall conclusions suggested that evidence at the community level were both lacking and pertinent to improved implementation (38). Even though the purpose this review was to provide an overview of experiences from sub-Saharan Africa, the scoping extended to the South-East Asian region and only included 13 publications from sub-Saharan Africa of the total 39 included studies (38). Thus, while the evidence-based recommendations from these reviews are comprehensive and may meet the needs of policy makers and immunization program managers in some LMICs, the findings may not be generalizable to the African context.

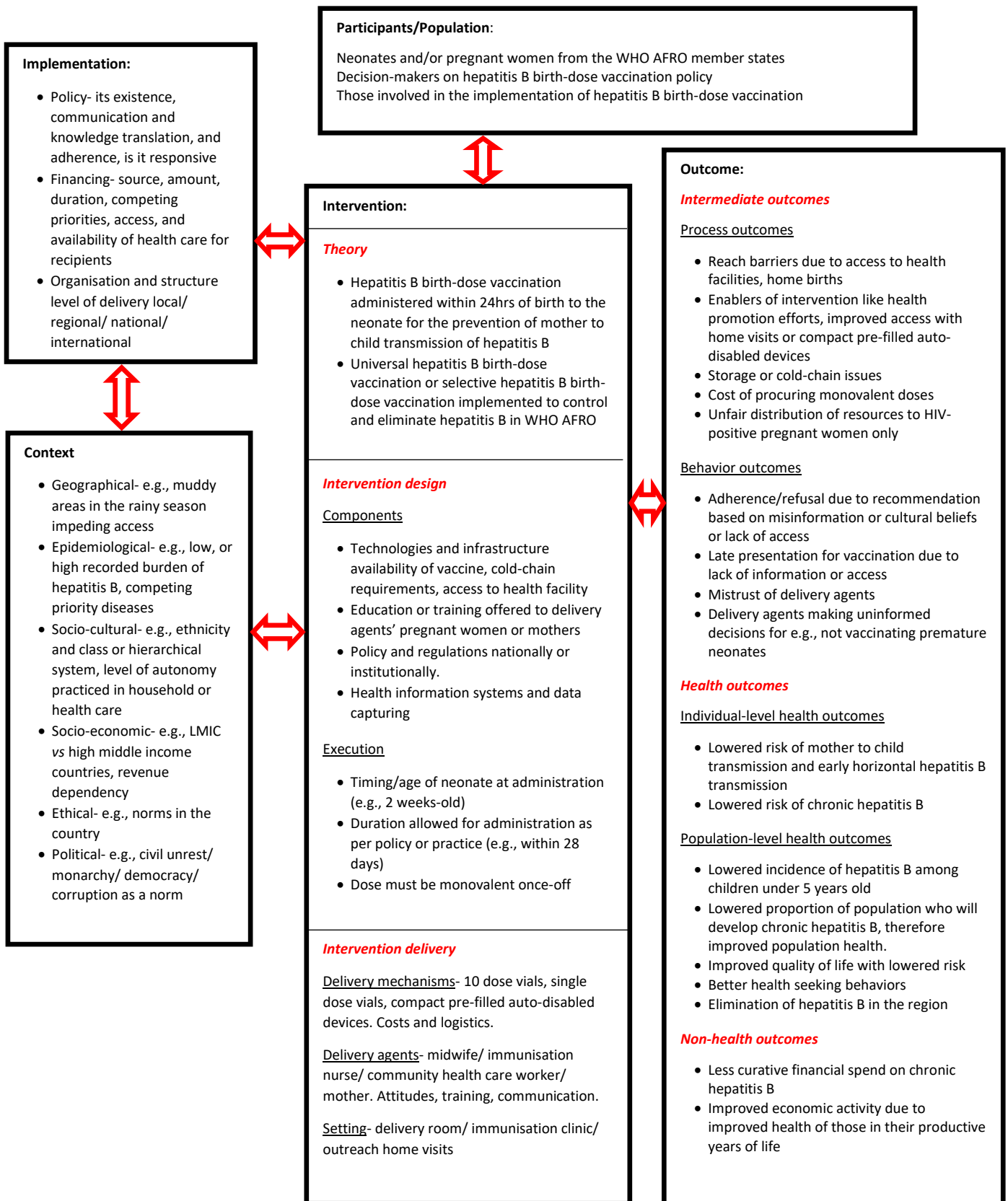
The lack of synthesized evidence needed to inform health system strengthening efforts to support hepatitis B birth-dose vaccination programs in Africa, creates challenges in the adoption and effective performance of this critical intervention within member states. The recognition of health system strengthening as a requirement for the success of health programs, has been highlighted by global health initiatives like that of Gavi, the Vaccine Alliance, through their health system strengthening funding window (30). Health system strengthening aims for a sustained improvement in the architecture of the health system in order to ensure optimal service delivery and ultimately improved health outcomes within the population (80). Though this system-wide approach has now been recognized as more sustainable than that of vertical program strengthening, analyzing the complexity of health systems performance has been difficult (30).

#### **2.8.4 A systems-based logic model for assessing complexity of hepatitis B birth-dose vaccination programs**

Though several conceptual frameworks have attempted to capture the elements of health system performance in its entirety (79,80,83,84), the WHO health systems framework has become the most quoted framework in recent works (30). This framework, as mentioned before, is not without limitations, most concerning is its simplistic design reducing the health system to a ‘complicated’ one (with building blocks that make up a whole) as opposed to a ‘complex’ system (dynamic with multiple feedback loops) (30). The lack of interactions and inter-relations between the building blocks fails to depict the processes of the system, behavioral change, context, and durability overtime (30). However, due to its simplicity it serves as a convenient tool, understood by researchers of different disciplinary backgrounds and allowing for comparisons across different interventions or studies (30). Mounier-Jack *et al.*, recommend that the WHO health systems framework should be used in a more flexible manner and be adapted to the research question through formative research and piloting (30). To maintain the convenience of interpretation of the WHO health system framework but still accommodate for the characteristics of an immunization intervention, the analytical model developed by Amponsah-Dacosta *et al.*, was considered in this review (85). This logic model combines the 8 components of routine immunization with the 6 WHO building blocks resulting in 6 cross cutting themes, namely: (i) the governance and policy landscape; (ii) the capacity of the health workforce; (iii) the availability of potent vaccines, cold chain and logistics systems; (iv) the quality of health service delivery; (v) the state of health information and community partnerships; and (vi) the availability of equitable and sustainable health financing; (80,86). Although the model factors in the unique regional and country-level

context (85), it fails to highlight the complexity in both the system and intervention. As complexity is not limited to the characteristics of the intervention but may exist in the implementation or context, a model sensitive to these aspects is required, affording adequate detail for a complex explanation (36,87)

It is with these specifications that Rohwer *et al.*, developed a systems-based logic model tailored for systematic reviews of complex interventions, *see Appendix B* (87). The model depicts the system in which the interaction between the participants, the intervention, and the context takes place (87). The arrows represent the possible points of interaction between the concepts in the system (87). The intervention is divided into theory, design and delivery with the expansion of details beneath each of these subheadings including aspects of execution and delivery agents among others; implementation requires details on policy, financing, provider, organization and structure; context requires the description of the geographical, epidemiological, socio- cultural and economic, ethical, legal, and political landscapes; and outcomes are further categorized into short term, intermediate and long term, with accommodation for further details on the nature of outcomes such as process or behavioral outcomes (87). This model provides a means of conceptualizing complexity and making findings of evidence syntheses more accessible to a broad range of decision and policy makers (87). We adopted the template proposed by Rohwer *et al.*, to develop a system based-logic model for understanding complexity of hepatitis B birth-dose vaccination programs and the health systems that deliver them (**Figure 2**). This model is best used in conjunction with the list of characteristics identifying sources of complexity in **Table 3**. This logic-model maps out the possible sources of complexity of hepatitis B birth-dose vaccination programs and highlights the interactions influencing its outcomes. As an analytical tool for systematic reviews, this model serves as a means to recognize common themes emerging from the evidence and offers possible explanations for system-wide effects.



**Figure 2.** Systems-based logic model for understanding complexity of hepatitis B birth-dose vaccination programs (Source: Author; drawing on the theoretical concepts of the systems-based logic model by Rohwer *et al.*,) (84)

### 3. Study rationale and research question

Our scoping review confirmed the urgent need to address the performance of hepatitis B birth-dose vaccination programs for the prevention of HBV MTCT in Africa. Despite the decade-old global recommendation, and regional commitment for the inclusion of universal hepatitis B birth-dose vaccine into national immunization schedules, the lack of consistency in the performance of hepatitis B birth-dose vaccination programs among African states has been acknowledged as a key concern and may be related to issues within broader health systems. Evidently, it is crucial to explore the system-wide reasons for the state of hepatitis B birth-dose vaccination programs within this region. We propose a systematic review embracing the effects of potential complexity within the system, the intervention causal pathway or the intervention itself. By identifying sources of complexity among one or all these domains, we hope to offer an explanation on how they interact and better explain the current poor performance of hepatitis B birth-dose vaccination programs in the region.

#### 3.1 Research question

Does (*and how does*) the complexity of the health system and/or intervention influence the performance of hepatitis B birth-dose vaccination programs in Africa?

#### 3.2 Review objectives

To address this research question, the following objectives will be explored:

1. To identify the potential sources of complexity associated with the implementation of hepatitis B birth-dose vaccination programs and the health systems that deliver them.
2. To describe the dynamic interactions at the intersection of hepatitis B birth-dose vaccination programs and the health systems within Africa.
3. To describe how the complex interactions (*see objective 2*) influence the performance of hepatitis B birth-dose vaccination programs in Africa.
4. To describe the potential research, policy, and practice implications of the findings of this systematic review for scaling up hepatitis B birth-dose vaccination programs within Africa.

### 4. Methods

The purpose of this research is both exploratory and explanatory, in an attempt to provide complex explanations for the current performance of hepatitis B birth-dose vaccination programs in Africa. Qualitative research has been described as an “in-depth enquiry in order to understand the phenomena and their relationships” (88). It explores questions of usability, meaningfulness, feasibility, and appropriateness of interventions and could be used to explore why implementation of some interventions are unsuccessful despite proven effectiveness (89,90). Therefore, a qualitative systematic review approach will be adopted as it better aligns with our research question and objectives.

The Joanna Briggs Institute (JBI) guidelines for conducting qualitative systematic reviews employs a meta-aggregation as opposed to a meta-ethnographic approach (89). Essentially the meta-aggregation approach does not seek to reinterpret the findings of primary studies but rather is sensitive to the practicality and usability of these findings (89). This practice seeks to draw generalizable statements in the form of recommendations to guide practitioners and policy makers (91), and one of the strengths of the JBI-approach is its focus on formulating recommendations for action (89). Given the overall purpose of this systematic

review study, the JBI-approach will be adopted. This review approach will be executed alongside the pragmatic approach to dealing with complexity in systematic reviews, recommended by Petticrew *et al.*, (36). The updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) statement will be consulted to ensure all recommended information is captured (92). The PRISMA 2020 statement includes checklists, explanation and elaboration, and a flow diagram, all of which are intended to assist in the planning and conduct of systematic reviews, see **Appendix C** (92).

This review study will be conducted in two phases: phase 1 involves the scoping review (detailed already, above in the Literature review section) while phase 2 will be a qualitative systematic review. Phase 1 has provided the foundation and mapped out what is known on hepatitis B birth-dose vaccination in Africa. Phase 2 will use insights gained in phase 1 on the complexity of interventions and health systems to guide the synthesis of relevant evidence. Following the outcome of phase 1 and 2, research, practice and policy recommendations will be made to ensure knowledge translation of the findings.

#### 4.1 Phase 1 Scoping Review

This phase of the review study has been completed and the findings reported above<sup>5</sup>. As previously noted, the scoping review was conducted as a preliminary step to map the evidence available on hepatitis B birth-dose vaccination programs in Africa, which was essential to formulating the research question for the systematic review to be conducted in phase 2. This phased approach is particularly helpful when researching topics with large magnitudes of literature, as is the case for hepatitis B birth-dose vaccination programs (93,94). This further assists in understanding the scope of the current evidence and the identification of knowledge gaps and research priorities (93,94). The formulation of the research questions, search terms and key themes are therefore evidence based (93,94). This phase of the study was guided by the JBI guidelines on scoping reviews together with the PRISMA extension for Scoping Reviews (PRISMA-ScR) checklist, see **Appendix D** (89,95).

Initially the approach to the scoping review was to broadly assess the scope of evidence available on the status of hepatitis B birth-dose vaccination in LMICs. Several electronic databases and platforms were consulted for peer-reviewed literature, namely: PubMed, Scopus, Web of Science and EBSCOhost (Academic Search Premier, Africa-Wide Information, CINAHL, Health Source: Nursing/Academic Edition, APA PsycInfo). Additionally, grey literature was sourced from organizational websites like WHO (<http://www.who.int/>), UNICEF (<https://www.unicef.org/>) and Gavi, the Vaccine Alliance (<http://www.gavi.org/>). Supplementary searches for peer-reviewed and grey literature were sourced by reviewing bibliographies and performing additional internet searches on Google Scholar. Only relevant literature published in English were considered. Literature published within the last 22 years (2000–2022) were included in order to map the progress of hepatitis B birth-dose vaccination in LMICs overtime and ensure the synthesis of a wide scope of evidence. The search strategy developed for this scoping review is presented in **Table 4**. A total of 991 records were retrieved from all the databases searched. After manual de-duplication, followed by abstract, title and eventual full text review, 72 unique records were identified. A decision to focus on the African region was made as the need for intervention far outweighed that in other LMICs. Of the 72 records, 46 reported on relevant research done in the African region. An additional 22 published literature sources were identified through supplementary searches and eligible for inclusion. Overall, 88 literature sources were included in the scoping review. These literature sources varied across study type, and included quantitative and qualitative

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<sup>5</sup> The requirement for this minor dissertation is to write this section in the past tense, as it has already been completed at this stage and is reported above.

empirical studies, scoping and systematic reviews, commentaries and expert opinions and international guidelines, reports, and theses.

**Table 4.** Literature search strategy for the scoping review phase

Query No.	Search Terms
#1	Hepatitis B OR Hepatitis B Vaccines [Mesh]
#2	Hepatitis B OR Hep B OR HBV OR Hepatitis B vaccine [keywords]
#3	#1 OR #2
#4	Birth dose OR birth-dose OR BD or birth dose vaccine OR birth-dose vaccine OR BD vaccine [keywords]
#5	Deprived Countries OR Deprived Population OR Deprived Populations OR Developing Countries OR Developing Country OR Developing Economies OR Developing Economy OR Developing Nation OR Developing Nations OR Developing Population OR Developing Populations OR Developing World OR LAMI Countries OR LAMI Country OR Less Developed Countries OR Less Developed Country OR Less Developed Economies OR Less Developed Nation OR Less Developed Nations OR Less Developed World OR Lesser Developed Countries OR Lesser Developed Nations OR LMIC OR LMICS OR Low GDP OR Low GNP OR Low Gross Domestic OR Low Gross National OR Low Income OR Lower GDP OR lower gross domestic OR Lower Income OR Middle Income OR Poor Countries OR Poor Country OR Poor Economies OR Poor Economy OR Poor Nation OR Poor Nations OR Poor Population OR Poor Populations OR poor world OR Poorer Countries OR Poorer Economies OR Poorer Economy OR Poorer Nations OR Poorer Population OR Poorer Populations OR Third World OR Transitional Countries OR Transitional Country OR Transitional Economies Afghanistan OR Albania OR Algeria OR American Samoa OR Angola OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Byelarus OR Belorussia OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Botswana OR Brazil OR Bulgaria OR Burma OR Burkina Faso OR Burundi OR Cabo Verde OR Cape Verde OR Cambodia OR Cameroon OR Central African Republic OR Chad OR China OR Colombia OR Comoros OR Comores OR Comoro OR Congo OR Costa Rica OR Côte d'Ivoire OR Cuba OR Djibouti OR Dominica OR Dominican Republic OR Ecuador OR Egypt OR El Salvador OR Equatorial Guinea OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Gaza OR Georgia OR Georgia Republic OR Ghana Malaysia OR Maldives OR Mali OR Marshall Islands OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palau OR Papua New Guinea OR Paraguay OR Peru OR Philippines OR Principe OR Romania OR Ruanda OR Rwanda OR Samoa OR Sao Tome OR Senegal OR Serbia OR Sierra Leone OR Solomon Islands OR Somalia OR South Africa OR South Sudan OR Sri Lanka OR St Lucia OR St Vincent OR Sudan OR Surinam OR Suriname OR Swaziland OR Syria OR Syrian Arab Republic OR Tajikistan OR Tadjikistan OR Tajikistan OR Tadjik OR Tanzania OR Thailand OR Timor OR Togo OR Tonga OR Tunisia OR Turkey OR Turkmen OR Turkmenistan OR Tuvalu OR Uganda OR Ukraine OR Uzbek OR Uzbekistan OR Vanuatu OR Venezuela OR Vietnam OR West Bank OR Yemen OR Zambia OR Zimbabwe
#6	#3 AND #4 AND #5
<p><b>Note:</b> MeSH- Medical Subject Headings (<a href="http://www.nlm.nih.gov">http://www.nlm.nih.gov</a>); LMIC filter- database specific LMIC filters have been compiled by the Health Sciences Faculty library, University of Cape Town (UCT). The full filter is available from the website (<a href="https://www.medical.lib.uct.ac.za/">https://www.medical.lib.uct.ac.za/</a>).</p>	

## 4.2 Phase 2 Systematic Review

A systematic review employs a rigorous and defined approach to reviewing literature on a particular topic of focus (96). In this study and as part of phase 2, an electronic search for peer reviewed literature on hepatitis B birth-dose vaccination programs delivered by health systems in Africa will be performed. The exploration of this literature aims to provide a description and explanation for the performance of complex interventions in complex health systems, with the hepatitis B birth-dose serving as a proxy for complex interventions.

The literature search and screening will be conducted by the primary reviewer (TR) with oversight from the co-reviewers (EAD and JO). Briefly, electronic databases and platforms such as PUBMED (including MEDLINE), EBSCOhost (including Academic Search Premier, Africa-Wide Information, CINAHL, Health Source:

Nursing/Academic Edition, APA PsycInfo) Scopus and Web of Science (excluding MEDLINE) will be searched. Recommendations of relevant publications from co-reviewers will also be considered and screened. This literature search will be performed using keywords, MeSH<sup>6</sup> terms and synonyms of search terms guided by the scoping review and the systematic review question (96). Boolean operators like 'AND' and 'OR' will be used to combine key search terms and synonyms related but not limited to the intervention (terms such as hepatitis B birth dose vaccination, hep B BD) and systems performance (terms such as barriers, enablers, factors, health system). Additionally, terms not explicitly related to the health system but found to be relevant to the performance of hepatitis B birth-dose vaccination in the African context will be included in the search strategy. Examples of these terms include, home births, vaccine supply, maternal education, decision making autonomy and timeliness. No language restrictions will be applied in order to reduce the likelihood of publication and language bias, especially given the multi-lingual context of Africa.

#### 4.2.1 Inclusion criteria

1. Only peer-reviewed primary research articles will be included in the systematic review.
2. Eligible literature will include those published from 2009–2022. Due to the WHO recommendation of universal hepatitis B birth-dose vaccination for all member states since 2009 (23), this time frame would ensure that relevant and recent literature sources will be retrieved. The time filter will potentially provide information to assess change over time.

#### 4.2.2 Exclusion criteria

1. Research conducted in countries other than member states of the WHO AFRO will be excluded. Due to the ongoing commitment of the WHO Africa regional office towards viral hepatitis elimination (24,27), research will focus on member states.
2. Research only investigating hepatitis B infant vaccinations administered from 4-6 weeks, or any vaccination programs other than the hepatitis B birth-dose vaccination program.
3. Published literature without abstracts or summaries, or full texts that are inaccessible for review.

All search results will be imported from the respective databases to Mendeley Reference Manager<sup>®</sup> (97). After duplicate removal in Mendeley<sup>®</sup>, literature sources will be imported to Rayyan<sup>®</sup>, a web-based application for systematic reviews (98). The screening of titles and abstracts will then be conducted, applying the inclusion and exclusion criteria, and earmarking articles eligible for full text review. Full texts will then be screened in Rayyan<sup>®</sup>. Critical appraisal of full texts selected for inclusion will then be performed.

#### 4.2.3 Critical appraisal

The full texts selected for inclusion will undergo a quality evaluation by assessing the appropriateness and agreement of the research question and objectives, the selection and conduct of the methodology, and the analysis and applicability of the findings reported. This process will be performed using the critical appraisal tools developed by the Critical Appraisal Skills Programme and the Mixed Method Appraisal Tool, *see Appendix E and F for examples of these tools* (99,100). Both appraisal tools, have been used in previous qualitative systematic reviews (101–103). Additionally, an assessment scale developed by Dufault and Klar (104), and adapted by Cortes-Ramirez (105) will be used to evaluate the quality of any selected studies with ecological designs (**Appendix G**). This assessment scale has also been used in previous systematic reviews (105,106). A summary of the quality appraisals will be captured on a database and made available to two independent

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<sup>6</sup> MeSH- Medical Subject Headings thesaurus is a controlled and hierarchically organized vocabulary produced by the National Library of Medicine. It is useful when searching biomedical and health related information (<http://www.nlm.nih.gov>).

reviewers (EAD and JO). After further appraisals by EAD and JO have been completed and consensus is reached among all three reviewers, the final decision of which full texts are eligible for inclusion in the systematic review will be made.

#### 4.2.4 Data extraction

After consensus is reached on the eligible articles to be included in this systematic review, data will be extracted. Guided by the systems-based logic model developed during phase 1 of this study, a data extraction form will be created, providing a standardized systematic record of the data summaries attained from every literature source. The data extraction form will also ensure traceability and validity of the data extracted and will serve as the foundation for appraising, analyzing, and interpreting the body of evidence (107). To improve reliability, the data extraction process will be supervised and audited by EAD and JO. This serves as an opportune step in resolving discrepancies emerging prior to data analysis. The data extraction sheet will be designed in Microsoft Excel as one continuous table. For ease of interpretation and legibility, a template of this data extraction sheet – presented as 4 table sections which run concurrently – is provided in **Table 5**.

#### 4.2.5 Data analysis

Synthesis and analysis of the data will be performed using the final audited data summaries formulated and guided by the data extraction sheet and logic model. Among the different types of qualitative data analysis, thematic analysis has long been considered the foundational analytical method for qualitative research (108) and the go-to approach in qualitative systematic reviews (109). Thematic analysis is particularly useful in its applicability to a wide range of research questions and approaches, producing rich, in-depth, and complex accounts of data sets (108,109). For these reasons, the thematic analysis approach will be most suitable in exploring and identifying possible sources of complexity in the implementation of hepatitis B birth-dose vaccination programs in the African context.

Guiding the process of thematic analysis will be the three broad steps suggested by Thomas & Harden and the three cross-cutting steps of the JBI meta-aggregative review approach (89,109). According to Thomas and Harden, the first stage involves data immersion and coding of the text using both inductive and deductive approaches (109,110). Thereafter, the coded extracts will be used to search for and develop themes capturing the main concepts emerging from the text (108,109). It is at this step that the logic model will be of particular use as it helps to categorize coded extracts and identify emerging themes. The detailed description housed in the logic model will enrich this review by improving the validity, reliability, and efficiency at this stage of the analysis process. Lastly, using the thematic extracts, analytical themes will be generated seeking to provide nuanced and rich explanations of the review findings (108,109). Similarly, the 3 steps in the JBI process include 1) extraction of findings with an accompanying illustration (quotation) and a level of credibility<sup>7</sup> assigned to each finding; 2) developing categories (themes) that are sufficiently similar and house at least two findings; 3) developing one or more synthesized findings that are of at least two categories (89). Additionally, themes and codes broadly developed from the scoping review will be used to enhance the data analysis process. Flexibility will be maintained throughout the analysis process to accommodate emergent or unanticipated themes.

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<sup>7</sup> The three levels of credibility are as follows: 1) Unequivocal — findings accompanied by an illustration that is beyond a reasonable doubt and thus not open to challenge; 2) Credible – findings accompanied by an illustration lacks clear association with it and therefore open to challenge; 3) Not Supported – findings are not supported by the data.

Table 5. Template of the data extraction sheet (Source: Author)

Study ID					Study/literature details										Intervention theory and design			
No.	First Author	Year	Title	Country	Type of literature	Language	Aim of study/literature	Study design	Study duration	Participant Type	Population Size	Sampling	Data collection method	Study limitations	Ethical considerations/ Author reflexivity/ Informed consent	Practice in study: Universal or selective hepatitis B birth-dose vaccination	Presence of national guideline/policy instated on hepatitis B birth-dose vaccination	Presence of institutional guidelines/policy on hepatitis B birth-dose vaccination
1.																		
2.																		
3.																		

Intervention theory and design (continued...)					Intervention execution and delivery									
Training of delivery agents	Education/knowledge of pregnant women or mothers	Monitoring system in place: evidence of feedback and feedforward mechanisms present	Access to infrastructure/ health facility / immunization service	Access/ availability of required technologies (cold chain, vaccine)	Timing of vaccine administration	Time range allowed for vaccine administration	Adherence to data capturing	Delivered agent	Influential delivery agent characteristic/s (soft and hard skills)	Setting of delivery	Type of Vaccine used (Brand/supplier)	Mechanism of vaccine (10 dose/single dose/auto-disabled device)	Cost of vaccine	Logistics of supply

Implementation						Context					
Policy			Financing			Geographical barriers/enablers	Epidemiology of the country (Burden of hepatitis or other diseases)	Socio-economic and cultural factors (e.g., household autonomy, societal hierarchy)	Socio-economic country climate	Ethical norms	Political structure (e.g., unrest/ monarchy/ democracy/corruption)
Knowledge translation of policy (Top down)	Adherence to policy	Responsiveness of policy	Source of finance for intervention	Duration of finances for intervention (e.g., if donor funding)	Competing financial priorities within context of country						

Outcomes				
Process outcomes	Behavior outcomes	Individual outcomes	Population level-outcomes	Non-health outcomes
(e.g., reach barriers/ enablers improving access/ cost implications influencing delivery)	(e.g., adherence issues based on cultural practices, late presentation due to technologies available like 10-dose vials only)	(e.g., lowered risk of MTCT hepatitis B of investigated sample)	(e.g., evidence better health seeking behaviors among pregnant women, decreased hepatitis B incidence of under 5 in the country)	(e.g., less financial expense on chronic hepatitis sufferers, improved, health promotion among pregnant women and mothers)

## 5. Rigor

Several aspects already mentioned in this protocol have been employed to ensure reliability and trustworthiness of the proposed review study. Firstly, the selection of a systematic review study design assists in minimizing bias by reviewing and selecting literature in an open and systematic method. Secondly, the development of the review protocol enhances transparency and trustworthiness by detailing the study design and methods to be used (111). Thirdly, the risk of selection and publication bias is lessened as no language restrictions will be imposed during the literature search. Fourthly, the use of a data extraction sheet and logic model further enhances the validity, transparency, and reproducibility by ensuring all relevant information will be extracted and accurately recorded, mapping the development of the data sets for analysis. Fifthly, it is important that the researcher upholds an account of reflexivity in the research, remaining cognizant of her own assumptions and documenting where this might influence her interpretation of the findings (112). Sixthly, the use of published appraisal tools to assess the quality of each included study will minimize bias. Lastly, reviewer triangulation, peer debriefing and provision of detailed descriptions of the context when analyzing data sets will further enhance the trustworthiness of the findings emanating from this systematic review study (113).

## 6. Ethical considerations

The direct involvement of human participants is not a feature of this proposed systematic review study. The sources of literature to be used in conducting the systematic review are published and accessible in the public domain. Therefore, there will be minimal to no direct risk to health systems or intervention programs analyzed in this study. These reasons negate the need for formal ethical clearance. Worth noting is the risk of exposure of poorly functioning hepatitis B birth-dose vaccination programs or health systems in specific countries. However, the researcher acknowledges the ethical obligation to conduct a comprehensive systematic review without prejudice or preference as well as provide due recognition to the works of cited investigators where appropriate. It is anticipated that the proposed research may offer insights into scaling up implementation of complex health interventions like the hepatitis B birth-dose vaccination programs and optimizing the performance of the health systems that deliver them. These insights could be translated into policy recommendations and practice guidelines made accessible to key decision makers such as National Immunization Technical Advisory Groups.

## 7. Study limitations

The recent coronavirus pandemic places minimal to no limitations on the conduct of this systematic review as no primary data collection or direct contact with participants need to be made. Although other LMICs may find the research useful, generalizability of the study findings to areas outside of the geographical focus of this review study (i.e., African region), may be limited. The geographical focus of this systematic review is largely motivated by the ongoing poor performance of hepatitis B birth-dose vaccination programs in Africa compared to other regions of the world (20,57). Additionally, the lack of robust systematic review evidence within the region, adopting a complex health systems approach, has been discussed previously in the Literature review section. Lastly, using hepatitis B birth-dose vaccination as a proxy for complex interventions in a complex health system might not provide an exhaustive insight into the performance of all complex health interventions.

## 8. Knowledge translation

Due to its relevance to global efforts towards the elimination of viral hepatitis as a public health threat, especially within the African region, the findings of this study will be shared with key stakeholders such as the WHO Africa regional office and the Coalition for Global Hepatitis Elimination. Given that this work is co-hosted by the Vaccines for Africa Initiative (VACFA, <http://www.vacfa.uct.ac.za/>), there will be a unique opportunity to share the findings of this systematic review with a diverse range of key stakeholders (members of National Immunization Technical Advisory Groups, healthcare providers, EPI managers, members of the pharmaceutical industry, academic researchers and scientists) involved in national immunization programs across Africa through VACFA's Annual African Vaccinology Course. It is anticipated that the findings of this systematic review will contribute useful recommendations for policy and practice when implementing complex interventions in complex health systems. Therefore, we plan to re-package the findings into policy briefs and present it through vaccinology and health systems-related platforms accessible to relevant stakeholders. The findings of this review study will be available in thesis format on the relevant University of Cape Town portal. In addition, the manuscript emanating from this thesis will be submitted for publication in the internationally accredited peer-reviewed journal, *Frontiers in Public Health*.

## 9. Timeline

The expected timeline of this proposed systematic review study will span a two-year period. This is inclusive of the initial scoping of the literature till the final thesis submission for completion of the intended degree. Research activities and milestones are depicted in **Table 6**.

**Table 6** Timeline of research milestones (Source: Author)

Component	Activity	Date
<b>Part A</b> Protocol development and literature review	<i>Research conceptualization</i>	May 2021 – June 2021
	<i>Scoping review: Literature search and screening</i>	June 2021 – August 2021
	<i>Scoping review: Data extraction and analysis</i>	August 2021 – September 2021
	<i>Scoping review: Write up</i>	September 2021 – December 2021
	<i>Scoping review: Draft submission for expert checks</i>	January 2022
	<i>Scoping review: Implementing draft edits</i>	January 2022 – March 2022
	<i>Overall protocol finalization</i>	March 2022 – April 2022
<b>Part B</b> Journal-ready systematic review manuscript	<i>Systematic review: Literature search and screening</i>	April 2022 – May 2022
	<i>Systematic review: Data extraction and analysis</i>	May 2022 – September 2022
	<i>Systematic review: Write up</i>	September 2022 – February 2023
	<i>Systematic review: Draft submission for expert checks</i>	February 2023
	<i>Systematic review: Implementing draft edits</i>	March 2023 – May 2023
	<i>Intent to submit</i>	June 2023
	<i>Submission for examination</i>	June–July 2023

## 10. Study budget

This systematic review study does not require any dedicated funding. Any unanticipated expenses will be borne by the researcher. By design this systematic review study will not incur any costs during the conduct of the research.

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## PART B: JOURNAL MANUSCRIPT

### Towards contextualized complex systems approaches to scaling-up hepatitis B birth-dose vaccination in the African region: A qualitative systematic review

*Targeted journal: Frontiers in Public Health*<sup>1</sup>

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#### Abstract

**Background:** Despite the longstanding implementation of universal hepatitis B infant vaccination programs, the World Health Organization African (WHO AFRO) region maintains the highest prevalence (2.5%) of chronic hepatitis B virus (HBV) infection among children  $\leq 5$  years of age. Scaling-up hepatitis B birth-dose vaccination across this region could avert ~500 000 annual deaths caused by HBV-related liver disease and advance global progress towards eliminating viral hepatitis. Such efforts will benefit from high quality, locally generated evidence syntheses which meet the needs of policy makers and implementers.

**Objective:** To describe whether – *and how* – complexities within the health system or intervention influence the performance of hepatitis B birth-dose vaccination programs in the WHO AFRO.

**Methods:** Using a complexity perspective, we conducted a qualitative systematic review of literature published between 2009–2022. A Boolean search strategy retrieved relevant literature indexed in PubMed, EBSCOhost databases, Scopus, and Web of Science, with supplementary searches conducted to identify any missed articles. No language restrictions were applied. Data extraction, synthesis and analysis were guided by a systems-based logic model tailored to systematic reviews of complex interventions.

**Results:** Our search yielded 672 published records. Of these, 28 (26 in English, 2 in French) were judged to be eligible for inclusion. Among the 12 WHO AFRO member states represented, the origin of evidence weighted highest in Nigeria (n=12) and Senegal (n=5). The performance of hepatitis B birth-dose vaccination programs across member states was influenced by underlying complexities across eight cross-cutting themes: (i) availability and interpretation of hepatitis B birth-dose vaccination policies, (ii) capacity of vaccine supply and cold chain systems, (iii) availability of equitable and sustainable financing, (iv) capacity and capability of health care workers (HCWs), (v) immunization monitoring systems and impaired feedback loops, (vi) influence of context vs system design on the timeliness of hepatitis B birth-dose vaccination, (vii) maternal knowledge and socio-economic factors, and (viii) wider contextual factors (geography, climate, cultural practices).

**Conclusion:** This systematic review draws on the complex links between the intervention design and the existing health systems of WHO AFRO, providing a complex explanation on the reasons why simply introducing the vaccine might not lead to timely uptake or improved coverage. Our findings suggest countries looking to improve program performance, and those planning on adopting the intervention, will benefit from assessing components of the intervention design that require responsiveness and flexibility (vaccine accessibility and delivery), or inflexibility (policy interpretation); where stakeholders require support (HCWs and government ministries); and where innovation is required to fit the complex interventions (information systems and supply chains).

**Keywords:** *Hepatitis B; Hepatitis B virus; Vaccine; Birth-dose; Health systems; Complexity; Africa*

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<sup>1</sup> See **Appendix K** for Frontiers in Public Health author guidelines.

<sup>2</sup> For the purpose of this thesis, the student is the first and sole author of this systematic review.

## 1. Introduction

Vaccination of newborns within 24 hours of life with a single dose of the hepatitis B vaccine, also known as hepatitis B birth-dose vaccination, is pivotal to preventing mother-to-child-transmission (MTCT) of hepatitis B virus (HBV) infection. Acquisition of HBV infection through MTCT is a major public health concern as this carries a 90% risk of progression to chronic HBV infection, leading to liver cirrhosis, end-stage liver disease, liver cancer and premature death (1). Globally, 296 million persons are chronic carriers of HBV, with the highest prevalence rates borne by the World Health Organization (WHO) Western Pacific (5.9%) and African (WHO AFRO) regions (7.5%) (2). Of particular concern within the WHO AFRO is the fact that 2.5% of children under the age of five years currently live with chronic hepatitis B despite being entirely vaccine preventable (2). This disease burden is unacceptably higher than that in any other region in the world, and without urgent intervention, portends derailment of the global progress towards eliminating viral hepatitis as a significant public health threat by 2030 (3).

Among the available strategies for the prevention of chronic HBV infection, hepatitis B vaccination has been recognized as the most effective (4). Universal hepatitis B infant vaccination initiated at 4 or 6 weeks of age, has long been implemented in all 47 WHO AFRO member states (5), achieving over 70% coverage since 2014 (6). Despite this, the region maintains the highest burden of chronic HBV infection among under five-year-olds, surpassing the global prevalence of 0.9% (2). There are significant gaps in existing interventions aimed at controlling the burden of chronic HBV infection within Africa. The WHO recommendation on hepatitis B birth-dose vaccination for the prevention of HBV MTCT has been in place since 2009 (4,7). Further to this, the World Health Assembly in 2016, endorsed the WHO goal to eliminate hepatitis B as a global public health threat by 2030, in part by achieving 90% coverage of timely hepatitis B birth-dose and infant vaccinations (8,9). Steady progress has been made in the global arena with 111 of 194 WHO member states adopting national hepatitis B birth-dose vaccination programs, although the coverage rate (42%) remains a concern (8,10). While the Western Pacific has been able to attain a hepatitis B birth-dose vaccination coverage of 78% in response to its regional burden of disease, the 17% achieved across the 15 WHO AFRO member states that have thus far adopted hepatitis B birth-dose vaccination policies, is a dismal contrast (10).

Recognizing the inequitable implementation and poor program performance of hepatitis B birth-dose vaccination in Africa, several studies have sought to identify what the contributing determinants are. These note the current state of hepatitis B birth-dose vaccination programs in Africa is underpinned by a multiplicity of factors including, weak service delivery and inefficiencies across broader health systems, limited skilled health workforce trained to attend to birth and conduct post-natal visits, and the absence of political will to implement the program (9,11). It is important to note that previous evidence syntheses on this research focus have relied on limited empirical data from the African region, which tends to provide limited exploration of attendant systemic factors (12,13). Two scoping reviews applied a systems-based approach to categorize findings and present recommendations on scaling-up hepatitis B birth-dose vaccination programs (12,13). Though both reviews effectively utilized theoretical models, offering improved insights into determinants of program performance, neither addressed issues of complexity; either in the intervention itself or the broader systems delivering it. Further to this, while one review was conducted in sub-Saharan Africa, it only included 13 of 39 studies from Africa (12), and the other review found none of the studies from Africa eligible for inclusion (13).

It has been established that complex interventions are likely to have profound system-wide effects, more evident among weak health systems (14), and therefore may deserve increased attention in the research

agenda. Petticrew *et al.*, offer a pragmatic approach to conducting robust systematic reviews across complex interventions, supported by a comprehensive list of characteristics used to identify sources of complexity from either the intervention itself or from the intervention's causal pathway (15). Hepatitis B birth-dose vaccination programs meet the definition of a complex intervention on account of the limited degree of flexibility in the timing of administration (within 24 hours after birth) to achieve maximum effectiveness, the occurrence of multiple mediators and moderators of effect throughout its implementation process, and the presence of feedback loops where changes in behavior among the people at the center of the program (including program implementers, external partners and donor agencies, policy- and decision- makers, and end users) encourage further behavioral change and thereby influence the performance and outcomes of the intervention (15,16). To bridge the knowledge gap and support rational reforms to existing policy, practice, and research, guided by locally generated evidence, we examine if (*and how*) complexity of the health system and / or intervention influence the performance of hepatitis B birth-dose vaccination programs in the WHO AFRO region.

## 2. Methods

Using a complexity perspective, an exploratory qualitative systematic review study was conducted in two phases aimed at improving our limited understanding of the interaction between hepatitis B birth-dose vaccination programs and health systems in Africa. The first phase involved a scoping review which then informed the execution of the qualitative systematic review in phase 2. Phase 1 was essential in gaining an in-depth and up-to-date understanding of the hepatitis B birth-dose vaccination landscape in the region, highlighting the challenges of its implementation in differing contexts. A primary outcome of the scoping review was an adapted systems-based logic model for understanding complexities underlying the implementation of hepatitis B birth-dose vaccination programs, *see Part A* (16). The themes derived from the logic model were then used to organize and analyze the findings of this systematic review alongside methodological guidance from Petticrew *et al.*, (15) on conducting systematic reviews of complex interventions. Furthermore, this systematic review adopted the Joanna Briggs Institute (JBI) approach to qualitative synthesis (17) and was conducted in line with the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) statement (18).

### 2.1 Literature search strategy

A Boolean search strategy comprising key search terms and search term synonyms was developed drawing on the target population, intervention, and outcomes. Using this search strategy, peer-reviewed literature was sought from several electronic databases and platforms, namely, PUBMED (including MEDLINE), EBSCOhost (Academic Search Premier, Africa-Wide Information, CINAHL, Health Source: Nursing/Academic Edition, APA PsycInfo), Scopus, and Web of Science (excluding MEDLINE). The complete strategy for each database is provided in **Appendix H**. Supplementary searches were also conducted by reviewing bibliographies of key articles in order to identify any relevant records that may have been missed by the electronic database searches. Further to this, recommendations on key literature from co-reviewers were obtained and Google Scholar alerts activated to assist in the identification of any upcoming research in the field throughout the review period. Search terms used for Google Scholar alerts included "Hepatitis B birth dose vaccine OR vaccination OR vaccinated", "Africa OR African", "deprived country OR countries OR populations". The final literature search date was 30 September 2022.

## 2.2 Eligibility criteria

Literature sources were included if they met the following criteria: empirical studies of quantitative, qualitative, or mixed methods study designs involving human participants; primary studies conducted in one or more of the WHO AFRO member states; and research exploring hepatitis B birth-dose vaccination as a primary or secondary outcome measure. Only articles with accessible abstracts and full texts were included in this review. The search was limited to literature published between 2009–2022, due to the WHO recommendation of universal hepatitis B birth-dose vaccination for all member states since 2009 (7,19). This time frame ensured relevant and recent literature sources were retrieved and allowed for the observation of country progress in the adoption and implementation of hepatitis B birth-dose vaccination programs. We did not place any restriction on the language of publication in order to lessen the likelihood of language and publication bias, especially given the multi-lingual context of Africa. Literature sources were excluded if they were found to, (i) only measure epidemiological outcomes of vaccination; (ii) investigate hepatitis B infant vaccination administered from 4 or 6 weeks after birth or vaccination programs other than hepatitis B birth-dose vaccination; and (iii) involve research conducted in non-WHO AFRO member states. Furthermore, reviews, modelling studies, reports and commentaries were excluded from this systematic review.

## 2.3 Literature screening and selection

All search results were imported from the respective databases to Mendeley Desktop® reference manager (20). After removal of duplicates in Mendeley®, literature sources were exported to Rayyan®, a web-based application for systematic reviews (21). Further duplicates were then detected and resolved. Thereafter title and abstract screening continued in Rayyan®, guided by the eligibility criteria. Full texts of studies earmarked for potential inclusion were then retrieved and reviewed for relevance and eligibility. The literature search and screening process was conducted by the primary author (TR) with supervision from co-reviewers (EAD and JO). Where discrepancies arose, a decision was made through discussion and consensus among all reviewers.

## 2.4 Critical appraisal

Following the selection of full texts for inclusion, each eligible study underwent a quality appraisal. This process assessed the appropriateness and agreement of the research question and objectives; the selection and conduct of the methodology, and the analysis and applicability of the findings reported. Critical appraisal tools developed by the Critical Appraisal Skills Programme (22), the Mixed Methods Appraisal Tool (23) and the assessment scale by Dufault and Klar (24) adapted by Cortes-Ramirez (25) were used. Templates of these appraisal tools can be found in **Appendix E, F, G**. The current practice of quality appraisals encourages a description of the judgement of ratings, as opposed to an overall score (22,23). However, this can be problematic when attempting to report the overall results of multiple appraisal tools applied in a single systematic review. In this systematic review, metrics were developed and used to describe the overall judgement of quality for each study. The Mixed Methods Appraisal Tool scoring was based on the 2011 version (26) and has been used in previous systematic reviews (27,28). Overall scores were calculated as a percentage of the criteria met (20%–100%) (26). In the case of mixed methods studies the percentage of the lowest study component was awarded as the overall score (26). Similarly, we quantified responses to questions in the Critical Appraisal Skills Programme tool (Yes=1, No=0, Can't tell=0.5) as done in other systematic reviews (29,30). Overall scores calculated were judged as low, medium, or high-quality dependent on their correlated scores within the first-, second- or third- thirds of the total, respectively. The adapted Dufault and Klar assessment scale correlated scores with the overall judgement from low (<5 points) to high (>8 points)

relevance (25). Studies considered to be of low quality were not automatically excluded but reviewed and discussed among co-reviewers in order to further evaluate its relevance and value against the quality shortfalls identified. Twenty-one studies were appraised using the Mixed Methods Appraisal Tool, six using the Critical Appraisal Skills Programme tool and one using the adapted Dufault and Klar assessment scale. Three papers were judged as being of lower quality. Notably, those employing a mixed method design (n=2) were inclined to perform better on the quantitative study components compared to the qualitative ones, which brought down their overall quality ratings. The lowest rated study was a cross-sectional study as it did not include details on sample representativeness, or control for possible confounding or modifying factors. None of those judged as low quality were excluded as the data still provided considerable value within context. Nevertheless, overall average scores were high (see **Appendix I**). Furthermore, ethical consideration and rigor were assessed by reviewing evidence of author reflexivity and affiliations, transparency on sources of research funding, and declarations of potential conflicts of interest.

## **2.5 Data extraction**

The data extraction process was guided by the adapted systems-based logic model tailored to systematic reviews of complex interventions, developed during the preceding scoping exercise and drawing on the workings of Rohwer *et al.*, on how to make sense of complexity in systematic reviews (16). A study-specific data extraction sheet was designed using this logic model to identify essential variables and interactions within hepatitis B birth-dose vaccination programs, such as: context, intervention design/delivery/execution, and intermediate/health and non-health outcomes. The data extraction sheet provided a standardized systematic record of the data summaries attained from every literature source, ensuring traceability and validity of the data extracted. This process was led by the primary author and audited by co-reviewers.

## **2.6 Data synthesis and analysis**

Descriptive, analytical, and qualitative data extracted from eligible studies were synthesized. Relevance and organization of the data was driven by the theoretical model, and broadly categorized as a feature of implementation, intervention, context, or outcomes. An inductive thematic analysis process was then undertaken with the development of codes and relevant themes. Themes were interpreted for underlying complexities of the intervention or through possible interaction with contextual factors in the intervention causal pathway. In studies where national hepatitis B birth-dose vaccination policies have been adopted, an exploration of both enabling factors and constraints to program implementation was done. In those studies where hepatitis B birth-dose pilot interventions or in-depth inquiries have been conducted in the absence of nationwide program adoption, an exploration of anticipated influential factors was performed.

## **3. Results**

A total of 672 published records yielded from the literature search. These consisted of 666 articles retrieved via electronic databases, 4 from supplementary bibliographic searches, one from a co-reviewer recommendation and another through a Google Scholar search alert. After deduplication, title and abstract screening, and full text review, 28 articles were judged to be eligible for inclusion in this systematic review, see **Figure 1**.

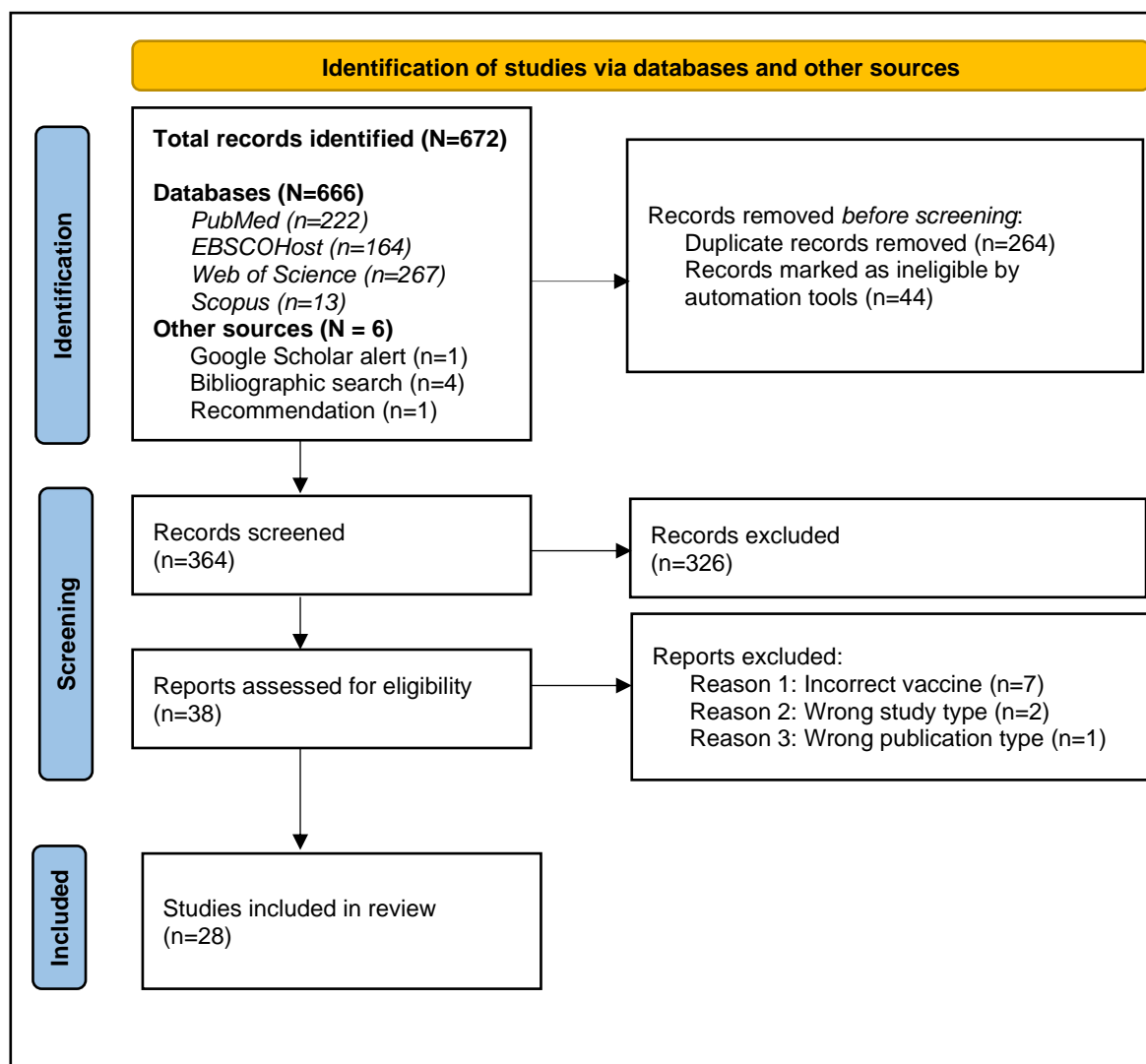


Figure 1 PRISMA flow diagram of literature search and selection process (Source: Author)(18).

### 3.1 Characteristics of included studies and study participants

The 28 studies included in this systematic review reported on findings from 12 African states namely: Nigeria, Senegal, Uganda, The Gambia, Mozambique, São Tomé and Príncipe, Burkina Faso, Ethiopia, Côte d'Ivoire, Benin, Namibia, and Botswana. Included in this tally was one multi-country study reporting findings from five African countries (Nigeria, Namibia, Botswana, São Tomé and Príncipe, and The Gambia) (31). The evidence distribution weighted greatest in Nigeria ( $n=12$ ), followed by Senegal ( $n=5$ ). Two studies reported on global findings with results aggregated by region. Of these findings only those relating to the African region were extracted and synthesized. Of the 28 included studies, 26 were published in English and 2 in French. A member of the research team who is a native French speaker worked closely with the primary author (TR) to screen, extract and analyze data from these papers with oversight from the co-reviewers. A summary of the characteristics of included studies can be seen in **Table 1**.

Of the 28 studies, 25% ( $n=7$ ) were conducted at a time when the relevant countries did not have a national policy for hepatitis B birth-dose vaccination in place. Seventy-one percent of studies ( $n=20$ ) were conducted in settings that had implemented universal hepatitis B birth-dose vaccination, while 14.3% ( $n=4$ ) employed selective hepatitis B birth-dose vaccination, and 10.7% ( $n=3$ ) did not report their implementation strategy. The

multi-country study (n=1) reported on both universal and selective hepatitis B birth-dose vaccination programs in the individual countries investigated, see details in **Appendix J**.

Most studies (64.3%; n=18) adopted quantitative cross-sectional designs. The remainder used qualitative (n=2), quantitative cohort (n=4), mixed methods (n=3) and quasi-experimental (n=1) study designs as shown in **Table 1**. Based on the methodology, a cross-sectional study was more accurately judged and appraised as having used an ecological study design. One of the qualitative studies included a cost-effectiveness analysis, however for the purpose of this systematic review only the qualitative outcomes were assessed and analyzed.

Mother-infant pairs were the largest population group and source of information amongst the studies. In total 18 (64.3%) of the included studies extracted data from mother and infants, even though only nine studies (32%) directly identified mother-infant pairs as their study population. Disaggregation of study populations further detailed pregnant women (n=4; 14.3%), mothers (n=1; 3.5%), infants/children (n=6; 21.4%), health care workers (HCWs) (n=6; 21.4%), health facilities (n=3; 10.7%) and countries (n=2; 7.1%). Among those studies involving pregnant women, two were longitudinal studies which provided further information on infants born to these cohorts upon follow-up. Data sources of health facilities and countries included regional experts in the field, informants from the Ministry of Health (MoH), HCWs involved in vaccination services, and partner or stakeholder organizations.

The included studies predominantly focused on identifying factors associated with the performance of hepatitis B birth-dose vaccination programs (14/28, 50%). Of interest, 9/14 (64.3%) studies specifically focused on adherence to the timeliness of hepatitis B birth-dose vaccination of which 7/9 (77.8%) were conducted in Nigeria. A limited number of studies (4/28, 14.3%) evaluated the performance and outcome of broader routine immunization-related programs, with hepatitis B birth-dose vaccination serving as one of several performance indicators. These studies were able to demonstrate vaccine effectiveness in real-life settings. One other study (1/28, 3.6%) determined vaccine efficacy when comparing hepatitis B birth-dose vaccination followed up by two vs three doses of the hepatitis B vaccine in infancy. The remainder were concerned with knowledge, awareness, practice, or perception of hepatitis B birth-dose vaccination (9/28, 32.1%) among key populations such as HCWs (5/9, 55.3%) and pregnant women or mothers (4/9, 44.4%), see details in **Appendix J**.

**Table 1.** Summary of characteristics of included studies (Source: Author)

Characteristic	Categories among included studies	No. of studies
<b>Country (N=28)</b>	Nigeria	12
	Senegal	5
	São Tomé and Príncipe	1
	The Gambia	1
	Uganda	1
	Burkina Faso	1
	Mozambique	1
	Côte d'Ivoire	1
	Ethiopia	1
	Benin	1
	Global	2
	Multi-country (Botswana, Namibia, The Gambia, Nigeria, São Tomé and Príncipe)	1
<b>Language (N=28)</b>	English	26
	French	2
	Universal	20

<b>Vaccination strategy (N=28)</b>	Selective	4
	Universal and selective	1
	Not reported	3
<b>Study design (N=28)</b>	Quantitative cross-sectional	18
	Quantitative cohort	4
	Qualitative	2
	Mixed methods	3
	Quasi experimental	1
<b>Study population (N=28)</b>	Mother-infant pairs	9
	Infants/children	6
	Mothers	1
	Health care workers	3
	Pregnant women	4
	Countries	2
	Health facilities	3
<b>Primary focus of study (N=28)</b>	Factors associated with vaccination performance	14
	Evaluation of broader immunization-related programs	4
	Efficacy of hepatitis B vaccination programs regiments	1
	Knowledge, awareness, perceptions, and practice in key populations	9

### 3.2 Sources of complexity in hepatitis B birth-dose vaccination programs

Eight cross-cutting themes were identified across the included studies. These themes describe the complexity produced at the intersection of hepatitis B birth-dose vaccination programs and health systems. These eight themes are listed in **Table 2** and are further unpacked individually below. In terms of theme frequency, the theme on the ‘influence of wider contextual factors on timely hepatitis B birth-dose vaccination’ was most frequently identified (19 of 28 studies) and the ‘role of immunization monitoring systems and impaired feedback loops’ the least frequent (11 of 28 studies). The balance between the frequency and the depth of exploration among themes was notable. For example, the theme on the ‘influence of maternal knowledge and socio-economic factors on timely hepatitis B birth-dose vaccination’ was recurrent and detailed (18 of 28 studies), whereas the ‘availability of equitable and sustainable financing for hepatitis B birth-dose vaccination programs’ though repeatedly referred to (17 of 28 studies), possessed the least in-depth exploration of its mechanisms and function.

**Table 2.** Frequency of themes identified among included studies (Source: Author)

Theme	Frequency of theme	Example of theme	Study (Author, year)
i. Availability and interpretation of hepatitis B birth-dose vaccination policies	13	National policy on hepatitis B birth-dose allows for the at-birth vaccination to be administered up until 14 days post birth	Okenwa et al., 2019 (48)
ii. Capacity of hepatitis B birth-dose vaccine supply and cold chain systems	15	Stock outs ranked 3 <sup>rd</sup> in the reasons for delay of vaccination among mothers	Danjuma et al., 2020 (57)
iii. Availability of equitable and sustainable financing for hepatitis B birth-dose vaccination programs	17	Pregnant women concerned about unaffordable cost of vaccine and charges they may carry once vaccination implemented in the country	Nankya-Mutyoba et al., 2021 (47)
iv. Capacity and capability of HCWs delivering hepatitis B birth-dose vaccination programs	16	Only ~50% of the medical practitioners surveyed thought it safe to administer hepatitis B birth-dose vaccine at birth	Jaquet et al., 2017 (44)
v. Role of immunization monitoring systems and impaired feedback loops	11	The absence of columns documenting the time at administration of hepatitis B birth-dose vaccine makes establishing timeliness difficult	Bassoum et al., 2022 (37)

vi. Influence of context vs system design on the timeliness of hepatitis B birth-dose vaccination	16	Mothers identified the lack of vaccine delivery on Friday evenings, weekends, or public holidays among the major reasons for delayed vaccination	Bada et al., 2022 (58)
vii. Influence of maternal knowledge and socio-economic factors on timely hepatitis B birth-dose vaccination	18	Maternal secondary education level was positively associated with timeliness of vaccination	Ibraheem et al., 2019 (55)
viii. Influence of wider contextual factors on timely hepatitis B birth-dose vaccination	19	In the primary health care system of The Gambia, village based TBAs and village HCWs are supervised by community nurses as more than 40% of deliveries occurred at home.	Miyahara et al., 2016 (46)

These themes were located across the twelve member states described in the characteristics of included studies. All eight themes were present in the literature emanating from Nigeria, followed by six themes identified among studies conducted in São Tomé and Príncipe and Senegal. A summary of the findings and geographic spread of the themes among the included studies can be seen in **Figure 2**.

### 3.3 Availability and interpretation of hepatitis B birth-dose vaccination policies

The influence of policy was not explicitly investigated by any of the studies included in this review. Among the 13 studies briefly touching on the direct or indirect role of policy in the implementation of hepatitis B birth-dose vaccination programs, it was important to note the variations in interpreting global recommendations, often resulting in disparate outcomes. The selective vaccination policy in São Tomé and Príncipe was found to be a principal barrier to achieving high hepatitis B birth-dose vaccine coverage rates in the country (31). In studies conducted in Nigeria, guidelines from the National Primary Health Care Development Agency allow for hepatitis B birth-dose vaccination to be administered up until two weeks after birth (48–50,55). This guideline was open to misinterpretation, likely misleading both HCWs and mothers into assuming that vaccination between day 0 and day 14 would infer the same level of protection or effectiveness against MTCT. The average age at hepatitis B birth-dose vaccination in Nigeria ranged across 6 days (54), 12 days (53), 14.3 days +/- 15.6 days (56), and 28.4 days +/- 40.4 days of life (52), with only one study presenting an average age of 1 day (57). In 2015, Nigeria revised its policy and Expanded Programme on Immunization (EPI) strategies to emphasize timely hepatitis B birth-dose vaccination within 24 hours of birth (31). Although well-meaning, this led to further misinterpretation, with HCWs assuming administration of the birth-dose should only be delivered within 24 hours or not at all (33). This revised policy led to an overall 30% drop in coverage of hepatitis B vaccinations across 27 health facilities in one study (33). In a later study (conducted between 2017–2018), 1.3% of mothers from Enugu State in Nigeria recommended the hepatitis B birth-dose vaccination policy should mandate vaccination within 24 hours to improve timely uptake (48). Also noteworthy was a similar case of policy misinterpretation in Namibia where the national recommendation on hepatitis B birth-dose vaccination allows for administration up until 2 weeks post birth (31), although further insights were not provided on the performance of the program in the context of this local policy.

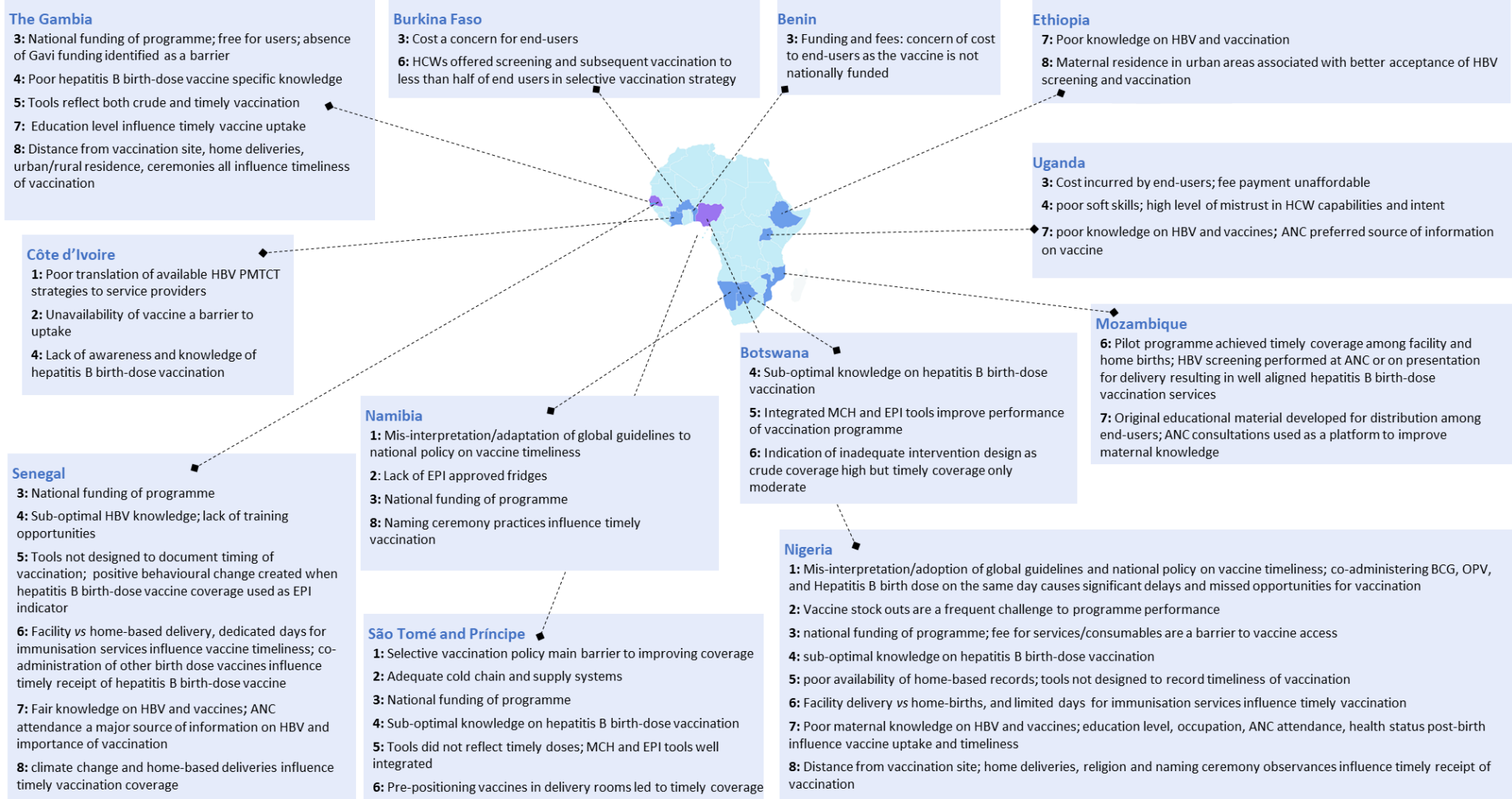
Plausible reasons for the misinterpretation of hepatitis birth-dose vaccination policies at the national level may be drawn from the influence of other birth-dose vaccination policies, such as those for *Bacillus Calmette-Guérin* (BCG) and oral polio vaccine (OPV). In instances where guidelines state that the birth-dose of OPV should be administered before 2 weeks of life (56) and BCG before 12 months of age (55) it was observed that HCWs in some countries tended to group birth-doses, leading to delays in administering the hepatitis B birth-dose vaccine. Accordingly, in a study conducted by Ibrahim *et al.*, it was suggested that the 14-day policy on administering BCG and OPV birth-doses affects the timely receipt of the hepatitis B birth-dose vaccine in

Nigeria, as HCWs often wait to administer them together (53). In Senegal however, a study exploring the perspective of HCWs on the acceptability and perceived challenges of implementing hepatitis B birth-dose vaccination found that they demonstrated good understanding of the need to vaccinate, the health benefits and the recommended timing (40). One HCW described their approach to home birthed neonates, grouping those presenting before and after 24 hours post birth (40). This interpretation of the policy by the HCWs acknowledges their understanding of the time sensitive nature of hepatitis B birth-dose vaccination (40). To the contrary, midwives in Côte d'Ivoire cited "ignorance" on available HBV MTCT prevention strategies as one of their reasons for not administering the birth-dose vaccine (35).

Only two of the included studies addressed the importance of written guidelines or standard operating procedures at the health facility level, especially in instances of vaccinating premature or very low birth weight (VLBW) infants. This includes a study by Moturi *et al.*, which noted that only 26% of facilities in Nigeria and 36% of facilities in Namibia (31) had written protocols, whereas the five health facilities (of differing levels of care) studied in São Tomé and Príncipe did not have any available (43). High hepatitis B birth-dose vaccine coverage rates observed in a Nigerian private hospital was associated with adopting facility guidelines in the form of a discharge checklist which included a hepatitis B birth-dose vaccination check in place (31).

**COLOUR KEY:** ■ Multiple findings across themes ■ Moderate findings across themes ■ Minimal findings across themes

**THEME KEY 1:** Availability and interpretation of hepatitis B birth-dose vaccination policies; **2:** Capacity of hepatitis B birth-dose vaccine supply and cold chain systems; **3:** Availability of equitable and sustainable financing for hepatitis B birth-dose vaccination programs; **4:** Capacity and capability of HCWs delivering hepatitis B birth-dose vaccination programs; **5:** Role of immunization monitoring systems and impaired feedback loops; **6:** Influence of context vs system design on the timeliness of hepatitis B birth-dose vaccination; **7:** Influence of maternal knowledge and socio-economic factors on timely hepatitis B birth-dose vaccination; **8:** Influence of wider contextual factors on timely hepatitis B birth-dose vaccination



**Figure 2** Summary of findings among available literature on the performance of hepatitis B birth-dose vaccination programs within health systems across African states (Source: Author)

### 3.4 Capacity of hepatitis B birth-dose vaccine supply and cold chain systems

Survey respondents participating in a global study conducted by Chang *et al.*, proposed improvements in vaccine supply, delivery, and storage as an approach to enhance global prevention of hepatitis B (38). As part of this survey study, local experts addressed the need to improve access to vaccines in hard-to-reach areas in Africa in order to reduce untimely administration of the hepatitis B birth-dose vaccine to neonates (38). In line with this, interrupted vaccine supply or stockouts were identified by mothers and pregnant women participating in six other studies as contributors to delayed vaccine uptake (47,48,53,54,56,57). Only two of the six studies rated stockouts as a major reason for delayed birth-dose vaccination (48,57). The proportion of mothers in each study who reported experiencing stockouts during visits to their health facilities can be seen in **Table 3**. Similarly, in three additional studies, HCWs found that unreliable vaccine supply chains, specifically vaccine stockouts, were limitations to the successful implementation of the hepatitis B birth-dose vaccination programs in their settings (35,40,41).

**Table 3** Incidents of stock-outs as identified by mothers for delayed hepatitis B birth-dose vaccination (Source: Author)

Study (Author, year)	Aim	Country	Participants surveyed (N)	% Reporting vaccine stockouts	Summary findings on vaccine supply
Okenwa et al, 2019 (48)	Assess uptake of timely hepatitis B birth-dose and reasons for non-receipt	Nigeria	254	20.1	Vaccine stockouts were identified as the 4 <sup>th</sup> highest reason among mothers for delayed vaccination.
Ibrahim et al, 2022 (53)	Establish timeliness and associated factors for delayed uptake	Nigeria	277	5.1	Apart from those who offered no reason (26%), stockouts ranked 8 <sup>th</sup> among reasons listed for delayed presentation for vaccination.
Ibraheem et al, 2022 (54)	Determine age at presentation for birth-dose and associated factors	Nigeria	439	6.8	Unavailability of vaccines were rated the 4 <sup>th</sup> highest among mothers who proffered reasons for delayed presentation for vaccination.
Sadoh et al, 2013 (56)	Assess factors contributing to delay in initiating immunization	Nigeria	148	1.3	Stockouts tied with “no money for transport” as the lowest ranked reason for delayed presentation for birth-dose vaccination.
Danjuma et al, 2020 (57)	Assess timeliness and identify barriers and predictors of at-birth vaccination	Nigeria	174	19	Vaccine stockouts were identified as the 3 <sup>rd</sup> highest barrier to timely administration of at-birth vaccines.
Nankya-Mutyoba, 2021 (47)	Explore awareness and perceptions of HBV, liver cancer and birth-dose vaccination	Uganda	Not applicable	Not applicable	Vaccines are at times absent from the health units, preventing neonates from receiving the scheduled dose

While vaccine stockouts have had a negative impact on hepatitis B birth-dose vaccination programs in Africa, improvements in the supply chain have been noted in the region. Only two of 78 facilities investigated across African countries reported experiencing stockouts in one multi-country study (31), where findings in another study reported the duration of stockouts lasting less than 2 weeks (43). Multiple studies included in this review indicate that vaccines are supplied by central government (43,46,53,55) in a process coordinated by state or regional health teams. A central area or depot is then accessible for the collection of vaccines to districts and facilities (46,53,55). Two studies conducted in Nigeria for example, note that collection from these central areas by vaccinators takes place 2–3 times a week (53,55). In the state of Kano, Nigeria, a direct-to-facility-delivery approach was trialed (33). This initiative resulted in a statistically significant decrease in vaccine stockouts and an increase in stock adequacy levels due to reduced bottlenecks at the local government authority cold stores (33). The HCWs participating in this study reported being able to afford more time to direct patient care and

health facility management, and less time away from their posts in order to collect vaccines (33). A year after the initial roll-out and implementation of the initiative, an increase in vaccination coverage was noted with positive results in the coverage of nearly all vaccinations monitored in Kano (33). However, coverage of the hepatitis B birth-dose vaccine decreased owing to misinterpretation of the national policy as described previously (33). Explicit information on vaccine supply to private health facilities was not available from the included studies, although one study reported on the exchange between Namibian and Nigerian private facilities and their respective MoH, where vaccine supply was received in exchange for monthly reports including coverage data (31).

Regarding adequate and sustainable storage, it has been noted among the evidence-base that power outages influence the functioning of cold chain systems, leading a HCW in Senegal to suggest the use of solar energy as an alternative power source (40). Accordingly, a study conducted in The Gambia reported the use of solar panels to operate vaccine fridges (46), although no details were provided on whether this improved the cold chain system. The matter of EPI approved fridges was mentioned in two studies as either absent or working well. Moturi *et al.*, note that 52% of Nigerian and 12% of Namibian facilities studied lack EPI approved fridges while facilities in São Tomé and Príncipe, Botswana, and The Gambia were found to have good quality cold chain systems (31). Further to this, all five facilities in São Tomé and Príncipe assessed by Hagan *et al.*, possessed EPI approved fridges with vaccines being monitored twice a day (43).

### **3.5 Availability of equitable and sustainable financing for hepatitis B birth-dose vaccination programs**

In-depth exploration of the funding mechanisms for hepatitis B birth-dose vaccination programs was largely absent from the included studies. In one study assessing 62 countries including 13 African member states, it was revealed that 55% had their hepatitis B birth-dose vaccines covered by government funding and 5% by private insurance (38). Miyahara *et al.*, addressed the lack of funding support from Gavi, the Vaccine Alliance for hepatitis B birth-dose vaccination programs compared to the pentavalent vaccine in eligible countries within Africa (46). It has been reported that increased national health expenditure per capita correlates with higher hepatitis B birth-dose vaccine coverage rates ( $p=0.03$ ), highlighting the need to strengthen domestic investments to supplement support from external sources (34). In the study assessing direct-to-facility vaccine supply for example, the initiative was reported to have been funded by a tripartite agreement involving the Bill and Melinda Gates Foundation, the Dangote Foundation, and the Kano State Government of Nigeria (33). The inclusion of state funding was aimed at encouraging greater political will and country ownership (33). Similarly, a hepatitis B birth-dose pilot program in Mozambique was reported to have received funding from Médecins Sans Frontières (Doctors Without Borders) in partnership with the national MoH (45).

Where financial accessibility of the hepatitis B birth-dose vaccine is concerned, seven studies reported that hepatitis B birth-dose vaccination was free for users as part of their national immunization schedule, particularly in public health facilities (31,38,40,43,51,54,55). Moturi *et al.*, made note of the existence of fee payments for hepatitis B birth-dose vaccination in private facilities in Botswana and Nigeria (31). End users are required to pay a fee to cover the cost of services, in some instances due to consumable shortages, despite the vaccine itself being free (31,41,48). In a quasi-experimental study conducted in Nigeria investigating the perceptions of mothers before and after HCW sensitization, 80% of respondents judged the fees charged to supplement shortages in consumables to be reasonable (41). However, in another study conducted in Nigeria, 6.3% of mothers participating in a study reported fee payment for immunization as their reason for delayed vaccination (48). Some mothers (8.1%) in this study recommended the vaccine should be entirely free of charge

in order to improve timely uptake in Enugu State, south-east Nigeria (48). In Uganda pregnant women residing in both urban and rural settings believed the cost of the hepatitis B birth-dose vaccine to be unaffordable, and raised concerns of charges it would carry when implemented (47). Similarly, the pilot study on prevention of MTCT (PMTCT) of HBV in Burkina Faso, reported the cost of the hepatitis B birth-dose vaccine to be \$7.76 USD, incurred entirely by the consumer (42). Other costs borne by the consumer included those for HBV screening tests, treatments, and vaccination (42). The authors acknowledge that the costs of all tests, treatments, screening, and vaccines need to be considered in relation to the income levels in Burkina Faso (42). In Benin, Accrombessi *et al.*, also elaborate on the high out-of-pocket expense of hepatitis B birth-dose vaccination, costing \$8 USD, given that the vaccine had not been included in the national immunization schedule at the time of the study being conducted (32). In this same study, it was reported that HCWs recommended hepatitis B birth-dose vaccination to mothers according to their financial means (32). No further details were provided on how HCWs in this study assessed parents' financial capabilities prior to recommending the hepatitis B birth-dose vaccine (32).

### **3.6 Capacity and capability of HCWs delivering hepatitis B birth-dose vaccination programs**

A dominating theme within the included studies was the lack of training for vaccinators or other HCWs involved in hepatitis B birth-dose vaccination programs. Two main population groups offered valuable insights on this, end users (mothers or pregnant women) (41,48), and HCWs themselves (31,35,38,40,43,44,56). In the qualitative component of a mixed method study conducted in Senegal, overall attitudes, and beliefs among HCWs on hepatitis B birth-dose vaccination was judged to be good. Generally, HCWs lacked basic knowledge on HBV and had limited access to hepatitis B birth-dose specific training, although 85% knew the first dose should be administered within 24 hours of birth (40). Interestingly, in this same study, those predominantly involved in vaccination services (46%) were more likely to have middle or lower levels of formal education (72%) but were also more likely to have received HBV-specific training (72%) (40). Of those who were mainly involved in antenatal care (ANC) and activities (54%), only 47% had received HBV-specific training (40). In a São Tomé and Príncipe study, 80% of facilities received training on hepatitis B birth-dose vaccination and HCWs in all five sites studied were aware that administration of the birth-dose should be within 24 hours post birth (43). A study conducted to assess the knowledge and attitude among medical practitioners working in an urban setting in Senegal, reported that 21% attained low HBV knowledge scores (40). Among these medical practitioners, a low level of knowledge was attributed to not attending any HBV-specific lectures after basic medical training (odds ratio or OR 6.0 [95% CI 1.4–26.4]) (44). Among the total population of medical practitioners studied, only 51.2% thought it safe to administer vaccines to newborns, of which the rest linked misconceptions of infertility (48%) or neurological disorders (37.8%) to the vaccination (44). In a multi-country study, the lack of training for HCWs specific to hepatitis B birth-dose vaccination ranged from 56% in The Gambia to 88% in Botswana (31). Knowledge of the recommended administration window was high but suboptimal knowledge of contraindications and age-limits were noted (31). False contraindications reported included prematurity, VLBW, and acutely ill but stable infants (31). Additionally, breastfeeding was delayed and discouraged by HCWs in a São Tomé and Príncipe study until after the hepatitis B birth-dose vaccine was administered for fear of MTCT of HBV (31). Similar findings were observed in another São Tomé and Príncipe study where health centers were less likely to vaccinate VLBW, premature, or clinically unstable neonates (43). In Senegal, immediate hospitalization of neonates was significantly associated with poorer outcomes of timely hepatitis B birth-dose vaccination (adjusted odds ratio or AOR 0.42, [95% confidence interval or CI 0.26-0.68]), whereas weighing neonates increased the chances of timely vaccination (AOR 3.90, [95% CI 1.79 – 8.53]) (37).

Both these practices could be related to the lack of knowledge on contraindications, and the confidence to vaccinate only when the infants weight indicates a better perceived assessment of health. An alternate and plausible explanation offered relates to reluctance among HCWs to vaccinate hospitalized or VLBW neonates in order to avoid any adverse events being linked to the vaccine or the vaccinators themselves (37). In contrast, a related study in Senegal found that immediate hospitalization of neonates after birth increased the odds of benefitting from co-administration of birth-dose vaccines by 1.74 times, when compared to those not requiring hospitalization after birth (AOR 1.74, [p=0.002]) (36). Weighing the newborn was also associated with better chances of co-administration of birth-dose vaccines (p=0.006) (36). Miyahara *et al.*, discuss the need to improve hepatitis B birth-dose vaccination awareness and training among delivery agents in The Gambia as no difference in timing was found between those delivered in health facilities and those born elsewhere (46). Similarly, in a Nigerian study, despite frequent contact with the health care system (92.2% of pregnant women attended ANC consultations and 81.1% delivered in a health facility) only 57.7% of women cited receiving information from HCWs on when to commence hepatitis B birth-dose vaccination (56). Furthermore, sources of information on hepatitis B birth-dose vaccination were further disaggregated into nurses (28.1%), ANC visits (20.3%), immunization sessions (17.2%), doctors (1.6%), unspecified HCWs (4.1%) and unspecified hospital activity (10.6%) (56). This finding supports that of a study conducted in Uganda where mothers reported that HCWs provided limited communication regarding vaccination needs, discouraging their involvement in the program (47). In two HBV PMTCT pilot programs conducted in Burkina Faso and Mozambique, training of HCWs on HBV prophylaxis, screening, counselling, and vaccination was conducted prior to rolling out the program (42,45). In Mozambique, Loarec *et al.*, indicate that training was given to project nurses, MoH nurses and midwives alike, consisting of a 1-day training course or on-the-job training (45). Despite training of HCWs on HBV prophylaxis, screening, and counselling in the Burkina Faso pilot program, less than half of the pregnant women accessing services during this pilot were offered hepatitis B screening (42). Sub-optimal screening practices led to missed opportunities to identify and timely vaccinate at-risk neonates. Reasons for poor HBV screening and targeted birth-dose vaccination practices reported by midwives in a study conducted in Côte d'Ivoire, include lack of awareness, lack of time, increased workload, and lack of or unavailable vaccines (35). Consequently, 41.4% of midwives reported not performing screening, while 52.3% reported not administering hepatitis B birth-dose vaccination to HBV exposed newborns (35). To mitigate such practices, a study in Nigeria trained HCWs by sensitizing them to improve the quality of immunization services (41). Post-intervention, a significant increase was found among mothers of the study group across two criteria; those who found information provided to them on immunization adequate; and those who correctly identified the number of visits left to complete the immunization schedule (41).

Regarding non-technical skills and communication of HCWs, younger pregnant women in Uganda viewed HCWs as rude and uncaring (47). They were also described as often not providing important information about newborns, including communication on vaccination requirements (47). This discouraged the buy-in of mothers and limited demand for the hepatitis B birth-dose vaccine, leading to missed opportunities for vaccination (47). Delayed vaccination was also linked with mistrust of HCWs (47). Pregnant women expressed concern about HCWs handling their newborns and administering injectables (47). They instead preferred oral vaccines over injectables as it reduced the risk of HCWs making errors when administering vaccines (47). The quasi-experimental study in Nigeria on the other hand, found that pre-intervention, 80% of women in both study and control groups felt that HCWs treated them with respect, were approachable and polite (41). Further to this, a statistically significant increase was observed among respondents in the study group post-intervention who rated HCWs approachable (p<0.05) (41). Lastly, another aspect of the capability of HCWs explored in the

evidence-base was the importance of delegating duties. Across facilities studied in the five African countries, senior oversight by medical practitioners was not required in order to deliver hepatitis B birth-dose vaccination, allowing midwives and other qualified cadres of HCWs to administer vaccinations without undue delays (31).

### **3.7 Role of immunization monitoring systems and impaired feedback loops**

Of the 28 included studies, 11 touched on data collection and information systems, with multiple studies referring to reliance on vaccination cards to monitor the administration of hepatitis B birth-dose vaccines (31,36,37,43,45,46,48–52). The monitoring process should serve as an active feedback loop, encouraging improvements as vaccine coverage outputs guide future operations of the program. However, if monitoring systems are inaccurate or data collection tools are inadequately designed (i.e., not fit for purpose), feedback loops are unlikely to be effective in improving programs and broader systems functioning. In the HBV PMTCT pilot program in Mozambique, reference to the suboptimal quality and completeness of data was accepted as a characteristic of the real-world setting (45). The dilemma in monitoring the accuracy of hepatitis B birth-dose vaccination coverage was recurrently linked to the reliance on home-based immunization records. In studies conducted in Nigeria, only 27.3% of children had their immunization cards available in one study (52) while 44% of mothers in another offered verbal confirmation of vaccination due to unavailable or ambiguous home-based records (50). The reliability of vaccination history recall is of course questionable as was demonstrated in a study conducted in Senegal which noted disparities between hepatitis B birth-dose vaccination coverage based on reports by mothers/caregivers versus that recorded in home-based or facility records (37). Overall, vaccination coverage reported by mothers/caregivers in this study was approximately 10% less than that recorded in home-based or facility vaccination records (37). In another study conducted in Senegal, the availability of home-based records was found to be associated with high co-administration rates of birth-dose vaccinations, with those having home-based records reported to be 6.88 times more likely to receive co-administered birth-dose vaccines compared to those without (AOR=6.88, [p=0.006]) (36).

Health facility records have frequently been used to correlate the accuracy of vaccination coverage or to determine the timeliness of hepatitis B birth-dose vaccine administration (37,48,49). Again, in Senegal, Bassoum *et al.*, found that hepatitis B birth-dose vaccine coverage rates were largely concordant between home-based records (82.3%) and health facility registries (84.1%), with similar trends noticed in coverage of other birth-dose vaccines (37). However, in the absence of columns dedicated to documenting the time of vaccination, establishing timeliness required calculation of the difference between the date of birth from health facility records and the date of hepatitis B birth-dose vaccine administration (37,48,49). This was instrumental in determining the large discrepancy between crude hepatitis B birth-dose coverage (88.5%) and valid timely doses (42.1%) (37). In São Tomé and Príncipe, although all 5 study sites provided written documentation, the date of hepatitis B birth-dose vaccination was not recorded and therefore establishing timeliness was not possible (43). Practices among facilities in The Gambia included adapting EPI records to reflect both timely and crude hepatitis B birth-dose vaccination (31). These studies underscore the need for clear and appropriate policies and guidelines, without which information systems cannot be designed to be fit for purpose, disrupting feedback processes, and rendering data like vaccine coverage and timeliness less useful for appropriate action.

In the multi-country study conducted by Moturi *et al.*, facilities in all five participating countries (Nigeria, Namibia, Botswana, São Tomé and Príncipe, and The Gambia) reported having designated columns for

recording hepatitis B birth-dose vaccination in their EPI reporting and recording tools, although older versions of these tools (without these columns) were still circulating in some facilities (31). In addition, tally sheets and reporting forms at facilities were routinely updated, but none of the maternity registers were modified with columns to record receipt of hepatitis B birth-dose vaccines (31). In health facilities in São Tomé and Príncipe, maternal child health (MCH) and the EPI tools were integrated, facilitating collaboration on implementing the hepatitis B birth-dose vaccination program (31). Similarly, health facilities in Botswana recorded data on hepatitis B birth-dose vaccination in both EPI tools and delivery registries (31). One study described a possible knock-on effect of monitoring, where timely hepatitis B birth-dose vaccination was used as an EPI performance indicator and may have encouraged better timely coverage of the vaccine when compared to other birth-dose vaccines in the study (BCG=13.9%; OPV=30%; hepatitis B birth-dose vaccine=42.1%) (36).

### 3.8 Influence of context vs system design on the timeliness of hepatitis B birth-dose vaccination

Twelve of the included studies explored timeliness of hepatitis B birth-dose vaccination. Even among those studies where measurement of timely vaccine administration or factors associated with delayed hepatitis B birth-dose vaccination were not the primary focus, timeliness emerged as an important challenge. Frequently reported determinants of timely vaccination among the studies reviewed ranged from institutional deliveries and health facility type, inaccessibility of immunization services and vial dosage and co-administration of birth-dose vaccines. Across the evidence-base, a valid or timely dose was often defined as vaccination on the day of birth or the day thereafter. However, time frames used to assess timeliness of hepatitis B birth-dose vaccination differed across countries and studies but frequently fell within day 0–1, day 0–7, and day 0–14, although in a study conducted in The Gambia, birth-dose vaccinations were recorded even after 6 and 12 months after birth (*see Table 4*). The summarized data presented in *Table 4* reflects two key findings on the timeliness of hepatitis B birth-dose vaccination in the region; (i) that the vaccine is typically administered between days 0–1 or 0–7 after birth with wide coverage rates ranging between 1.1% – ~92.4%, and (ii) that generally, vaccine coverage rates tend to increase with increasing age with the highest rates frequently recorded from day 0–14 and over.

**Table 4.** Timeliness and coverage of the hepatitis B birth-dose vaccine in WHO AFRO member states (Source: Author)

Study (Author, year)	Country	Hepatitis B birth-dose vaccination coverage (%)							Median / mean <sup>†</sup> age at receipt of vaccine
		Crude	*Day 0–1	Day 0–7	Day 0–14	Day 0–28	6 m	12 m	
Bassoum et al, 2022 (37)	Senegal	88.1	42.1	-	-	-	-	-	-
Périeras et al, 2021 (51)	Senegal	71.5	54.4	58.2	-	-	-	-	-
Okenwa et al, 2019 (48); and Okenwa et al, 2020 (49)	Nigeria	-	26.2	-	-	-	-	-	-
Ibrahim et al, 2022 (53)	Nigeria	-	11	26.3	68.5	-	-	-	12 days
Miyahara et al, 2016 (46)	The Gambia	-	1.1	5.4	-	58.4	93.1	93.3	24 days
Loarec et al, 2022 (45)	Mozambique	83.4	89.4	-	-	-	-	-	-
Guingane et al, 2020 (42)	Burkina Faso	-	78.3	-	-	-	-	-	-
Sadoh et al, 2014 (52)	Nigeria	-	-	31.7	39.0	43.9	-	-	28 <sup>†</sup> days ± 20.4 days
Ibraheem et al, 2022 (54)	Nigeria	75.1	20.5	~52.4	~68.1	~79.4	-	-	6 days

Sadoh et al, 2013 (56)	Nigeria	-	1.3	43.1	70.6	89.5	-	-	9 days
Danjuma et al, 2020 (57)	Nigeria	-	~53.8	~92.4	-	-	-	-	1 day
Ibraheem et al, 2019 (55)	Nigeria	~100	~49.8	~87.8	~94.6	~100	-	-	2 days
Bada et al, 2022 (58)	Nigeria	99	33	91	-	-	-	-	-
Olakunde et al, 2021 (50)	Nigeria	53	-	-	-	-	-	-	-
Moturi et al, 2018: (31)	The Gambia	84	7	-	-	-	-	-	11 days
	Nigeria	23	13	-	-	-	-	-	-
	Botswana	94	74	-	-	-	-	-	-
* Defined as vaccination on the day of birth or the day thereafter. - timeframe not recorded. ~ Approximation of hepatitis B birth-dose vaccination coverage value as disaggregated coverage among the 3 birth-doses (OPV, BCG, hepatitis B birth-dose) was not available in the respective study. † mean age at receipt of vaccine									

Ibraheem *et al.*, report that in Nigeria, the hepatitis B birth-dose vaccine performs the poorest when comparing crude coverage rates of all three birth-doses: 75.1% vs 91.2% for BCG and 82.1% for OPV, respectively (54). More importantly, this study observed that 20.6% of infants presented for all three birth dose vaccinations beyond day 28, with the majority (78.8%) not presenting on day 0–1 (54). This finding agrees with those from previous studies conducted by Sadoh *et al.*, which showed poor adherence to timely birth-dose vaccinations in Nigeria, where only 1.3% of neonates presented within 24 hours of birth in one study (56) and 56.1% of children received their hepatitis B birth-dose vaccine beyond day 28 in the other (52). In contrast, two other studies conducted in Nigeria reported better compliance to timely administration of hepatitis B birth-dose vaccination as the majority in one study presented (49.8%) within one day after birth and only 5.4% of infants beyond 14 days (55), while in the other study, 53.8% of infants received their birth-dose vaccinations within 24 hours after birth with nearly a third presenting between day 1–7 (57). Despite reporting the highest crude coverage estimates (98%) of hepatitis B birth-dose vaccination, the Kweneng District of Botswana in fact had the lowest timely estimates (62%) compared to other districts in the country (31). A noteworthy knock-on effect of untimely hepatitis B birth-dose vaccination is the further delay in uptake of hepatitis B infant vaccinations, as highlighted in studies from Senegal, Nigeria and globally (38,51,52).

The influence of institutional delivery on access to the hepatitis B birth-dose vaccine emerged as a prominent sub-theme under timely administration. Institutional delivery rates in WHO AFRO was positively and significantly associated with optimal coverage of the hepatitis B birth-dose vaccine ( $\rho=0.89$ ;  $p=0.04$ ), as reported by Allison *et al.*, (34). More specifically, among other included studies, seven found an association between institutional delivery and timely administration of the hepatitis B birth-dose vaccine (31,37,49,51,54–56). Neonates in a Senegalese study where most pregnant women (68.8%) delivered at a health facility, were 1.62 times more likely to receive timely hepatitis B birth-dose vaccination compared to their counterparts who were born elsewhere (AOR 1.62;  $[p=0.046]$ ) (37). In Nigeria, hospital delivery increased the odds of timely vaccination by 6-fold (OR 6.36,  $[95\% \text{ CI } 1.33-30.38]$ ) (55) and was a determinant of vaccination by day 0–1 compared to those presenting after day 1 (55). Despite most mothers (95.1%) delivering at a health facility in another Nigerian study, only 26.9% of the infants studied were administered timely doses, however the authors still observed a significant association between delivery at a health facility offering immunization services and the timely receipt of the hepatitis B birth-dose vaccine (49). This was advantageous to those delivering at such a health facility compared to those who did not (AOR 5.39,  $[95\% \text{ CI } 2.45-11.87]$ ) (49). Another study used a 1-week metric and reported that 50% of those delivering at a health facility and only 20.7% of those delivering outside of health facilities presented within this time frame for birth-dose vaccinations (56).

Though not a statistically significant finding, Bassoum *et al.*, found high facility delivery (71.8%) in Senegal to be an enabling factor for the co-administration of birth-dose vaccines (36). Similarly in another Senegalese study, being born at home as opposed to a health facility was significantly associated with non-adherence to timely administration of the hepatitis B birth-dose vaccine at the 10% threshold (AOR 2.02, [p=0.077]) (51). Furthermore, HCWs in Senegal who were interviewed as part of a study by Djaogal *et al.*, expressed their view of home deliveries being a barrier to timely vaccination and suggested sensitizing women to give birth in health facilities (40).

When stratified by health facility type, public facilities were favored over private ones where timely administration of the hepatitis B birth-dose vaccine was concerned (49,57). Danjuma *et al.*, for example, found that private health facilities in North-Central Nigeria were more likely to delay hepatitis B birth-dose vaccination by 2-fold compared to public health facilities [AOR 2.616; p=0.003] (57). Another Nigerian study investigating the influence of the place of birth on the receipt of hepatitis B birth-dose vaccination among 12-24-month-old children found the odds of vaccination were low in private facilities (AOR 0.77, [95% CI 0.59-0.99]) and home deliveries (AOR 0.48, [95% CI 0.36-0.63]) (50). Further to this, the odds of vaccination among neonates delivered at home when compared to those delivered at a private health facility was also found to be significantly lower in this study (AOR 0.62, [95% CI 0.43-0.88]) (50). Among reasons offered by mothers for delayed vaccination, 8.5% listed having delivered at a private hospital, 3% having delivered at home and another 3% delivered at church (55). In comparison, 91.3% of mothers participating in the study by Okenwa *et al.*, identified the unavailability of the vaccine at the delivering facility more than the actual place of delivery as the reason for delayed vaccination (48). In this study, 95.05% of mothers delivered at health facilities, with the majority delivering at private health facilities (53.5%) and public primary level care facilities (24.7%), but only 63.77% delivered at a place where the vaccination was offered, inferring that birthing facilities did not always offer birth-dose vaccination (48). Contrary to the aforementioned studies, two other studies found minimal influence of the place of delivery on the timely administration of the hepatitis B birth-dose vaccine (45,46). In the Gambia, while 59.7% of neonates were delivered at a health facility, only 0.6% had been vaccinated by day 1 and 3.8% by day 7 (46). Such coverage rates were not much higher than those recorded for the 40.3% of infants delivered outside of health facilities (day 1 =1.3%; day 7 =5.2%) (46). Similarly, comparable coverage rates of timely vaccination between home births (80%) and facility delivery (75.4%) were recorded in the HBV PMTCT pilot program in Mozambique, although the proportion delivering at home (n=5) was much lower than those who delivered in health facilities (n=199) (45). It is important to note, that during this pilot program, follow-up processes were integrated into routine ANC consultation where women who missed appointments were contacted by phone and those presenting for delivery were screened and their HBV exposed infants vaccinated as soon as possible by midwives (45).

Another key sub-theme was the accessibility of immunization service and its influence on timely uptake of hepatitis B birth-dose vaccination. This emerged across findings from 11 included studies (31,37,46,48,51,53-58). Most frequently cited as a barrier to accessing timely hepatitis B birth-dose vaccination was the allocation of immunization services on certain days of the week. In Nigeria, vaccination services were reported to only be available from Monday to Friday, excluding weekends and public holidays (53-55), or on Tuesdays and Thursdays in other facilities (57,58). Exceptions were made when the number of deliveries were large enough to warrant vaccination on days other than the two routine vaccination days (57). In relation to this, mothers across six studies identified the lack of vaccine delivery on Friday evenings, weekends, or public holidays among the major reasons for delayed vaccination (53,54,56-58). Further reasons proffered by mothers for

delayed vaccination included having fixed days for immunization clinics (4.2%) (55), not delivering (75.6%) (48) or presenting on a routine facility immunization day (31.2%) (57), being given a later date to return for vaccination (11.2%) (53) or waiting for the day of BCG immunization services (30.3%) (56). In a study by Ibrahim *et al.*, where vaccination services were available Monday to Friday from 8:00 – 15:00, delivery on specific days of the week was not found to have any statistically significant association with timely receipt of the hepatitis B birth-dose vaccine (53).

Further to the discourse on service accessibility, other studies provide useful insights into how the design of broader services influence the performance of hepatitis B birth-dose vaccination programs within the African region. In The Gambia, reproductive and child health clinics responsible for vaccinations take place once or twice a week, and a set schedule of supplementary outreach clinics take place on the other days of the week (46). Périères *et al.*, report that four health care posts found in the most rural areas in Senegal provide vaccination services on a particular day of the week and offer outreach to the villages furthest from the post (51). This contrasts with the situation across the five health facilities studied in São Tomé and Príncipe where daily birth-dose vaccination services were routinely offered without any supplementary outreach services (43). High timely hepatitis B birth-dose vaccination coverage was recorded in São Tomé and Príncipe, particularly among facilities that store hepatitis B birth-dose vaccines in labor wards (31). This was confirmed by findings from Hagan *et al.*, where health facilities in São Tomé and Príncipe provided hepatitis B birth-dose vaccination in delivery rooms (43). Maternal recommendations for improving timely vaccination in a Nigerian study echoed these insights, suggesting pre-positioning vaccines in labor rooms (22.7%) and making the vaccine available at all birthing health facilities (14.8%) (48). In addressing the design of services and wider systems, it is also important to highlight the role of vaccine technologies. Of the 28 studies, four addressed the use of multi-dose vials for the three commonly administered birth-dose vaccinations within African states (37,46,53,55). Hepatitis B birth-dose vaccination supplied in a 10-dose vial is valid for use up to 4 weeks once opened under the correct storage conditions (37). In contrast, BCG is supplied in 20-dose vials and only valid for use for up to 6 hours after opening (37). As such, vials are unlikely to be opened unless 10–12 neonates present for vaccination. Should they be born on a day BCG is not administered, they are unlikely to receive the BCG vaccine on day 0–1 according to a study conducted in Senegal (37). This was considered as one of the contributing factors to the better performance of hepatitis B birth-dose vaccination compared to BCG and even OPV (42% vs 13.9% and 30%, respectively) in this study (37). However, these practices may limit feasibility of timely administration at the time of delivery as found in Miyahara *et al.*, where multi-dose vials were a barrier to integrating all three birth-dose vaccination programs within broader maternal and neonatal health services (46).

### **3.9 Influence of maternal knowledge and socio-economic factors on timely hepatitis B birth-dose vaccination**

Maternal factors emerged as a prominent theme across the included studies. These factors were maternal awareness and knowledge of HBV and vaccination, ANC attendance, the health and well-being of mothers and infants post-birth, maternal level of education, maternal occupation, and maternal wealth. In terms of maternal awareness and knowledge of HBV and hepatitis B vaccination, this was found to have a statistically significant effect on the adherence to timely receipt of the hepatitis B birth-dose vaccine as demonstrated in three studies (49,55,56). Among them, timely vaccination was 2.4 (AOR 2.36, [95% CI 1.38-4.03]) (49) and 3 (OR 3.06, [95% CI 1.16-8.23]) (55) times more likely among infants born to mothers with good overall knowledge on HBV and vaccination. In a study focusing on the co-administration of birth-dose vaccines, knowledge of co-

administration and vaccine timeliness among mothers was found to be associated with better co-administration rates, it also predisposed neonates to receive all birth-dose vaccines on the same day (36). Studies surveying maternal reasons for delayed presentation frequently identified the lack of knowledge on the timing of vaccination (48,54,56). In one of these studies, poor knowledge and awareness on the timing of vaccination was the third highest reason for delayed presentation as cited by 72.8% of mothers (48). In support of this trend, findings from Ethiopia demonstrated that 89.6% of pregnant women attained poor overall scores on HBV knowledge, performing poorly in categories on the viral origin (87%), MTCT (87%) and the existence of a vaccine (85%) (39). Similar themes emerged from a qualitative study conducted in Uganda which found sub-par knowledge among pregnant women participating in focus group discussions, contributing to their poor overall understanding of HBV and vaccinations (47). A notable observation was that both these studies were from countries yet to adopt hepatitis B birth-dose vaccination as part of their EPI. In Senegal and Nigeria where the hepatitis B birth-dose vaccine is part of the EPI, mothers were found to perform well when assessed on their knowledge of commencement of the vaccination schedule, the benefits and co-administration of birth-dose vaccines (36), vaccine timeliness, HBV MTCT, and disease awareness (49).

Additional factors influencing maternal knowledge and awareness of hepatitis B birth-dose vaccination include place of residence, access to media, improved socio-economic status, gravidas, and level of education. In Nigeria, residing in rural areas was a negative predictor (AOR 0.55, 95% CI [0.34-0.89]) of good maternal awareness and knowledge of HBV (49), whereas in Senegal, mothers with access to television were 1.7 times more likely to receive timely hepatitis B birth-dose vaccination compared to those without (37). This was likely due to better access to information and information sharing mediums (37). Dagnev *et al.*, further showed that in Ethiopia, increased monthly income and primigravida were positively associated with good HBV knowledge; those earning >4000 Ethiopian Birr were 3.2 times more likely to have good HBV knowledge than those earning <2000 Ethiopian Birr, and primigravidae were 2.9 times more likely to have good HBV knowledge than multigravidas (39). In addition, maternal education at both primary and secondary levels was associated with good HBV knowledge in this study (39). Good knowledge of HBV was then further associated with better attitudes towards HBV treatment, screening, and vaccination, as 57% of pregnant women were willing to have their babies vaccinated against HBV while 53% demonstrated favorable attitudes toward vaccination, screening, and hepatitis B treatment (39). A Nigerian study also demonstrated the positive effect of maternal tertiary education (AOR 2.10, 95% CI [1.28-3.46]) on good maternal knowledge and awareness of HBV (49). In Senegal, HCWs found that mothers or pregnant women tend to experience difficulties in understanding the concept of HBV when they had no formal education (40). A survey of global experts suggests inclusion of education on hepatitis B in public education campaigns with the aim of increasing public awareness and motivation to vaccinate (38). Accordingly, as part of the pilot program in Mozambique, original educational material was developed as well as advice given during screening to improve knowledge and awareness among women (45). This practice supports maternal recommendations to educate mothers and caregivers on HBV and available vaccinations as a means to improving the performance of hepatitis B birth-dose vaccination programs in Senegal (48).

Summary findings on the association between maternal education and timely hepatitis B birth-dose vaccination are presented in **Table 5**. Of the 18 studies providing information on maternal level of education, five studies found a positive relationship between educated mothers and timely receipt of the hepatitis B birth-dose vaccine, while five other studies found no association, and eight did not compare these two variables. Across the five studies that found significant associations between educated mothers and those

without any formal education (46,53–56), the most frequent positive correlation was found between mothers with a post-secondary education and hepatitis B birth-dose vaccination by day 7 post-birth (46,55,56). These mothers were two (AOR 2.43, 95% CI [1.17–5.07]) and three times (OR 3.29,  $p=0.02$ ) more likely than uneducated mothers to present within 7 days for vaccination in the Gambia and Nigeria, respectively (46,55), with one other Nigerian study observing a strong significant relationship between these variables ( $p=0.0001$ ) (56). Additionally, the odds of timely hepatitis B birth-dose vaccination by day 0–1 was higher among mothers with a post-secondary education (OR 3.6,  $p=0.013$ ) (55). In a Nigerian setting, mothers with a primary level of education were 17 times more likely (AOR 16.95  $p=0.026$ ) to receive timely hepatitis B birth-dose vaccination within 24 hours post-birth when compared to those with no formal education, followed by those with secondary (AOR 5.9  $p=0.033$ ) and tertiary (AOR 7.7  $p=0.029$ ) education (53). Health care workers in a Senegalese qualitative inquiry believed uneducated pregnant women or mothers were less compliant with vaccination schedules (39). Overall, findings from these studies suggest that any level of formal education among pregnant women and mother may have a positive influence on the performance and outcomes of hepatitis B birth-dose vaccination programs in the African region.

Both neonatal and maternal health concerns post-birth were reported to influence delayed hepatitis B birth-dose vaccination. The proportion of mothers identifying their ill health as a reason for delayed presentation for vaccination ranged from 7.6% (55), 12.3% (56) to 16.2% (54), where those who identified having undergone a caesarean section as their reason ranged from 5.9% (55) to 6.1% (53). In Uganda women felt they needed to recover from the stress of childbirth before their newborns could be safely vaccinated, while others who underwent an operation suggested delaying vaccination till the day of discharge (47). Superseding maternal ill health, was the health and well-being of the neonates, as the baby's ill health was cited among reasons for delayed hepatitis B birth-dose vaccination in five studies (53,55–57). The proportion of mothers identifying their neonates' ill health as a deterrent to timely vaccination ranged from 5.8% (57), 9.7% (55), 10.5% (53), 11.6% (56), to 24.4% (54) across included studies. Among these studies, a lesser proportion of mothers identified prematurity as their reason for delayed vaccination (4% and 0.8% in two studies) (55,57). The behavior and practices of HCWs influencing timeliness of the hepatitis B birth-dose vaccination among premature, clinically unstable, or low birth weight/VLBW infants has been highlighted previously under the theme on the capacity and capability of HCWs delivering hepatitis B birth-dose vaccination programs.

**Table 5.** Summary findings on the association between maternal education and timely hepatitis B birth-dose vaccination (Source: Author)

Study (Author, year)	Country	Participants (N)	Maternal level of education (%)				Association between education and timely vaccination	Summary findings
			No education	Primary	Secondary	Tertiary		
Okenwa et al, 2019 (48)	Nigeria	344	1.2	7.6	61.1	30.2	Not measured	37.2% of participants recommended improving HBV education of mother's caregivers
Okenwa et al, 2020 (49)	Nigeria	366	1.2	7.6	61.1	30.2	Tertiary education was associated with valid birth-dose (COR=1.7; AOR=1.2)	Tertiary education was associated with good maternal knowledge of HBV infection and vaccination
Olakunde et al, 2021 (50)	Nigeria	6143	43.1	14.3	33.4	9.3	Not measured	Level of maternal education was positively associated with receipt of vaccination when delivered at home and in public facilities
Périeres et al, 2021 (51)	Senegal	241	66.5	20.1	13.4 <sup>a</sup>	<sup>a</sup>	Level of maternal educational was not associated with non-adherence to birth-dose schedule (p=0.363)	Level of maternal education was not significantly associated with non-adherence to birth-dose schedule
Sadoh et al, 2014 (52)	Nigeria	150	2.7	27.7	23.6	45.3 <sup>b</sup>	Not measured	Low timely birth-dose coverage, age, sex and socioeconomic status found not to be associated with delayed uptake
Ibrahim et al, 2022 (53)	Nigeria	400	3.4	8.3 <sup>c</sup>	49.0	39.3	Education and timeliness AOR: primary=17; secondary=5.9; tertiary= 7.7	Level of maternal education associated with timeliness. Primary level education showed the biggest association compared to mothers with no education
Ibraheem et al, 2019 (55)	Nigeria	480	1.7 <sup>d</sup>	<sup>d</sup>	34.2	64.2	Post-secondary education and presenting on day 0-1: OR=3.6; day 2-7 OR=3.29	Post-secondary education was significantly associated with valid timely dose of hepatitis B birth-dose
Danjuma et al, 2020 (57)	Nigeria	355	2.3	5.9	23.9	67.9	No significant correlations at any level, Primary: p=0.95; Secondary: p=0.11; Tertiary: p=0.65	Level of maternal education was not significantly associated with delayed birth-dose vaccination
Bada et al, 2022 (58)	Nigeria	409	33.2 <sup>d</sup>	<sup>d</sup>	66.8 <sup>a</sup>	<sup>a</sup>	Level of education ≤ elementary schooling or ≥ secondary schooling was not associated with timely birth-dose (p=0.63)	No association found between maternal level of education and timely birth-dose
Ibraheem et al, 2022 (54)	Nigeria	1952	6.3%	4.3%	51.2%	38.1%	Tertiary education and presentation within day 1: OR = 1.6; (p=0.028)	Tertiary education was significantly associated with presentation for vaccination within day 1 post-birth
Bassoum et al, 2021 (36)	Senegal	726	57.4%	42.6% <sup>e</sup>	<sup>e</sup>	<sup>e</sup>	Not measured	Factors associated with co-administration of birth-dose vaccinations did not include maternal education
Bassoum et al, 2022 (37)	Senegal	832	54.1	45.9 <sup>e</sup>	<sup>e</sup>	<sup>e</sup>	Educated vs uneducated mothers and vaccination within 24 hours: p=0.503	No significant association between education level and vaccination within 24 hours
Dagneu et al, 2020 (39)	Ethiopia	1121	27.5 <sup>f</sup>	15.4	26.9	29.5	Not measured	Education was significantly associated with good HBV knowledge and attitude among pregnant women
Goodman et al (41)	Nigeria	300	Study = 36.7; Control= 37.7	Study= 39.3 Control= 41.4	Study= 16.7 Control= 14.0	Study= 7.3 Control= 7.3	Not measured	No multivariate analysis was done
Guingané et al (42)	Burkina Faso	2220	35.6	21.9	37	5.5	Not measured	Interestingly a ≥ secondary level of education of both parents was significantly associated with better retention to care, more so in fathers than mothers
Miyahara et al, 2016 (46)	The Gambia	10851	15.8 67.1 <sup>g</sup>	10.5	6.7	-	Higher educated mothers and vaccination by day 7 compared to uneducated mothers: AOR 2.43 (p=0.02)	Vaccine coverage by day 7 was significantly higher in children born to mothers with higher levels of education
Sadoh et al, 2013 (56)	Nigeria	153	<sup>d</sup>	72.5 <sup>d</sup>	27.5 <sup>a</sup>	<sup>a</sup>	≥ Secondary education more likely to present within the first week of life (p=0.0001)	Mothers educated beyond secondary level more likely to present for vaccination within the first week after birth
Nankya-Mutyoba et al, 2021 (47)	Uganda	70	-	48.6 <sup>h</sup>	51.4 <sup>h</sup>	-	Not measured	Participants were grouped by residence and education level. No other insights drawn on maternal education level

<sup>a</sup> Combined secondary and tertiary education. <sup>b</sup> Combined university degree or equivalent, and school certificate with teaching/other professional training. <sup>c</sup> Combined primary and Islamic education. <sup>d</sup> Combined no education and primary education. <sup>e</sup> Combined primary, secondary and tertiary education. <sup>f</sup> Combined no education and basic literacy

<sup>g</sup> Koranic education. <sup>h</sup> Intentional selection of education level for qualitative inquiry

Where maternal socio-economic determinants of timely hepatitis B birth-dose vaccination were addressed, maternal occupation was found to be significantly associated with timely vaccination in three studies, all of which were conducted in Nigeria (53,54,56). In a study conducted by Ibrahim *et al.*, types of occupations were categorized into five groups, with group 1 being the higher end comprising of occupations like senior civil servants, and group 5 the lower end representing those who were students or unemployed (53). Group 2 (non-academic professionals like nurses, medium size business owners, secondary school teachers, intermediate grade public servants) was negatively associated with timely receipt of the hepatitis B birth-dose vaccine within 24 hours (AOR 0.14, 95% CI [0.037-0.554]) (53). Another study found that the likelihood of vaccination by day 0–1 among petty traders and teachers was 4 and 1.5 times higher, respectively, than that among the unemployed (54). Sadoh *et al.*, applied a social class variable which combined ratings assigned for both parents' occupation and education level, with social class 1 being the lower end and class 4 the higher end of the spectrum (56). High social class was found to have a statistically significant association with presentation for vaccination within the first week after birth (56).

Closely related to maternal occupation, the influence of maternal wealth on the receipt of hepatitis B birth-dose vaccine was reiterated among studies. In three studies assessing the relationship between these variables, women's level of wealth was categorized in one of 5 quintiles, with the upper end being the richest and the lower end the poorest (36,46,50). No marked difference in the distribution of the population among the wealth quintiles were found in all three studies (36,46,50). Two of the three studies found no statistically significant correlation between maternal wealth and vaccination by day 7 (46), or co-administration of birth-dose vaccines (36). Contrary to this, Olakunde *et al.*, found that wealthier mothers had higher odds of receiving hepatitis B birth-dose vaccination when compared to the poorest category (AOR richest =3.05, richer =2.17, middle =1.55) (50). Noteworthy were the findings on maternal unemployment despite secondary education attainment. Most mothers in one Nigerian study were unemployed (48.7%) despite the majority attaining a secondary level of education (51.2%) (54). Similar findings in Nigeria demonstrate 50% of mothers with at least a secondary level education but high unemployment (59%), additionally the majority (47.8%) belonged to the middle class (53).

Among the included studies, maternal history of ANC attendance was another determinant of timely hepatitis B birth-dose vaccination. Antenatal services or facilities were also frequently identified as the preferred location or medium of attaining knowledge on HBV and vaccinations, *see Table 6*.

**Table 6.** Summary findings on ANC attendance and hepatitis B birth-dose vaccination (Source: Author)

Study (Author, year)	Country	Participants (N)	Antenatal care attendance (%)	Summary findings
Périeres et al., 2014 (51)	Senegal	241	96.2	Not attending ANC visits was not significantly associated with non-adherence to birth-dose schedule [p=0.8]
Ibrahim et al., 2022 (53)	Nigeria	400	96.5	No correlation between ANC attendance and timely administration
Sadoh et al., 2013 (56)	Nigeria	153	92.2	20.3% of mothers who identified the health system as their source of information on HBV and vaccination received their information from ANC visits
Ibraheem et al., 2022 (54)	Nigeria	1952	94.7	ANC attendance was not significantly associated with vaccination at day 0-1 [p=0.63]
Ibraheem et al., 2019 (55)	Nigeria	480	93.5	Women attending ANC were 10 times more likely to receive vaccination by day 0-1 and nearly 6 times more likely to present by days 2-7 when compared to those who did not attend ANC
Bassoum et al., 2021 (36)	Senegal	726	47.5 [<4 visits] 52.5 [≥4 visits]	82.2% of mothers received advice on vaccination during ANC visits

Bassoum et al., 2022 (37)	Senegal	832	46.4 [0-4 visits] 53.6 [ $\geq 4$ visits]	82.4% of mothers received advice on vaccination during ANC visits.
*Moturi et al., 2018 (31)	Namibia	n/a	97	No comment on association between coverage and ANC attendance in these two countries
	Nigeria	n/a	61	
	Botswana	n/a	94	In these 3 countries with high coverage rates of the hepatitis B birth-dose, high rates of ANC attendance are recorded. ANC provides an opportunity to educate on HBV and encourage facility delivery
	The Gambia	n/a	86	
	São Tomé and Príncipe	n/a	98	
Nankya-Mutyoba et al., 2021 (47)	Uganda	n/a	n/a	Pregnant women prefer receiving HBV education during ANC consultations.
<b>ANC- antenatal care; n/a- not applicable</b>				
<b>*Data regarding ANC attendance was derived from UNICEF 2016 report (<a href="http://www.data.unicef.org">www.data.unicef.org</a>)</b>				

In Nigeria, women who attended ANC consultations were 10 times more likely to present for vaccination by day 0–1 (AOR 9.55, 95%CI [1.75–52.12]) and nearly 6 times more likely to present by day 2–7 (OR 5.78, 95%CI [1.27–26.28]) compared to those who did not attend ANC (55). Across other WHO AFRO member states, hepatitis B birth-dose vaccine coverage rates were shown to be high in instances of high ANC attendance (31). Similar correlations between ANC attendance and timely administration of the hepatitis B birth-dose vaccine were however not demonstrated in other studies (51,53,54). Pregnant women in Uganda preferred getting information on HBV and vaccines at their ANC consultations as opposed to via post or electronic media (47). In an exploration of the source of health information available to mothers, the health system was identified as the main source specifically on commencement of birth-dose vaccination (57.7%), of which 20.3% of mothers named ANC sessions as their source (56). Similarly, 82.2% of mothers received advice on vaccination during ANC consultations and 85.3% received advice during post-natal visits which was associated with higher odds (AOR 1.72,  $p=0.01$ ) of co-administration of birth-doses (36). In a related study, an increased proportion of mothers in Senegal received advice on vaccination at post-natal visits (87.2%) compared to during ANC consultations (82.4%) (37). Although paternal factors were assessed in six of the included studies, an association with hepatitis B birth-dose vaccination or delayed vaccine uptake was not reported (36,37,42,51,53,54). Only the pilot program in Burkina Faso cited the level of education among fathers as being significantly associated with retention to care and HBV DNA testing among mothers, see **Table 5** (42).

### 3.10 Influence of wider contextual factors on timely hepatitis B birth-dose vaccination

It is critical to address how hepatitis B birth-dose vaccination programs perform in the local contexts where they are delivered. From our review of the evidence-base we identified key factors that influence, to varied degrees, how hepatitis B birth-dose vaccination programs function. These include geographical factors, cultural and religious beliefs or observances underpinning decision-making around home deliveries and post-birth practices, parental decision-making authority on child's health, concepts around maternal marital status and birth order of children, and the local historical or current political climate. With regards to geographical factors, physical distance, and climate issues such as seasonal weather conditions were highlighted in several studies as influencing the timeliness of hepatitis B birth-dose vaccination. In Nigeria for example, mothers attributed delayed hepatitis B birth-dose vaccination to an increased distance between their place of residence and vaccination sites, often requiring unaffordable transportation costs (48,54,55). Miyahara *et al.*, report that in The Gambia, increased distances of  $\geq 2$ km from the vaccination site decreased likelihood of vaccination by day 7 (AOR 0.41 [ $p<0.0001$ ]) but those residing in rural areas were more likely to be vaccinated by day 7 compared to those from urban or peri-urban areas (West rural AOR 6.13; East rural AOR 6.72 [ $p<0.001$ ]) (46). Even when assessing correlation of vaccination by day 1, rural areas fared significantly better than urban or

peri-urban areas (AOR 4.61, 95% CI [2.27-9.36]) in this study (46). Two health system design factors were advantageous to this Gambian cohort; 50% of infants lived within 1km of vaccination clinics and village HCWs performed an active role in informing rural mothers of the dates of outreach clinics (46). Unlike their counterparts in The Gambia, pregnant women residing in urban areas in Ethiopia were two times more likely than rural residents to have good attitudes towards HBV transmission, screening, and vaccination (39). By adopting a service delivery structure involving three strategies, fixed, advanced, and mobile strategies, Senegal has been able to expand access to vaccination services (36,37). The fixed strategy is designed to provide vaccination services at fixed health centers to those living within a 5km radius, while the advanced strategy targets those staying between 5–15km from health centers with services rendered at health huts or sites by the staff from the main health centers. The mobile strategy on the other hand, targets those living >15km from the health centers (37). With this service model, Bassoum *et al.*, observed that 66.1% of mothers lived within 5km from a health center and this was found to be an enabling factor for co-administration of birth-dose vaccines (36). Interestingly, in another study by Bassoum *et al.*, findings showed that although 70.1% of the sample population lived <5km from a health center, this was not associated with hepatitis B birth-dose vaccination within 24 hours of life (37). In addition to physical distance, it has been demonstrated that being born in the dry season is associated with a 1.97 times higher likelihood of non-adherence to the hepatitis B birth-dose vaccination schedule when compared to those born in the wet season (51). Reasons proffered in a Senegalese study for this outcome include migration during the dry seasons which reduced the likelihood of adherence to the vaccination schedule (51).

The constraints of home delivery practices within Africa have been previously addressed under the theme on the influence of context *vs* system design on the timeliness of hepatitis B birth-dose vaccination. As an extension to this, we provide an overview of studies describing the proportion of home births and the availability of traditional birth attendants (TBAs) or unskilled providers as well as outreach services in **Table 7**. From a survey conducted among African experts, 92% reported limited vaccine resources for neonates born outside of health facilities (38). In this same study, ~22% of participating African countries reported that the proportion of deliveries outside of health facilities was in the region of 40% or higher (38). In a Nigerian study where the majority of participants were rural residents (60.5%), over 50% of women delivered at home with a high rate of unskilled birth attendants (54.1%) (50). Thirty-three percent of those who delivered at home received hepatitis B birth-dose vaccinations whereas the vaccine coverage rate among neonates delivered in both private and public health facilities was over 75% (50). It is also worth noting that of those who did not receive their hepatitis B birth-dose vaccine, majority (69.5%) were delivered by unskilled birth attendants (50). Home deliveries in Senegal were also associated with non-adherence to the hepatitis B birth-dose vaccination schedule (AOR 2.02,  $p=0.07$ ) (51). In The Gambia, home deliveries (40.3%) and assistance by TBAs (29.8%) are prominent components of the broader health system (46). In this primary health care system, village based TBAs and village HCWs are supervised by community nurses (46). Contrary to findings from Nigeria and Senegal, timely vaccination in The Gambia has been shown to favor those infants born at home. While coverage remains unacceptably low, relatively higher vaccine uptake by day 0–1 for home deliveries (1.3%) compared to deliveries in health centers (0.8%) and hospitals (0.5%) likely reflect the health systems design in The Gambia which accommodates the local realities of home deliveries (46). There is clear demand for designing vaccination systems that make careful considerations for long-established birthing practices rather than dismantling them altogether. Pregnant women taking part in focus group discussions in Uganda expressed concerns about the availability of the vaccine to those who prefer home births and TBAs (47). Despite this, none of the health facilities studied across Namibia, Nigeria, Botswana, The Gambia, and São

Tomé and Príncipe, had formal vaccine outreach services catering to home deliveries in the multi-country study (31).

**Table 7.** Availability of hepatitis B birth-dose vaccine outreach services for home deliveries (Source: Author)

Study (Author, year)	Country	Participants surveyed (N)	Home deliveries (%)	Traditional birth attendants or unskilled provider (%)	Vaccine outreach services
Miyahara et al (46)	The Gambia	1490	40.3	29.8	Yes
Périers et al (51)	Senegal	241	20.5	Not mentioned	Yes
Okenwa et al (2019) (48)	Nigeria	344	2.9	2	Not mentioned
Olakunde et al (50)	Nigeria	6143	58	54.1	Not mentioned
Ibraheem et al (2019) (55)	Nigeria	480	4.8	0.8	Not mentioned
Bassoum et al (2022) (37)	Nigeria	832	31.2	Not mentioned	Not mentioned

While we anticipated that ethical norms, cultural practices, and religion would be important considerations for timely uptake of the hepatitis birth-dose vaccine, such topics were rarely addressed in the evidence-base. Some of the limited data available highlighted how mothers from some core northern states in Nigeria were discouraged from leaving their homes with their babies before the name giving ceremony held on day 7 (54). Accordingly, it was reported that 6.4% of mothers delayed vaccination until after the naming ceremony (54) as did those participating in another Nigerian study where 6.5% of the mothers delayed presenting for vaccination as they were “waiting for after the naming ceremony” (53). This was also highlighted as a cultural practice in both Nigeria and The Gambia in the multi-country study (31). Additionally, waiting to circumcise male babies seven days after birth was given as a reason by 3.2% of mothers in a study conducted in Nigeria (56). In Uganda, a study investigating maternal perceptions and preferences of hepatitis B birth-dose vaccination highlighted participants’ belief that newborns should not be out of the mothers’ sight in order to remain protected. Mothers suggested the handling of newborns be done in their presence, especially during vaccinations (47). Another cultural perspective cited in two of the included studies was the decision-making authority within the household. Only 0.6% and 1.1% of mothers participating in the two studies proffered paternal non-consent as a reason for delayed presentation for hepatitis B birth-dose vaccination (53,54). Another study identified the unavailability of husbands among reasons for delayed presentation for hepatitis B birth-dose vaccination (56). In Senegal, one study found that 97.5% of decisions concerning the child’s health were made by the mother, or both the mother and father, as opposed to somebody other than the parent (36).

Findings from the long-term observational study in The Gambia noted participants from the Fula ethnicity had significantly lower chances (AOR 0.60, 95%CI [0.40-0.91]) of receiving the hepatitis B birth-dose vaccine by day 7 compared to the majority Wolof ethnicity (46). In Senegal, among the Serer ethnic population, HBV was likened to a dietary problem commonly managed by traditional medicine (40). In Ethiopia, HBV is known as “Yewefe Bashita” and thought to be transmitted through bat feces and urine, and as such, the local population was unaware of the importance or need for clinical treatment (39). Religion as a contextual determinant was assessed in three studies, two of which found a significant association with hepatitis B birth-dose vaccination. Infants born to Christian mothers in Nigeria had twice the odds of vaccination by day 0–1 than those born to Muslim mothers (54). Another Nigerian study found that religion was a significant determinant for home births (50), where the odds of receiving hepatitis B birth-dose vaccination were 0.66 times lower among Muslims

when compared to Christians (50). It is important to note that 61.3% of the population in the latter study were from the Islamic faith (50).

In terms of birth order, findings appeared inconclusive among three Nigerian studies reporting on the determinant of timely vaccination (53, 54, 58). One study demonstrated higher birth order (3<sup>rd</sup> born) increased the likelihood of hepatitis B birth-dose vaccination within 24 hours by 6-fold when compared to the 1st born (53). To the contrary, lower birth order (between 2nd–4th born) was associated with 1.5 times the odds of timely vaccination when compared to the 5th born in another study (54), whereas no association between parity and timely vaccination was found in the other study (58). In Loarec *et al.*, authors discuss concerns of the high fertility rate in Mozambique (4.85 births per female in 2018) which when considered together with high home birth rates in some non-urban settings has important implications for access to timely vaccination (45). Globally, the increasing number of live births per woman was found to be inversely proportional to hepatitis B birth-dose vaccination coverage ( $p=0.01$ ) (34). In this regard, discussions in this publication centered around higher birth rates likely overwhelming the health system and thereby impacting the capacity to provide timely birth-dose vaccines (34). Lastly, only two studies addressed the influence of conflicts or unrest on the performance of hepatitis B birth-dose vaccination programs. In examining the low coverage and timeliness of hepatitis B birth-dose vaccination in 2018 compared to that in 2017 in Senegal, Périères *et al.*, found that an HCW strike which took place between April–December 2018 had a considerable effect on national immunization services (51). Aina *et al.*, on the other hand, highlighted the insecurities across the north-eastern parts of Nigeria which caused migrations to stable states like Kano in the north-western parts of the country, and thereby negatively impacting on timely uptake of hepatitis B birth-dose vaccination (33).

#### 4. Discussion

The year 2030 is fast approaching bringing with it the race to the elimination of viral hepatitis (3). As HBV carries the largest burden among viral hepatitis infections, many regions have made positive strides towards controlling the epidemic, however the African region still lags far behind and has failed to meet interim regional goals set for 2020, in particular goals of reducing prevalence in children under 5 years old to <1%; 90% coverage of infant hepatitis B vaccines; and 25 countries adopting hepatitis B birth-dose vaccination (59,60). In comparison, although the Western Pacific region holds the highest prevalence of HBV chronic carriers (2), it has drastically improved coverage of both infant and birth-dose vaccinations with resultant reductions in the prevalence of chronic hepatitis B in under 5-year-olds to <1% (61). A series of innovative approaches have been adopted in the Western Pacific region, including using the hepatitis B birth-dose vaccine outside of the cold chain in Laos and the Solomon Islands, instilling national policies that encourage facility delivery and examination within the first 24 hours of birth in China and Cambodia, promoting awareness of communities on timely vaccine administration, and building the knowledge and capacity of HCWs on timely vaccination (61). Although contexts differ, it seems the African region could benefit from innovation in its approach to scaling up efforts towards hepatitis B elimination. In keeping, this qualitative systematic review applied a complex systems-perspective to assessing the current performance of hepatitis B birth-dose vaccination programs in the African region. Using this novel approach, we contribute synthesized evidence on factors underpinning the current shortfalls in program performance. We explore the various components of the intervention and describe how they dynamically interact with the health system complexity to produce outcomes that may affect the success or failure observed within the hepatitis B birth-dose vaccination programs in the Africa.

The source of complexity identified within the intervention itself lies in the permitted degree of flexibility (15) in the timely administration of hepatitis B birth-dose vaccine for optimal PMTCT of HBV. This further interacts with complexities prevalent across the causal pathway (15) of the vaccination program. This is demonstrated in the dynamics involved in the translation of policy or guidelines into practice. We found feedback loops created by misinterpretation of policy encouraged multiple stakeholders to continue a pattern of non-adherence to timely vaccination. When national policies allow for a 0–14-day timeframe for the receipt of the hepatitis B birth-dose vaccine (31,48–50,55), HCWs are likely to interpret the upper limit as inferring the same protection as a dose within 24 hours. This understanding would impact on their decisions and practices which in turn impacts the health seeking behaviors of mothers leading to a cascade of delayed behaviors. Consequently, mothers presenting for vaccination within 14 days was the most frequent timeframe noted in this review (53,54,56). Policy makers should take care to not compromise effective program performance when adapting international guidelines to local contexts. Similar complexities have been noted with co-administered birth-dose policies and the established co-dependent relationships serving convenience or wastage aversions in some settings (46). Reasons for delaying hepatitis B birth-dose vaccination while awaiting pairing with OPV or BCG (46,53) need to be further investigated in order to formulate pragmatic solutions that do not compromise vaccine effectiveness. Such solutions could include ordering smaller dose vials of BCG, thus improving the compliance of all three birth-dose vaccinations as perceived wastage will be minimized. Costing and cost-effective analysis comparing alternatives could guide decisions and recommendations in practice.

Although our findings demonstrate that deficits in supply are not the sole reason for poor program performance, it remains persistent as an important source of complexity (47,48,53,54,56,57). This has also been demonstrated in other reviews on hepatitis B birth-dose performance (5,12,13). Due to the connectivity of individual components of an intervention linked in a system, like that of the vaccine supply chain for service delivery, changes of one component easily influence the outcome of the entire system (15). Establishing a sustainable supply of the birth-dose decreases the chances of untimely or no vaccination (5). The logistics of immunization supply has been quoted as long being outdated and requiring nuanced approaches to keep up to date with vaccine requirements (33). Bottlenecks at collection points cause unnecessary delays and compete for HCWs time (33,62). It might be that more innovative strategies, like direct-to-facility supply could avoid bottlenecks and improve effective program performance (33). Further investigation may provide comparisons in coverage, feasibility and cost-effectiveness between traditional supply mechanisms and innovative strategies in guiding decision-makers on the best choice to optimize program performance.

Interventions are understood to be very susceptible to the effects of different contexts, creating certain capabilities when interacting (15). This is apparent in the complex interactions created between hepatitis B birth-dose vaccination and the system's context within the causal pathway. Varied sources of financial resources described as contributing to vaccination coverage include government health spending, donor funding or development assistance for health, out-of-pocket and prepaid private health spending (63). Among low-income countries, an increase in total health expenditure does not always translate into better health outcomes or vaccine coverage (63,64). In contrast, national or government health spending per capita and government spending per birth on routine vaccines, have been proven as positive predictors of vaccination coverage (63,34). A steady increase in national funding for fairly novice vaccinations in Africa, like the hepatitis B birth-dose vaccine, is likely to improve coverage and may be a suggested step for governments in the region. This review highlights how inadequately resourced hepatitis B birth-dose vaccination programs can result in exorbitant out-of-pocket payments which are important constraints to end-user buy-in and uptake of services.

In addition, these studies give impetus to the ongoing calls from diverse stakeholders, including global experts and civil society organizations, for Gavi to further its pivotal role across the region and honor its financial commitments to support the strengthening of existing programs while expanding roll-out of nationwide hepatitis B birth-dose vaccination programs across the region (65,66). Since the early 2000s financial resources for routine childhood vaccination programs have improved dramatically, largely owing to Gavi support in procuring vaccines at a reduced cost for 40 Gavi-supported African countries (65,67). In 2018, as part of their investment strategy, Gavi committed to providing support for hepatitis B birth-dose vaccination by 2021 but due to the COVID-19 pandemic, these intentions were deferred although currently being reconsidered following an impressive global movement (65). Even with Gavi support, it is imperative that national governments across the African region mobilize domestic investments as this has been shown to strengthen country ownership and secure the sustainability of the vaccination programs above dependence on donor funding (63). Collaboration between MoH, donor funders and researchers are vital in achieving a balance that creates better capabilities of the system in implementing the vaccination. The China-Gavi project was one such collaboration that helped to convince the Chinese government to introduce and fully fund hepatitis B birth-dose vaccination after attaining 75% coverage in 80% of Gavi project counties (68).

We found that the level of HBV specific knowledge among HCWs created behavioral change in end-users and HCWs themselves when interacting with the hepatitis B birth-dose vaccination program. The poor level of HBV specific knowledge among HCWs manifested in actions of delaying vaccination, lenient practices of screening in selective vaccination, and inaccurate or absent knowledge transfer from providers to mothers and pregnant women (35,44,45,47). This emphasizes the importance of increasing the basic knowledge among all HCWs, especially those involved with MCH activities as they are the first point of contact for pregnant women and the preferred source of HBV-related information according to mothers in the region (36,47). Improving the HBV knowledge of HCWs is likely more feasible when training is integrated with other disease model training efforts, like that of HIV (69). This serves as a low-cost intervention towards HBV elimination (70). Researchers need to investigate potential gaps of HBV knowledge in tertiary or formal training of HCWs in order to advise the Ministry of Education in adapting the curriculum to local contexts. Examples of education sessions and training on HBV among HCWs in Tanzania and Uganda have seen improvements in HBV knowledge but call on ongoing efforts to sustain improved basic knowledge of HBV among HCWs (69,70). Elloker et al., highlight the importance of embracing the ‘tangible software’ like knowledge and skills, systems and procedures, as well as the ‘intangible software’ such as values, norms, power, communication and relationships (71). In our review, knowledge and awareness (tangible software) of HCWs were investigated more frequently than their values, norms, communication or relationships (intangible software). However, we found dynamics of trust and power (intangible software) evident between HCWs and mothers in the handling of newborns and administering injections (41,47). It would be premature to draw conclusions on this potentially rich source of complexity based on our limited findings and this gap in research. Further research should explore these dynamics and its influence on the performance hepatitis B birth-dose vaccination. A qualitative research approach would be useful in uncovering the influence of inherent or learnt values and norms, communication skills and relationship power dynamics on program performance.

The interaction of the intervention design and hepatitis B birth-dose vaccination was widely observed as a focal point of complexity. Most infant vaccination programs are delivered on allocated days at immunization centers or clinics in Africa (53,54,55,57,58,72). Though this has been effective in delivering essential vaccines as part of the EPI globally (73,74), this program design feature is not the best fit when applied to hepatitis B birth-

dose vaccination programs as it leads to poorly accessible services and ultimately a delay in receipt of vaccination. We found this practice was only further compounded by several influential maternal and wider contextual factors such as maternal knowledge and awareness of the risk of HBV MTCT and prevention strategies (49,55,56), mother and infant's health post-birth (53,55,56,57), cultural and religious practices and beliefs (31,50,53,54), geographical factors of distance and seasonal change (48,54,55), favored home births (37,46,50) and maternal occupation and the level of education (46, 53–56). These characteristics act as mediators or moderators of the effects of the intervention (15). Aligning hepatitis B birth-dose vaccination with birth delivery services would be an important step in overcoming complexity at this intersection, allowing a more responsive intervention design that encourages vaccine effectiveness in both facility delivery and home births. This will require the efforts of a wide range of role players to plan an improved service. A collaboration between national immunization technical advisory groups (NITAGs), EPI, and MCH services would likely be the first steps in planning hepatitis B birth-dose programs that meet the timing needs of the vaccine and is responsive to the wider contextual factors of the setting. This alignment of services may look like the pre-positioning of vaccines in delivery rooms (43,48); ordering of single dose vials or compact pre-filled auto-disable injections (CPADs) for use in delivery centers and home births (75), the use of mobile vaccination initiatives combined with the outside-the-cold-chain use of the vaccine (61), training TBAs or village HCWs on the use of CPADs for countries with high volumes of home births (75) and formulating policies that shift responsibility of vaccine administration to the birthing facility or agent as opposed to immunization centers or agents (61,76). These strategies have proven useful in other LMICs or rural settings. For example, in rural China a policy assigning the responsibility of administering the hepatitis B birth-dose vaccine to the delivery institution has been implemented since 2002, and together with other policy reforms have assisted in increasing timely administration in birth cohorts of 2000 and 2017 from 80.3% to 91.3%, respectively (76). Similar practices within Africa have improved uptake of timely vaccination at birthing sites (31,43,48). The use of CPADs like the Uniject™ administered by village midwives have improved timeliness of home birthed populations in Indonesia, demonstrating good acceptability among recipients (75). Hepatitis B birth-dose vaccination has demonstrated stability outside-the-cold-chain (2-8°C) (77) and recommended for areas that lack reliable cold chains or have high home birth rates (4). Countries like the Solomon Islands and Laos have increased timely birth-dose vaccination by 150% and 27% respectively by using the vaccine outside-the-cold-chain (61). Further to this, buy-in from MoH officials and other bureaucrats would be required in order to support the needs of these initiatives by providing financial resources for the procurements of alternatives, as well as driving policy reform. Single dose vials and CPADs (75,78), in particular, carry greater expense and researchers may need to provide insight into whether these initiatives are feasible for the country in question. Research should also include social and behavioral investigations into adherence and acceptability of these nuanced strategies in the administration of hepatitis B birth-dose vaccine.

Further to changes aimed at the intervention design, changes in the moderators of effect, like maternal and contextual factors, could provide systemic change in the performance of the vaccination program. An example could be improving HBV awareness and knowledge of girls and women in the region. Using the schooling system, basic HBV knowledge and concepts could be taught as part of the curriculum in order to improve the level of understanding in the general population, especially the youth prior to child-bearing ages. In Nigeria a peer education intervention among secondary school students improved basic concepts of HBV and also earmarked teachers as a source of HBV information (79). Concepts taught in school have the potential to filter into households and the greater community. This suggests intersectoral engagement between Ministries of Education, Health and Social Development are necessary to assist in better prospects of program performance

by improving population understanding, uptake and acceptance of hepatitis B birth-dose vaccines. The commitment to promoting the education of the girl child should remain one of the cornerstone principles for improved maternal and child health (80). Similarly, where cultural or religious practices such as naming ceremonies and male circumcision influence delayed uptake of hepatitis B birth-dose vaccines, explorations of these socio-cultural practices should be conducted and carefully accommodated as part of the vaccination program in order to establish trust from local communities. Remaining respectful and responsive to unique populations, calls for strategic planning and social mobilization, engaging community, cultural and religious leaders to negate misconceptions, raise awareness and improve acceptance of the vaccination program. These cultural considerations are not isolated to the African region. A previous study suggests that mothers in Indonesia are encouraged to remain indoors with their newborns during the first 40 days of life (75). In this study it was reported that health promotion activities like face-to-face explanations during ANC visits, health promotion material such as handouts and even mass media campaigns via radio communication improved acceptance of the vaccination program among local communities of Indonesia (75). Further to this, our review noted the pivotal role of village HCWs and TBAs who were essential in raising awareness on outreach immunization services and improving timely uptake of hepatitis B birth-dose vaccination in rural settings with substantial home birthing practices (46). Similar strategies have been used in Papua New Guinea where village HCWs are critical to raising awareness (81). Where a system of community HCWs exists, they should be fully integrated into MCH and EPI programs and used as a satellite source of information or service delivery to enhance the performance of hepatitis B birth-dose vaccination programs.

Interactions between inadequate information systems and the delivery of timely vaccination contributes to limitations in accurate feedback on program performance (37,48,49). Appropriate reforms to monitoring and recording vaccination data (coverage and timeliness) could generate robust evidence that provides system-wide effects when integrated into planning. Adding separate columns to record the timing of vaccination in EPI forms and the addition of columns to maternal records and birthing registries upon delivery could be such modifications that not only improve feedback of data but also influence positive behavioral change among delivery agents (5,31). Another useful mechanism at this intersection is the use of hepatitis B birth-dose vaccination as a performance indicator (37). In The Gambia, the implementation of a timeliness monitoring system as a key performance indicator for the MoH at health facilities, led to overall improvements of timeliness rate and trend (82). This translated into positive behavioral change among HCWs, by a simple intervention of visualizing and acknowledgment of performance (82). This acts as a non-monetary incentive and helps HCWs to feel valued, encouraging further dedication and diligence. Immunization program planners and NITAGs may need to advocate for changes in recording systems to properly monitor progress and spearhead innovative strategies which encourage compliance.

Owing to the complexity of an intervention, or the complex interaction that occurs when integrated in a health system, findings and recommendations are expected to be multifaceted. We found the evidence analyzed in this review reiterated 5 major considerations when implementing hepatitis B birth-dose vaccinations in Africa. Firstly, the misinterpretation of policy significantly contributed to poor performance of the vaccination programs, this produced a cascade of adaptations and behavioral changes along a chain of stakeholders that ultimately derailed from the goal of preventing HBV MTCT. Secondly, the existing intervention design and the design of system infrastructure (information systems and supply chains) used for current immunization programs of the EPI may be inadequate in meeting the needs of an intervention with complex requirements like hepatitis B birth-dose vaccination. Innovative approaches are required in order to meet the needs of this

intervention and ensure programmatic success. Thirdly, acknowledging the contextual underpinnings and multiple influencing inherent factors of end-users is pertinent when designing programs. Program design should aim for adapting the program to be responsive to the context and not forced to fit a mold of similar interventions that have come before. Fourthly, recognizing the role of the HCW in the intervention design, as a source of HBV information, vaccine administrator, and as a complex system (human being) themselves is essential to provide tailored support to them in effectively delivering the program. Lastly, national governments buy-in in aligning financial resources and intersectoral collaboration among ministries of health, education and social development would provide a sustainable basis for program success in the region.

## **5. Strengths and limitations**

To the best of our knowledge, this qualitative systematic review study is the first to explore how key underlying complexities influence the performance of hepatitis B birth-dose vaccination programs in the African region. We retrieved and critically appraised literature sources published in both English and French and indexed in multiple electronic databases and repositories. By applying a systems-based logic model developed in a preceding scoping exercise and tailored to systematic reviews of complexity, we enhanced the reliability and validity of our data collection, synthesis, and analysis. Limitations in the generalizability of the review findings lie in the underrepresentation of other WHO member states while studies from countries like Nigeria and Senegal dominated the knowledgebase. However, it is important to consider that only 15 member states have so far adopted hepatitis B birth-dose vaccination policies. In addition, research capabilities and appetites may vary even across those same countries. Systematic review designs are subject to the biases and confounders inherent in component studies, and this should be considered when interpreting the findings of this review.

## **6. Conclusion**

Despite established vaccine effectiveness, hepatitis B birth-dose vaccination programs in the African region have not achieved expectant coverage, this may be a reflection of underlying complexities. This systematic review draws on the complex links between the intervention design and the broader health system, providing complex explanations as to why simply introducing the vaccine might not lead to timely uptake or improved coverage. Our findings suggest that African countries looking to improve program performance as well as those planning on implementing the intervention will benefit from carefully considering components of the intervention design that — require responsiveness and flexibility (vaccine accessibility and delivery), or inflexibility (policy interpretation); which stakeholders require further support (HCWs and government ministries); and where innovation is required (information systems and supply chains).

## **7. Data availability statement**

All data sources including the literature search strategy and a summary of extracted data are provided within the main text and supporting information (**Appendices**). Any additional data will be provided by the corresponding author upon reasonable request.

## **8. Author contributions**

The research was conceptualized by EAD and TR. TR conducted the literature search, screening, data collection and analysis, and quality appraisal with supervision from EAD and JO. TR wrote the first draft of this systematic

review with constructive input from EAD and JO. All authors approve the final version of this systematic review manuscript.

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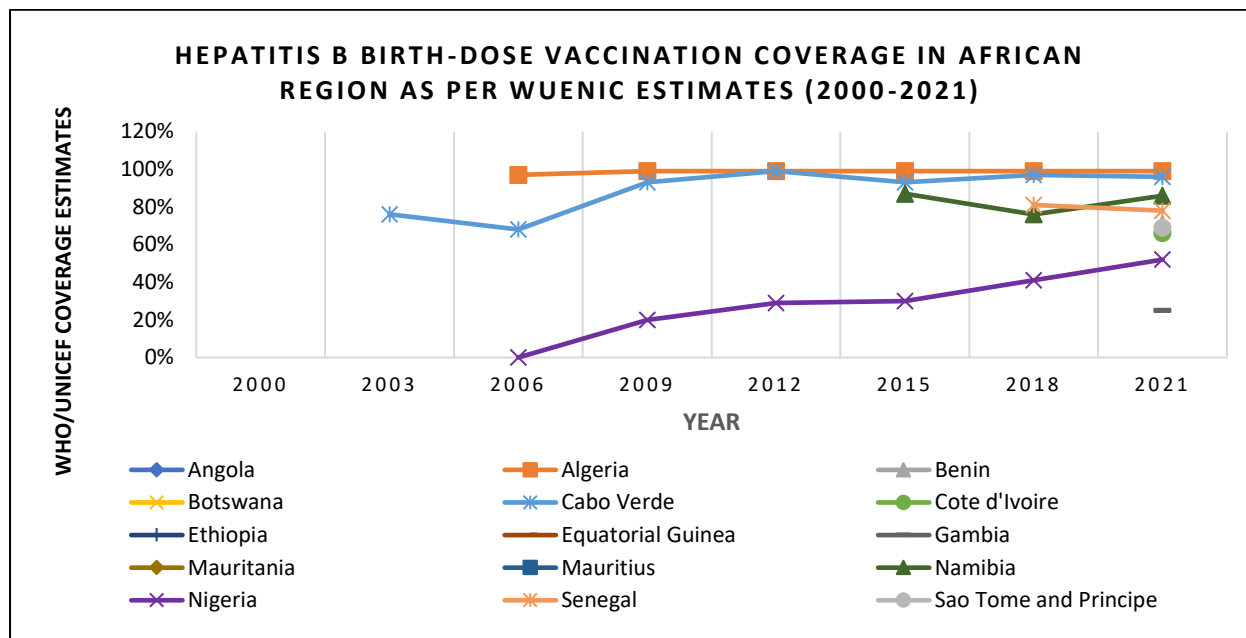
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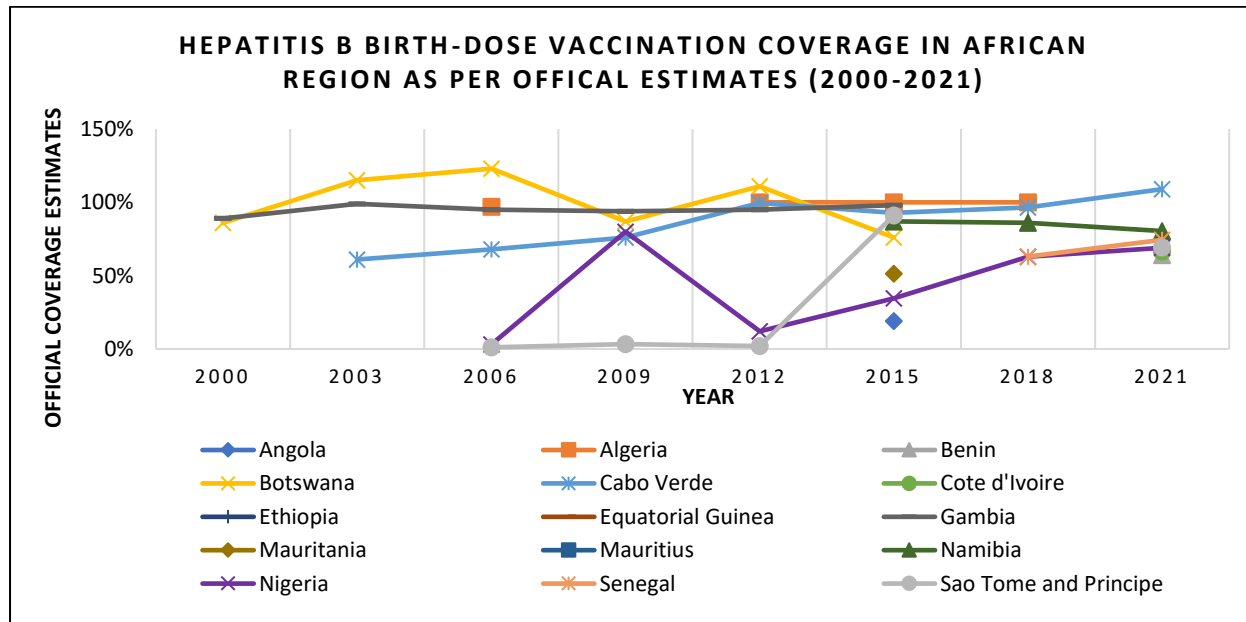
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## PART C: APPENDICES

## Appendix A. Coverage of hepatitis B birth-dose vaccination in the African region

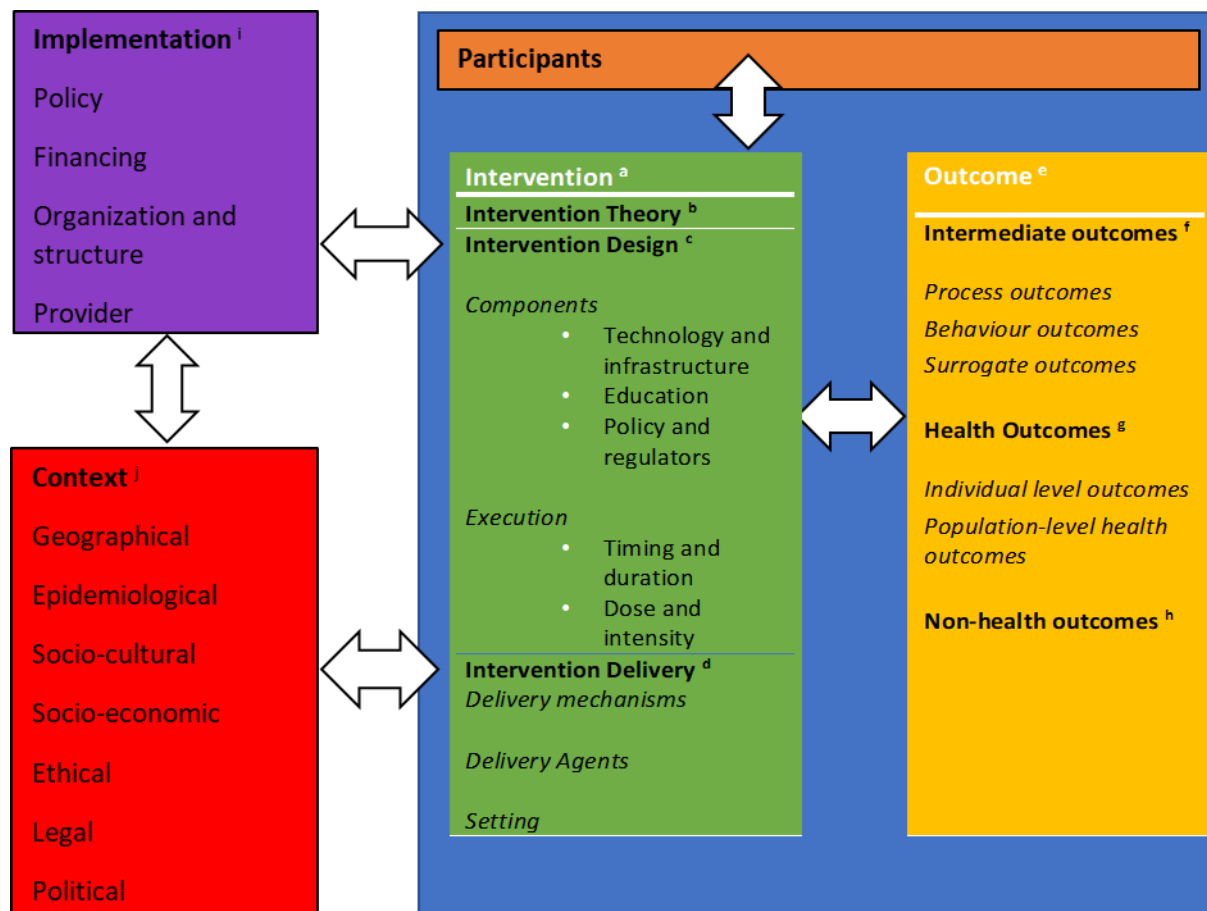


**Figure 1.** Coverage of hepatitis B birth-dose vaccination in the African region 2000-2021 according to WHO/UNICEF estimates of national immunization coverage (WUENIC) (20,58)



**Figure 2.** Coverage of hepatitis B birth-dose vaccination in the African region 2000-2021 according to official country estimates reported to WHO/UNICEF via the joint reporting form (20,58)

## Appendix B. Systems-based logic model template



**Figure 3.** Systems-based logic model template. Source: image and caption adapted from Rohwer et al (87)

<sup>a</sup> *Intervention* can refer to theory, design and/or delivery elements <sup>b</sup> *Intervention theory* refers broadly to the description of implicit or explicit ideas on how an intervention works, and is inclusive of the overall aims of the intervention. <sup>c</sup> *Intervention design* is descriptive of the “What?” of the intervention. The ‘execution’ provides a detailed prescription of intervention – elements of timing (when), duration (how long), dose (how much), and intensity (how often) are described. <sup>d</sup> *Intervention delivery* describes the “How? (delivery mechanisms)” “Who? (delivery agents)” and “Where? (setting)” of the intervention. Individualism of delivery agents form the basis of every organization and the potential organizational change. Their knowledge, skills, motivation, and beliefs are vital for success of intervention delivery. <sup>e</sup> *Outcomes* categorization may be depicted as short, intermediate, and long term. Outcomes should include both desired/positive outcomes and potential undesired/negative outcomes. <sup>f</sup> *Intermediate outcomes* can be divided into process, behavior and surrogate outcomes. *Process outcomes* can be described quantitatively or qualitatively, including elements of participation, implementation fidelity, reach, experience of barriers, contamination by study or non-study interventions of the comparison group, and the description of experiences of participants and intervention providers. *Behavior outcomes* include participant behaviors such as adherence or compliance which are important for the success of the intervention but may extend to include intended or unintended behavioral outcomes. “*Surrogate outcomes* are used as proxies for “hard” clinical outcomes and refer to direct, measurable, often short-term effects of an intervention”. <sup>g</sup> *Health outcomes* include specific clinical outcomes, such as morbidity and mortality, and may refer to broader outcomes, such as well-being, life expectancy, and quality of life (87). <sup>h</sup> *Non-health outcomes* includes relevant societal impacts of the intervention. <sup>i,j</sup> The *context* and *implementation* section awards due importance of the broader range of factors influencing the effectiveness of complex interventions. “The context and implementation for complex interventions framework provides an overarching approach for considering these two distinct but interacting dimensions”.

Rohwer A, Pfadenhauer L, Burns J, Brereton L, Gerhardus A, Booth A, Oortwijn W, Rehfues E. Series: Clinical Epidemiology in South Africa. Paper 3: Logic models help make sense of complexity in systematic reviews and health technology assessments. *J Clin Epidemiol* (2017) 83:37–47. doi: 10.1016/j.jclinepi.2016.06.012

## Appendix C. PRISMA 2020 checklist

**Table 1** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020) item checklist for systematic reviews (92)

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

## Appendix D. PRISMA-ScR checklist

**Table 2** Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (95)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
<b>Title</b>	1	Identify the report as a scoping review.	Click here to enter text.
<b>ABSTRACT</b>			
<b>Structured summary</b>	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Click here to enter text.
<b>INTRODUCTION</b>			
<b>Rationale</b>	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Click here to enter text.
<b>Objectives</b>	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Click here to enter text.
<b>METHODS</b>			
<b>Protocol and registration</b>	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	Click here to enter text.
<b>Eligibility criteria</b>	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Click here to enter text.
<b>Information sources*</b>	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Click here to enter text.
<b>Search</b>	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Click here to enter text.
<b>Selection of sources of evidence†</b>	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Click here to enter text.
<b>Data charting process‡</b>	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Click here to enter text.
<b>Data items</b>	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Click here to enter text.
<b>Critical appraisal of individual sources of evidence§</b>	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Click here to enter text.
<b>Synthesis of results</b>	13	Describe the methods of handling and summarizing the data that were charted.	Click here to enter text.
<b>RESULTS</b>			
<b>Selection of sources of evidence</b>	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Click here to enter text.

<b>Characteristics of sources of evidence</b>	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Click here to enter text.
<b>Critical appraisal within sources of evidence</b>	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	Click here to enter text.
<b>Results of individual sources of evidence</b>	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Click here to enter text.
<b>Synthesis of results</b>	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Click here to enter text.
<b>DISCUSSION</b>			
<b>Summary of evidence</b>	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Click here to enter text.
<b>Limitations</b>	20	Discuss the limitations of the scoping review process.	Click here to enter text.
<b>Conclusions</b>	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Click here to enter text.
<b>FUNDING</b>			
<b>Funding</b>	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Click here to enter text.

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MDJ, Horsley T, Weeks L, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann Intern Med* (2018) 169:467–473. doi: 10.7326/M18-0850

## Appendix E. Critical Appraisal Skills Programme Appraisal Tool



**CASP Checklist:** 10 questions to help you make sense of a **Qualitative** research

**How to use this appraisal tool:** Three broad issues need to be considered when appraising a qualitative study:

- ▶ Are the results of the study valid? (Section A)
- ▶ What are the results? (Section B)
- ▶ Will the results help locally? (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is “yes”, it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a “yes”, “no” or “can’t tell” to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

**About:** These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

**Referencing:** we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Qualitative) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

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Paper for appraisal and reference:

Section A: Are the results valid?

1. Was there a clear statement of the aims of the research?

Yes	
Can't Tell	
No	

HINT: Consider

- what was the goal of the research
- why it was thought important
- its relevance

Comments:

2. Is a qualitative methodology appropriate?

Yes	
Can't Tell	
No	

HINT: Consider

- If the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal

Comments:

Is it worth continuing?

3. Was the research design appropriate to address the aims of the research?

Yes	
Can't Tell	
No	

HINT: Consider

- if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

Comments:

4. Was the recruitment strategy appropriate to the aims of the research?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the researcher has explained how the participants were selected
- If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
  - If there are any discussions around recruitment (e.g. why some people chose not to take part)

Comments:

5. Was the data collected in a way that addressed the research issue?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the setting for the data collection was justified
- If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
- If the researcher has justified the methods chosen
  - If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
    - If methods were modified during the study. If so, has the researcher explained how and why
  - If the form of data is clear (e.g. tape recordings, video material, notes etc.)
    - If the researcher has discussed saturation of data

Comments:

6. Has the relationship between researcher and participants been adequately considered?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

Comments:

Section B: What are the results?

7. Have ethical issues been taken into consideration?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

Comments:

8. Was the data analysis sufficiently rigorous?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
  - To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

Comments:

9. Is there a clear statement of findings?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider whether

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

Comments:



Section C: Will the results help locally?

10. How valuable is the research?

HINT: Consider

- If the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature
- If they identify new areas where research is necessary
- If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used

Comments:

## Appendix F. Mixed Methods Appraisal Tool

**Table 3** Mixed Methods Appraisal Tool (MMAT), version 2018 (100)

Category of study designs	Methodological quality criteria	Responses			
		Yes	No	Can't tell	Comments
Screening questions (for all types)	S1. Are there clear research questions?				
	S2. Do the collected data allow to address the research questions?				
	<i>Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions.</i>				
1. Qualitative	1.1. Is the qualitative approach appropriate to answer the research question?				
	1.2. Are the qualitative data collection methods adequate to address the research question?				
	1.3. Are the findings adequately derived from the data?				
	1.4. Is the interpretation of results sufficiently substantiated by data?				
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?				
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?				
	2.2. Are the groups comparable at baseline?				
	2.3. Are there complete outcome data?				
	2.4. Are outcome assessors blinded to the intervention provided?				
	2.5. Did the participants adhere to the assigned intervention?				
3. Quantitative non-randomized	3.1. Are the participants representative of the target population?				
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?				
	3.3. Are there complete outcome data?				
	3.4. Are the confounders accounted for in the design and analysis?				
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?				
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research question?				
	4.2. Is the sample representative of the target population?				
	4.3. Are the measurements appropriate?				
	4.4. Is the risk of nonresponse bias low?				
	4.5. Is the statistical analysis appropriate to answer the research question?				
5. Mixed methods	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?				
	5.2. Are the different components of the study effectively integrated to answer the research question?				
	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?				
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?				

5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?					
<b>3. Quantitative non-randomized studies</b>	<b>Methodological quality criteria</b>				
<p>Non-randomized studies are defined as any quantitative studies estimating the effectiveness of an intervention or studying other exposures that do not use randomization to allocate units to comparison groups (Higgins and Green, 2008).</p> <p>Common designs include (this list if not exhaustive):</p> <p><b>Non-randomized controlled trials</b> The intervention is assigned by researchers, but there is no randomization, e.g., a pseudo-randomization. A non-random method of allocation is not reliable in producing alone similar groups.</p> <p><b>Cohort study</b> Subsets of a defined population are assessed as exposed, not exposed, or exposed at different degrees to factors of interest. Participants are followed over time to determine if an outcome occurs (prospective longitudinal).</p> <p><b>Case-control study</b> Cases, e.g., patients, associated with a certain outcome are selected, alongside a corresponding group of controls. Data is collected on whether cases and controls were exposed to the factor under study (retrospective).</p> <p><b>Cross-sectional analytic study</b> At one particular time, the relationship between health-related characteristics (outcome) and other factors (intervention/exposure) is examined. E.g., the frequency of outcomes is compared in different population subgroups according to the presence/absence (or level) of the intervention/exposure.</p> <p>Key references for non-randomized studies: Higgins and Green (2008); Porta et al. (2014); Sterne et al. (2016); Wells et al. (2000)</p>	<p>3.1. Are the participants representative of the target population?</p> <p>Explanations Indicators of representativeness include: clear description of the target population and of the sample (inclusion and exclusion criteria), reasons why certain eligible individuals chose not to participate, and any attempts to achieve a sample of participants that represents the target population.</p>				
	<p>3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?</p> <p>Explanations Indicators of appropriate measurements include: the variables are clearly defined and accurately measured; the measurements are justified and appropriate for answering the research question; the measurements reflect what they are supposed to measure; validated and reliability tested measures of the intervention/exposure and outcome of interest are used, or variables are measured using 'gold standard'.</p>				
	<p>3.3. Are there complete outcome data?</p> <p>Explanations Almost all the participants contributed to almost all measures. There is no absolute and standard cut-off value for acceptable complete outcome data. Agree among your team what is considered complete outcome data in your field (and based on the targeted journal) and apply this uniformly across all the included studies. For example, in the literature, acceptable complete data value ranged from 80% (Thomas et al., 2004; Zaza et al., 2000) to 95% (Higgins et al., 2016). Similarly, different acceptable withdrawal/dropouts rates have been suggested: 5% (de Vet et al., 1997; MacLehose et al., 2000), 20% (Sindhu et al., 1997; Van Tulder et al., 2003) and 30% for follow-up of more than one year (Viswanathan and Berkman, 2012).</p>				
	<p>3.4. Are the confounders accounted for in the design and analysis?</p> <p>Explanations Confounders are factors that predict both the outcome of interest and the intervention received/exposure at baseline. They can distort the interpretation of findings and need to be considered in the design and analysis of a non-randomized study. Confounding bias is low if there is no confounding expected, or appropriate methods to control for confounders are used (such as stratification, regression, matching, standardization, and inverse probability weighting).</p>				
	<p>3.5. During the study period, is the intervention administered (or exposure occurred) as intended?</p> <p>Explanations For intervention studies, consider whether the participants were treated in a way that is consistent with the planned intervention. Since the intervention is assigned by researchers, consider whether there was a presence of contamination (e.g., the control group may be indirectly exposed to the intervention) or whether unplanned co-interventions were present in one group (Sterne et al., 2016).</p> <p>For observational studies, consider whether changes occurred in the exposure status among the participants. If yes, check if these changes are likely to influence the outcome of interest, were adjusted for, or whether unplanned co-exposures were present in one group (Morgan et al., 2017).</p>				

## Appendix G. Assessment scale for ecological studies

**Table 4.** Assessment scale for appraisal of ecological studies adapted from Dufault and Klar (104, 105)

Category	Item	Description
<b>Study Design and focus (max = 4)</b>	Sample size (max = 2)	Number of ecological units included in the analysis as a proportion of the total number of units (3 levels: < 11% = 0 points; 11-79%= 1 point; >79%= 2 points)
	Level of inference (max = 1)	The results of the analysis are not used to draw inferences for individuals
	Pre-specification of ecological units (max = 1)	Ecological units are selected to suit the hypothesis (as opposed to seemingly motivated by convenience or necessity such as the use of districts, towns, or counties)
<b>Statistical Methodology (max = 5)</b>	Validity of statistical inference (max = 2)	Number of the ecological units per covariate (3 levels: 0-10 = 0 points; 10-20 = 1 point; >20 = 2 points)
	Use of covariates (max = 1)	Analysis adjusted for covariates (e.g., sociodemographic, environmental risk factors)
	Proper adjustment for covariates (max = 1)	Covariates are properly adjusted when regressed upon adjusted outcomes as recommended for ecological studies
	Spatial effects (max = 1)	Inclusion of spatial analysis
<b>Quality of reporting (max = 3)</b>	Statement of study design (max = 1)	Key elements of the study design are presented in the report
	Justification of study design (max = 1)	Justification of the ecological analysis, the rationale and the objectives are presented in the report
	Discussion of cross-level bias and limitations (max = 1)	Readers are cautioned about the limitations of the ecological design and/or the ecological fallacy.



	Seychelles[Text Word] OR "Sierra Leone"[Text Word] OR Somalia[Text Word] OR "St Helena"[Text Word] OR Sudan[Text Word] OR Swaziland[Text Word] OR Tanzania[Text Word] OR Togo[Text Word] OR Tunisia[Text Word] OR Uganda[Text Word] OR "Western Sahara"[Text Word] OR Zaire[Text Word] OR Zambia[Text Word] OR Zimbabwe[Text Word])
#9	#1 AND #4 AND #7 AND 8
#10	<b>Filters: Abstract availability, Full Text availability, Human studies, Published date 2009 – 2022</b>
<b>EBSCOhost Database</b>	
<b>Search</b>	<b>Query</b>
#1	AB Child* OR infant* OR neonat* OR newborn*
#2	AB ( Hepatitis B OR hep B OR HBV OR hepatitis B birth dose OR hepatitis B birth-dose ) AND AB ( Immuni* OR immuni* coverage OR immuni* program* OR immuni* initiatives OR Vaccin* OR vaccin* coverage )
#3	AB ( Healthcare workers OR healthcare professionals OR traditional birth attendants OR midwife OR midwives OR community health workers OR voluntary worker OR training OR skills building OR staff responsibilities OR standards OR staffing OR human resource* OR task shifting OR home care service OR community care OR outreach OR home visit OR cold chain OR cold temperature OR supply chain OR distribution OR drug storage OR medicine storage OR vaccine storage OR Uniject OR compact pre-filled auto-disabled device OR CPAD OR vials OR dose OR dosage OR birth delivery OR birth centre OR birth center OR health centre OR health center OR health facility OR health facilities OR monitor* OR regis* OR record OR data collection OR organization OR organisation OR administration OR management OR integrated OR immuni* program* AND cost analysis OR costs OR funds OR funding OR finance OR finances OR financial resource* OR Immuni* program* standards OR immuni* schedule OR timeliness OR timely OR 24 hours OR 24-hours OR knowledge OR attitudes OR practice* OR Policy makers OR policymakers OR polic* ) OR AB ( Barriers OR constraints OR obstacles OR challenges OR facilitators OR enablers OR factors OR determinants OR geographical barriers OR Seasons OR rainy season OR terrain OR distance OR access OR accessibility OR service access OR service accessibility OR quality OR availability OR affordability OR timing OR health decision making OR health decision-making OR maternal decision-making OR maternal decision making OR maternal autonomy OR maternal education OR maternal experience OR postnatal practices OR post natal practice* OR post-natal practice* OR socio-cultural practice* OR traditional beliefs OR Health systems OR Healthcare systems OR health systems performance )
#4	AB Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe
#5	#1 AND #2 AND #3 AND #4
#6	<b>Filters: Full text availability, Published date 2009 – 2022</b>
Notes	Search in: Academic Search Premier; Africa-Wide Information; CINAHL; Health Source: Nursing/Academic Edition; APA PsycInfo
<b>Web of Science Database</b>	
<b>Search</b>	<b>Query</b>
#1	AB=(Child* OR infant* OR neonat* OR newborn*)
#2	(AB=(Hepatitis B OR hep B OR HBV OR hepatitis B birth dose OR hepatitis B birth-dose)) AND AB=(Immuni* OR immuni* coverage OR immuni* program* OR immuni* initiatives OR Vaccin* OR vaccin* coverage)
#3	(AB=(Healthcare workers OR healthcare professionals OR traditional birth attendants OR midwife OR midwives OR community health workers OR voluntary worker OR training OR skills building OR staff responsibilities OR standards OR staffing OR human resource* OR task shifting OR home care service OR community care OR outreach OR home visit OR cold chain OR cold temperature OR supply chain OR distribution OR drug storage OR medicine storage OR vaccine storage OR Uniject OR compact pre-filled auto-disabled device OR CPAD OR vials OR dose OR dosage OR birth delivery OR birth centre OR birth center OR health centre OR health center OR health facility OR health facilities OR monitor* OR regis* OR record OR data collection OR organization OR organisation OR administration OR management OR integrated OR immuni* program* AND cost analysis OR costs OR funds OR funding OR finance OR finances OR financial resource* OR Immuni* program* standards OR immuni* schedule OR timeliness OR timely OR 24 hours OR 24-hours OR knowledge OR attitudes OR practice* OR Policy makers OR policymakers OR polic*)) OR AB=(Barriers OR constraints OR obstacles OR challenges OR facilitators OR enablers OR factors OR determinants OR geographical barriers OR Seasons OR rainy season OR terrain OR distance OR access OR accessibility OR service access OR service accessibility OR quality OR availability OR affordability OR timing OR health decision making OR health decision-making OR maternal decision-making OR maternal decision making OR maternal autonomy OR maternal education OR maternal experience OR postnatal practices OR post natal practice* OR post-natal practice* OR socio-cultural practice* OR traditional beliefs OR Health systems OR Healthcare systems OR health systems performance)
#4	AB=(Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR

	eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe)
#5	#1 AND #2 AND #3 AND #4
#6	<b>Filters: Published date 2009 – 2022</b>
<b>Scopus Database</b>	
<b>Search</b>	<b>Query</b>
#1	TITLE-ABS(Child* OR infant* OR neonat* OR newborn*)
#2	TITLE-ABS("Hepatitis B" OR "hep B" OR HBV OR "hepatitis B birth dose" OR "hepatitis B birth-dose") AND TITLE-ABS(Immuni* OR "immuni* coverage" OR "immuni* program*" OR "immuni* initiatives" OR Vaccin* OR "vaccin* coverage")
#3	TITLE-ABS-KEY("Healthcare workers" OR "healthcare professionals" OR "traditional birth attendants" OR midwife OR midwives OR "community health workers" OR "voluntary worker" OR training OR "skills building" OR "staff responsibilities" OR standards OR staffing OR "human resource*" OR "task shifting" OR "home care service" OR "community care" OR outreach OR "home visit" OR "cold chain" OR "cold temperature" OR "supply chain" OR distribution OR "drug storage" OR "medicine storage" OR "vaccine storage" OR Uniject OR "compact pre-filled auto-disabled device" OR CPAD OR vials OR dose OR dosage OR "birth delivery" OR "birth centre" OR "birth center" OR "health centre" OR "health center" OR "health facility" OR "health facilities" OR monitor* OR regis* OR record OR "data collection" OR organization OR organisation OR administration OR management OR integrated OR "immuni* program*" AND "cost analysis" OR costs OR funds OR funding OR finance OR finances OR "financial resource*" OR "Immuni* program* standards" OR "immuni* schedule" OR timeliness OR timely OR 24 hours OR 24-hours OR knowledge OR attitudes OR practice* OR "Policy makers" OR policymakers OR polic*) OR TITLE-ABS-KEY(Barriers OR constraints OR obstacles OR challenges OR facilitators OR enablers OR factors OR determinants OR "geographical barriers" OR Seasons OR "rainy season" OR terrain OR distance OR access OR accessibility OR service access OR "service accessibility" OR quality OR availability OR affordability OR timing OR health decision making OR "health decision-making" OR "maternal decision-making" OR "maternal decision making" OR "maternal autonomy" OR "maternal education" OR "maternal experience" OR "postnatal practice*" OR "post natal practice*" OR "post-natal practice*" OR "socio-cultural practice*" OR "traditional beliefs" OR "Health systems" OR "Healthcare systems" OR "health systems performance")
#4	TITLE-ABS-KEY(Africa OR African OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR "Cabo Verde" OR Cameroon OR Cameroun OR "Canary Islands" OR "Cape Verde" OR "Central African Republic" OR Chad OR Comoros OR Congo OR "Cote d'Ivoire" OR "Democratic Republic of Congo" OR Djibouti OR Egypt OR Eritrea OR eSwatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea- Bissau OR "Ivory Coast" OR Jamahiriya OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mayotte OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Principe OR Reunion OR Rwanda OR "Saint Helena" OR "Sao Tome" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "St Helena" OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zaire OR Zambia OR Zimbabwe)
#5	#1 AND #2 AND #3 AND #4
#6	<b>Filters: Published date 2009 – 2022</b>

## Appendix I. Quality appraisal summary of included studies

Table 6. Quality appraisal of included studies (Source: Author)

Author, year	Appraisal tool	Overall quality judgement
Accrombessi et al, 2020	MMAT	Green
Aina et al, 2017	MMAT	Red
Allison et al, 2017	Dufault & Klar	Green
Bagney et al, 2015	MMAT	Red
Bassoum et al, 2021	MMAT	Green
Bassoum et al, 2022	MMAT	Green
Chang et al, 2019	MMAT	Red
Dagneu et al, 2020	MMAT	Green
Djaogal et al, 2019	MMAT	Green
Goodman et al, 2013	MMAT	Green
Guingane et al, 2020	CASP	Green
Hagan et al, 2019	CASP	Green
Jaquet et al, 2017	MMAT	Green
Loarec et al, 2022	CASP	Green
Miyahara et al, 2016	CASP	Green
Nankya-Mutyoba et al, 2021	CASP	Green
Okenwa et al, 2019	MMAT	Green
Okenwa et al, 2020	MMAT	Green
Olakunda et al, 2021	MMAT	Green
Périeres et al, 2021	MMAT	Green
Sadoh et al, 2014	MMAT	Green
Ibrahim et al, 2022	MMAT	Green
Ibraheem et al, 2022	MMAT	Yellow
Ibraheem et al, 2019	MMAT	Green
Sadoh et al, 2013	MMAT	Yellow
Danjuma, 2020	MMAT	Green
Bada et al, 2022	CASP	Green
Moturi et al, 2018	MMAT	Yellow
<p><b>Overall judgement of quality: Mixed Methods Appraisal Tool (MMAT) calculated as a percentage of criteria met, mixed method designs awarded an overall score equivalent to the lowest rated study component of the study; Critical Appraisal Skills Programme (CASP) tools overall scores are calculated and then rated as being in the first, second or last third of the total with the overall judgement correlated as low, medium or high quality respectively; Dufault and Klar assessment scale overall judgement of relevance from low (&lt;5 points) to high (&gt;8 points) relevance. In this table: red = low quality; yellow = medium quality; green = high quality.</b></p>		

## Appendix J. Characteristics of included studies

Table 7. Characteristics of included studies (Source: Author)

Study No.	Author	Year	Title	Country	Study design	National policy on hepatitis B birth-dose vaccination*	Vaccination implementation strategy in study: Universal vs selective	Population group	Description of population	Study sample	Primary objective of the study
1	Accrombessi et al (32)	2019	Assessment of the anti-HBs antibody response in Beninese infants following 4 doses of HBV vaccine, including administration at birth, compared to the standard 3 doses regime: a cross-sectional survey	Benin	Cross-sectional	No	Universal	Mother-infant pairs	9-month-old infant and mother pairs	140 pairs	Vaccine efficacy of hepatitis B birth-dose included regimen
2	Aina et al (33)	2017	Preliminary results from direct-to-facility vaccine deliveries in Kano, Nigeria	Nigeria	Mixed methods (retrospective review)	Yes	Universal	Health facilities	Sentinel health facilities involved in vaccination services	27	Evaluation of vaccine supply program
3	Allison et al (34)	2017	Hepatitis B vaccine birth dose coverage correlates worldwide with rates of institutional deliveries and skilled attendance at birth	Global	Ecological study	Yes	Universal	Countries	Countries providing universal hepatitis B birth-dose vaccination	83	Factors associated with hepatitis B birth-dose implementation
4	Bagney et al (35)	2015	Evaluation of midwives' practices for the prevention of mother-to-child transmission of hepatitis B in Abidjan (Ivory Coast)	Ivory Cost	Cross-sectional	No	Selective	Midwives	Midwives recruited from different levels of health facilities	197	Knowledge, attitude and practice of HCWs regarding PMTCT of hepatitis B practices
5	Bassoum et al (36)	2021	Factors associated with co-administration of birth dose vaccines in Senegalese children	Senegal	Cross-sectional	Yes	Universal	Children	Children aged 12-23 months	726	Factors associated with implementation of birth-dose vaccines
6	Bassoum et al (37)	2022	Vaccination against tuberculosis, polio and hepatitis B at birth in	Senegal	Cross-sectional	Yes	Universal	Children	Children aged 12-23 months	832	Vaccination coverage and the factors associated

			Podor health district, Northern Senegal: cross-sectional study of vaccination coverage and its associated factors								with <b>timely</b> implementation
7	Chang et al (38)	2019	Survey of Impediments to Prevention of Mother-to-infant Transmission of Hepatitis B Virus by International Societies	Global	Mixed methods	Unspecified	Unreported	Countries	Local paediatric HBV experts representing country/ region, and global members of the societies of FISP GHAN	63 (13 African)	Identifying <b>obstacles</b> to hepatitis b vaccination implementation
8	Dagneu et al (39)	2020	Knowledge, attitude and associated factors towards vertical transmission of hepatitis B virus among pregnant women attending antenatal care in tertiary hospitals in Amhara region, northwest Ethiopia: A cross-sectional study	Ethiopia	Cross-sectional survey	No	Unreported	Pregnant women	Pregnant women attending ANC	1121	<b>Knowledge, attitude and practice</b> of end users regarding PMTCT of hepatitis B practices
9	Djaogol et al (40)	2019	Prevention and care of hepatitis B in the rural region of Fatick in Senegal: a healthcare workers' perspective using a mixed methods approach	Senegal	Mixed methods survey	Yes	Universal	HCWs	HCWs involved in activities related to maternal and child health	98	<b>Knowledge, attitude and practice</b> of HCWs regarding implementing hepatitis B PMTCT activities
10	Goodman et al (41)	2013	Health workers sensitization: effects on perceived quality of immunization services among mothers of under five children in Ilorin, North Central Nigeria	Nigeria	Quasi-experimental	Yes	Universal	Mothers	Mothers of children under 5 years old attending immunization clinic for the vaccines of HBV/OPV/BCG and DPT/OPV/BCG	300	<b>Perceived quality</b> of immunization services of mothers after HCW sensitization
11	Guingane et al (42)	2020	Identifying gaps across the cascade of care for the prevention of HBV mother-to-child transmission in Burkina	Burkina Faso	Prospective cohort	No	Selective	Pregnant women	Pregnant women attending ante-natal consultation at one of the 9 first-level health centers in the health district	2220	<b>Evaluation</b> of PMTCT hepatitis B program in real life setting

			Faso: Findings from the real world								
12	Hagan et al (43)	2019	Selective Hepatitis B Birth-Dose Vaccination in São Tomé and Príncipe: A Program Assessment and Cost-Effectiveness Study	São Tomé and Príncipe	Qualitative: Field assessment	Yes	Selective	Health facilities	Health facilities providing maternity services, including key informants in MoH, representatives of partners and representative organizations.	5	Evaluation of selective hepatitis B birth-dose vaccination program
13	Jaquet et al (44)	2017	Prevention and Care of Hepatitis B in Senegal: Awareness and Attitudes of Medical Practitioners	Senegal	Cross-sectional survey	No	Universal	Medical doctors	Certified medical doctors (specialists and general practitioners) practicing in the public sector of 3 major urban areas	127	Knowledge, attitude and practice of HCWs on HBV infection
14	Loarec et al (45)	2022	Prevention of mother-to-child transmission of hepatitis B virus in antenatal care and maternity services, Mozambique	Mozambique	Retrospective cohort	No	Selective	Pregnant women	Pregnant women (and their new-born infants) attending Chamanculo General Hospital	6775	Evaluation of PMTCT hepatitis B program in real life setting
15	Miyahara et al (46)	2016	Barriers to timely administration of birth dose vaccines in The Gambia, West Africa	The Gambia	Prospective cohort	Yes	Universal	Infants	Infants born in the Farafenni Health and Demographic Surveillance System between 2004-2014	10851	Coverage, timeliness and factors associated with birth-dose vaccine implementation
16	Nankya-Mutyoba et al (47)	2021	Hepatitis B birth dose vaccination for newborns in Uganda: A qualitative inquiry on pregnant women's perceptions, barriers and preferences	Uganda	Qualitative	No	Unreported	Pregnant women	Pregnant women attending routine antenatal clinic visits in Central Uganda	70	Awareness, barriers, perceptions and preference of pregnant women regarding hepatitis B birth-dose vaccination

17	Okenwa et al (48)	2019	Maternal reasons for non-receipt of valid Hepatitis B birth dose among mother-infant pairs attending routine immunization clinics, South-east, Nigeria	Nigeria	Cross-sectional survey	Yes	Universal	Mother-infant pairs	Mother-infant pairs attending immunization clinics in Enugu State of Nigeria	344	<b>Barriers</b> to birth-dose implementation as identified by mothers
18	Okenwa et al (49)	2020	Maternal knowledge and infant uptake of valid hepatitis B vaccine birth dose at routine immunization clinics in Enugu State – Nigeria	Nigeria	Cross-sectional survey	Yes	Universal	Mother-infant pairs	Mother-infant pairs attending immunization clinics in Enugu State of Nigeria	366	<b>Knowledge, awareness and factors</b> associated with uptake of <b>timely</b> hepatitis B birth-dose vaccination
19	Olakunde et al (50)	2021	The coverage of hepatitis B birth dose vaccination in Nigeria: Does the place of delivery matter?	Nigeria	Cross-sectional secondary analysis	Yes	Universal	Children	Children aged 12 – 23 months	6143	Vaccine <b>coverage</b> and the <b>associated</b> influence of place of delivery
20	Périers et al (51)	2021	Hepatitis B Vaccination in Senegalese Children: Coverage, Timeliness, and Sociodemographic Determinants of Non-Adherence to Immunisation Schedules (ANRS 12356 AmBASS Survey)	Senegal	Cross-sectional survey (part of the ANRS 12356 AmBASS survey)	Yes	Universal	Children	Children from the AmBASS survey born on or after 1 January 2016 (year of national hepatitis B birth-dose implementation)	241	<b>Coverage</b> and associated <b>factors</b> related to non-adherence to <b>timely</b> vaccination.
21	Sadoh et al (52)	2014	Hepatitis B infection among Nigerian children admitted to a children's emergency room	Nigeria	Cross-sectional descriptive study	Yes	Universal	Children	All children aged between 2 months and 15 years admitted to children's emergency room of the University of Benin Teaching Hospital	150	<b>HBV Prevalence</b> , and vaccination coverage <b>and timeliness</b>
22	Ibrahim et al (53)	2022	Factors associated with timeliness of hepatitis B birth dose: A cross-sectional study in North-Western Nigeria	Nigeria	Cross-sectional	Yes	Universal	Mother-infant pairs	Infants and their respective mothers/caregivers presenting at the immunization clinic for their first vaccination dose	400	<b>Factors</b> associated with <b>timely</b> vaccine implementation

23	Ibraheem et al (54)	2022	Assessment of the Timely Administration of Birth Dose Vaccines in Northern Nigeria and Associated Factors	Nigeria	Cross-sectional study (secondary analysis)	Yes	Universal	Mother-infant pairs	Mother/caregiver and infant pair presenting for birth-dose vaccines at the 5 different immunization centers in 5 different Northern Nigerian states	1952	<b>Factors</b> associated with <b>timely</b> vaccine implementation
24	Ibraheem et al (55)	2019	Determinants of Timely Presentation for Birth Dose Vaccination at an Immunization Centre in North-central Nigeria	Nigeria	Cross-sectional	Yes	Universal	Mother-infant pairs	Mother-infant pairs attending immunization centre of General Hospital, Ilorin for first vaccination.	480	<b>Factors</b> associated with <b>timely</b> vaccine implementation
25	Sadoh et al (56)	2013	Factors contributing to delay in commencement of immunisation in Nigerian infants	Nigeria	Cross-sectional descriptive study	Yes	Universal	Mother-infant pairs	Mother-infant pairs presenting for the commencement of immunization at the Child Welfare clinic of the Institute of Child Health, University of Benin, Benin City.	153	<b>Factors and maternal reasons</b> associated with vaccine implementation, specifically <b>timeliness</b>
26	Danjuma et al (57)	2020	At-Birth Vaccination Timeliness: An Analysis of Inborns in the Highlands of Jos, North-Central Nigeria	Nigeria	Cross-sectional	Yes	Universal	Mother-infant pairs	Mother/guardian- newborn (birth weight $\geq$ 1.8kg) pair in the lay-wards of Jos University Teaching Hospital and Fertile Ground Hospital	355	<b>Factors and obstacles</b> associated with <b>timely</b> vaccine implementation
27	Bada et al (58)	2022	Factors associated with receipt of a timely infant birth dose of hepatitis B vaccine at a tertiary hospital in North-Central Nigeria	Nigeria	Retrospective cohort (secondary analysis)	Yes	Universal	Mother-infant pairs	Mother-infant pairs at a tertiary hospital in North-Central Nigeria	409	<b>Factors</b> associated with <b>timely</b> hepatitis B birth-dose vaccine implementation
28	Moturi et al (31)	2018	Implementing a birth dose of hepatitis B vaccine in Africa: Findings from assessments in 5 countries	Nigeria, Namibia, Botswana, The Gambia, São Tomé and Príncipe	Cross-sectional	Yes	Universal (Nigeria, Namibia, Botswana, The Gambia) and Selective (São Tomé and Príncipe)	Health Facilities	Health facilities providing delivery services	78	<b>Knowledge, attitudes, and practices</b> among HCWs surrounding hepatitis B birth-dose vaccination

\*Hepatitis B birth-dose vaccination availability at the time the studies were conducted. HCWs- health care workers; PMTCT- prevention of mother to child transmission; MoH- Ministry of Health; AmBASS survey- this is a large population-based survey which aims to study the epidemiology, and socioeconomic and public health impacts of HBV chronic infection in specific contexts; FISPCHAN- Federation of the international societies for pediatric gastroenterology, hepatology and nutrition; (DPT)/HBV/OPV/BCG- (Diphtheria, pertussis, tetanus)/hepatitis B virus / oral polio virus/tuberculosis

## Appendix K. Frontiers in Public Health author guidelines



### Author guidelines

For full guidelines please refer to [Author Guidelines](#)

As a primary goal, the abstract should render the general significance and conceptual advance of the work clearly accessible to a broad readership. References should not be cited in the abstract. Leave the Abstract empty if your article does not require one – please see the “Article types” on every Frontiers journal page for full details.

#### 1 Introduction

For **Original Research Articles**, **Clinical Trial Articles**, and **Technology Reports** the introduction should be succinct, with no subheadings. For **Case Reports** the Introduction should include symptoms at presentation, physical exams and lab results.

#### 2 Article types

For requirements for a specific article type please refer to the Article Types on any Frontiers journal page. Please also refer to [Author Guidelines](#) for further information on how to organize your manuscript in the required sections or their equivalents for your field<sup>1</sup>.

#### 3 Manuscript Formatting

##### 3.1 Headings

You may insert up to 5 heading levels into your manuscript as can be seen in “Styles” tab of this template. These formatting styles are meant as a guide, as long as the heading levels are clear, Frontiers style will be applied during typesetting.

##### 3.2 Equations

The equations should be inserted in editable format from the equation editor.

$$f(x) = a_0 + \sum_{n=1}^{\infty} \left( a_n \cos \frac{n\pi x}{L} + b_n \sin \frac{n\pi x}{L} \right)$$

##### 3.3 Figures

Frontiers requires figures to be submitted individually, in the same order as they are referred to in the manuscript. Figures will then be automatically embedded at the bottom of the submitted manuscript. Kindly ensure that each table and figure is mentioned in the text and in numerical order. Figures must be of sufficient resolution for publication. Figures which are not according to the guidelines will cause substantial delay during the production process. Figure legends should be placed at the end of the manuscript. Please see [here](#) for full Figure guidelines

##### 3.4 Permission to reuse and Copyright

Permission must be obtained for use of copyrighted material from other sources (including the web). Please note that it is compulsory to follow figure instructions.

##### 3.5 Tables

Tables should be inserted at the end of the manuscript. Tables must be provided in an editable format e.g., Word, Excel. Tables provided as jpeg/tiff files will **not be accepted**. Please note that very large tables (covering several pages) cannot be included in the

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<sup>1</sup> For Original Research articles, please note that the Material and Methods section can be placed in any of the following ways: before Results, before Discussion or after Discussion.

final PDF for reasons of space. **These tables will be published as [Supplementary Material](#) on the online article page at the time of acceptance. The author will be notified during the typesetting of the final article if this is the case.**

## 4 Nomenclature

### 4.1 Resource Identification Initiative

To take part in the Resource Identification Initiative, please use the corresponding catalog number and RRID in your current manuscript. For more information about the project and for steps on how to search for an RRID, please click [here](#).

### 4.2 Life Science Identifiers

Life Science Identifiers (LSIDs) for ZOOBANK registered names or nomenclatural acts should be listed in the manuscript before the keywords with the following format:

urn:lsid:<Authority>:<Namespace>:<ObjectID>[:<Version>]

## 5 Additional Requirements

For additional requirements for specific article types and further information please refer to “Article types” on every Frontiers journal page.

## 6 Conflict of Interest

All financial, commercial or other relationships that might be perceived by the academic community as representing a potential conflict of interest must be disclosed. If no such relationship exists, authors will be asked to confirm the following statement:

*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

## 7 Author Contributions

The Author Contributions section is mandatory for all articles, including articles by sole authors. If an appropriate statement is not provided on submission, a standard one will be inserted during the production process. The Author Contributions statement must describe the contributions of individual authors referred to by their initials and, in doing so, all authors agree to be accountable for the content of the work. Please see [here](#) for full authorship criteria.

## 8 Funding

Details of all funding sources should be provided, including grant numbers if applicable. Please ensure to add all necessary funding information, as after publication this is no longer possible.

## 9 Acknowledgments

This is a short text to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors.

## 10 Reference styles

The following formatting styles are meant as a guide, as long as the full citation is complete and clear, Frontiers referencing style will be applied during typesetting.

### 10.1 Science, Engineering and Humanities and Social Sciences references

For articles submitted in the domains of Science, Engineering or Humanities and Social Sciences please apply Author-Year system for in-text citations. For Humanities and Social Sciences articles please include page numbers in the in-text citations

For some examples please click [here](#).

For more examples of citing other documents and general questions regarding reference style, please refer to the [Chicago Manual of Style](#).

### 10.2 Health, Physics and Mathematics references

For articles submitted in the domain of Health or the journals Frontiers in Physics and Frontiers in Applied Mathematics and Statistics please apply the Vancouver system for in-text citations.

In-text citations should be numbered consecutively in order of appearance in the text – identified by Arabic numerals in the parenthesis [square parenthesis for Physics and Mathematics].

For some examples please click [here](#).

For more examples of citing other documents and general questions regarding reference style, please refer to [Citing Medicine](#).

### **11 Supplementary Material**

Supplementary Material should be uploaded separately on submission, if there are Supplementary Figures, please include the caption in the same file as the figure. Supplementary Material templates can be found in the Frontiers Word Templates file.

Please see the [Supplementary Material section of the Author guidelines](#) for details on the different file types accepted.

### **12 Data Availability Statement**

The datasets [GENERATED/ANALYZED] for this study can be found in the [NAME OF REPOSITORY] [LINK]. Please see the “Availability of data” section of [Materials and data policies in the Author guidelines](#) for more detail