Accelerating the momentum to achieve global elimination of hepatitis B infection: a scoping review of hepatitis B guidelines to reduce mother to child transmission

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Summary

Progress towards achieving global elimination of hepatitis B virus (HBV) by 2030 remains unsatisfactory. Prevention of mother to child transmission is crucial but current Clinical Practice Guidelines (CPGs) gave diverse recommendations, creating confusion and leading to significant challenges in the practical implementation across various regions owing to global inequity. We reviewed 47 CPGs on the management of hepatitis B during pregnancy against twelve important clinical questions. Of 47 guidelines, 80.9% (38/47) supported the universal approach to HBV screening. To select women for antiviral prophylaxis, 78.7% (37/47) recommended the use of HBV DNA levels, while 31.9% (15/47) recommended the use of HBeAg. Of 37 guidelines recommending HBV DNA levels, 94.6% (35/37) recommended a viral load threshold of >200,000 IU/mL to initiate antiviral prophylaxis. Of 16 guidelines addressing the mode of delivery, 87.5% (14/16) encouraged vaginal birth. Of 30 guidelines addressing breastfeeding, 60% (18/30) recommended breastfeeding. However, controversies were found in the optimal timing of HBV disease evaluation during pregnancy and the ideal timing to stop antiviral prophylaxis after delivery. Of 36 guidelines addressing the timing to initiate antiviral prophylaxis, 25% (9/36) advised starting prophylaxis between 24 and 28 weeks, while 75% (27/36) suggested other timings or provided vague descriptions. Of 38 guidelines addressing birth-dose vaccination, 42% (16/38) emphasized the importance of "vaccination as soon as possible after birth." These deficiencies and discrepancies among CPGs could significantly impede global HBV elimination.

Keywords: Antiviral; Hepatitis B virus; Pregnancy; Vaccine; Viral load; Vertical transmission

Introduction

Hepatitis B (HBV) infection represents a serious global health challenge, with increasing mortality rates, resulting in 1.1 million deaths worldwide in 2022.[1] World Health Organization (WHO) published a global strategy aiming to reduce new incidence by 90% and mortality by 65%, which will avert 9.6 million new infections and save 2.85 million lives if these goals are achieved by 2030.[2,3] Eliminating mother to child transmission (MTCT) of HBV is a crucial component of this strategy, as MTCT remains a major route of HBV transmission worldwide since peripartum infections pose a higher risk of developing chronic hepatitis B infection. Approximately 90% of those infected as neonates, 30% of children infected at 1–4 years old, and less than 5% of those infected as adults will become a chronic carrier.[4]

The identification of hepatitis B infected individuals, coupled with antenatal maternal antiviral prophylaxis and immunoprophylaxis of infants, serve as cornerstone preventive strategies integral to guide elimination of HBV MTCT, though their implementations and successes vary across regions. For example, despite these effective interventions, the prevalence of hepatitis B surface antigen (HBsAg) in children under five years old in 2020 was 2.53% in the African region, falling short of the WHO target of <1% in the same year and seems a long way from the target of achieving <0.1% in 2030.[5,6]

To accelerate the momentum and reach global MTCT elimination as set by WHO, high-quality, people-centered, and evidence-based Clinical Practice Guidelines (CPGs) to guide clinicians in managing individuals with hepatitis B during pregnancy are essential. Many hepatitis B management CPGs are available, but discrepancies exist.[7–53] These could create confusion and lead to significant challenges in the practical implementation across various regions owing to global inequity. We assumed that an ideal CPG should contain a comprehensive framework describing the best strategy for MTCT prevention from disease evaluation to treatment options, as well as feasible alternatives for practical implementation in resource-limited areas. Therefore, we developed 12 critical clinical questions based on

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various crucial elements for successful MTCT prevention. The objectives of this scoping review are to compare and evaluate all available hepatitis B CPGs against these 12 clinical questions, as well as to identify areas that require further research.

Methods

Protocol and registration

A scoping review of CPGs was conducted, and the review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; identification CRD42024539624). The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping review (PRISMA-ScR) checklist.

Search strategy and selection criteria

Two independent reviewers (KWC and YRL) searched the literature, screened abstracts and titles, and selected studies. Any discrepancies were resolved through discussion with a third author (MTYS). Five electronic databases (CINAHL, Embase, Medline, Web of Science, Cochrane Library) were searched up to May 2024 to identify CPGs reflective of current practice. The search strategy involved two key concepts: hepatitis and CPGs or recommendations or consensus, using the keywords 'hepatitis', 'guideline', 'recommendation', 'consensus', and 'pregnancy'. This search was further complemented by searching the following guideline repositories for relevant hepatitis CPGs: Google Scholar, National Institute for Health and Care Excellence Evidence Search, CPG Infobase, Scottish Intercollegiate Guidelines Network, Guidelines International Network, ECRI Guidelines Trust, Australian CPGs, and The Coalition for Global Hepatitis Elimination. To ensure comprehensive inclusion of pertinent documents utilized or referred to by clinicians, recommendations or consensus documents authored by national or international professional groups were also incorporated. Despite the methodological differences in the development of these documents, their functional equivalence to CPGs were recognized. We excluded all CPGs with the latest editions published before 2018 as robust evidence on the use of maternal antenatal antiviral prophylaxis became available since 2018. We included all updated versions of CPGs that covered the diagnosis, treatment, and/or prevention of hepatitis developed by local, regional, national, or international groups or affiliated governmental organizations. There were no language restrictions.

Data items and synthesis

Twelve critical clinical questions were developed to identify the scope of this review (Table 1). These questions were formulated based on the assumption that an ideal CPG should contain a comprehensive framework describing the best strategy for MTCT prevention, and should consider the mechanisms of immunoprophylaxis failure and strategies to prevent MTCT during antepartum, intrapartum, and postpartum periods.[54] Data extraction was based on these clinical questions.

Two complementary approaches were employed to synthesize the extracted data. First, recommendation mapping was conducted to collect and compare recommendations from various CPGs to identify areas of consensus or disagreement. Second, a reference frequency analysis was performed to assess the prevalence of specific clinical questions within CPGs, thereby identifying the most influential research areas and potential gaps to date.

Quality assessment

The full-text version of the each CPGs was independently evaluated by four authors to determine whether they met the inclusion criteria and to appraise their quality critically (KWC, YRL, TSTA, and MTYS). The Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, a widely used and extensively cited tool in the literature, was employed for this critical appraisal process.[55] The instrument consists of 23 items across six domains (domain 1: scope and purpose, domain 2: stakeholder involvement, domain 3: rigor of development, domain 4: clarity of presentation, domain 5: applicability, and domain 6: editorial independence) and two additional items (overall guideline assessment and recommendation for use). CPGs were considered

1	Which population should be screened for hepatitis B infection during pregnancy?
2	How and when should HBsAg-positive pregnant women be evaluated during pregnancy?
3	What are the indications for initiating maternal antenatal antiviral prophylaxis to prevent MTCT?
4	Which antiviral agent should be used during pregnancy as prophylaxis to reduce the risk of MTCT?
5	When should antenatal antiviral prophylaxis be started in indicated women?
6	When should the antiviral prophylaxis be discontinued after delivery?
7	Can prenatal or intrapartum invasive testing be performed in HBsAg-positive pregnant women?
8	What is the preferred mode of delivery among HBsAg-positive pregnant women?
9	Is breastfeeding contraindicated in HBsAg-positive pregnant women and those taking antiviral prophylaxis or therapy?
10	When should the birth-dose hepatitis B vaccine and hepatitis B immunoglobulin be administered for infants of HBsAg-positive pregnant women?
11	When should post-vaccination serological testing be performed among infants born to HBsAg-positive pregnant women?
12	How should vaccine non-responders born to HBsAg-positive pregnant women be managed?

Table 1: **Clinical questions to identify the scope of this review.**

high quality if they scored more than 60% in domain three (as its high score typically corresponds to high scores in other domains), and two other domains. Moderate quality was defined as having three or more domains scoring more than 60% (without including domain 3). Low quality did not meet any of the above criteria.

Reporting on HBV DNA levels

HBV DNA levels should be reported as IU/mL but copies/mL was used in five CPGs. WHO suggested using the conversion factor of 1IU/mL ~5.3 copies/mL. However, the conversion factor could be different if the DNA platforms used a different methodology, particularly with the use of in-house PCR technique. Therefore, direct standard conversion may give imprecise assessment.[56] To maintain clarity from original CPGs, we used IU/mL whenever possible, and utilised copies/mL if it was the sole unit stated in the CPGs.

Role of the funding source

There was no funding source for this study.

Result

A total of 24,662 records were identified through database searches. After deduplication, excluding articles that did not meet the inclusion criteria, a total of 47 CPGs published after 2018 were included for descriptive analysis and critical appraisal.[7–53] Fig. 1 shows the PRISMA flow diagram.

Characteristics of CPGs

Supplementary Table S1 presents the general characteristics of the 47 included CPGs published between January 2018 and April 2024.[7–53] Of the included literature, Asia accounted for the majority of included hepatitis B CPGs (n = 16), followed by America (n = 12), Europe (n = 7), Africa (n = 6), Australia (n = 2) and Oceania (n = 1). Three CPGs were published by global

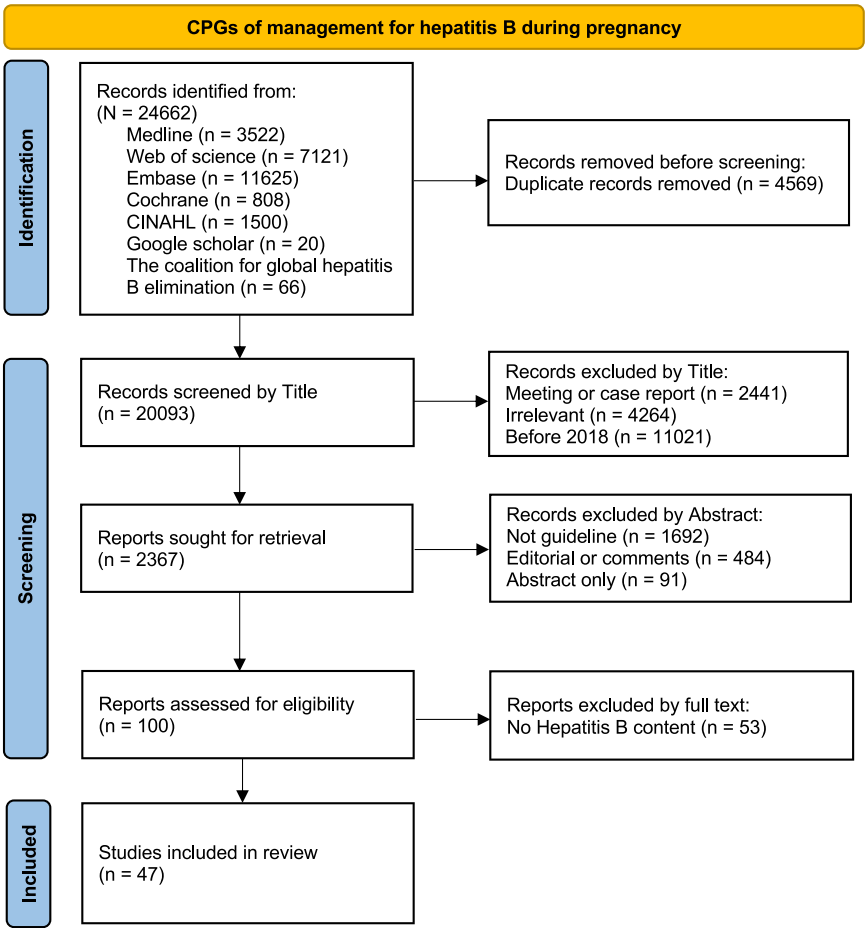

Fig. 1: The CPGs searching flowchart of PRISMA.

organizations. Furthermore, 22 were produced by high-income countries, and the remaining 22 were from low- and middle-income countries. 12 CPGs specifically focused on managing hepatitis B during pregnancy.

Quality assessment of CPGs

The quality assessment scores for the 47 CPGs are presented in Supplementary Figure S1 and Supplementary Table S2. 10 (21.3%) CPGs were assessed as high quality, 18 (38.3%) were moderate quality, and 19 (40.4%) were low quality. There was a high degree of concordance among scores by reviewers (overall weighted Cohen's κ 0.91, 95% CI 0.89–0.94).

The highest average domain score of all CPGs was 'Scope and Purpose' (median 93%, IQR 83–100%), and all CPGs had a score ≥70% except two. The 'Applicability' domain had the lowest score (median 27%, IQR 12–40%), and only 3 CPGs had a score ≥60%. Another domain with suboptimal performance was 'Editorial Independence' (median 43%, IQR 0–83%), 18 CPGs did not provide information about funding and conflict of interest. The other domains were 'Clarity of Presentation' (median 90%, IQR 80–94%), 'Stakeholder Involvement' (median 59%, IQR 48–68%), and 'Rigor of Development' (median 31%, IQR 22–51%).

Summary of CPGs

Tables 2 and 3 collate the recommendations from all included CPGs on antenatal and neonatal management. Table 4 details the proportion of CPGs that addressed each clinical question.

Population and approach for screening hepatitis B virus

Of 47 guidelines, 80.9% (38/47) described the approach and timing for screening HBV during pregnancy. All thirty-eight CPGs agreed that pregnant women should be universally tested for HBsAg as early as possible during pregnancy.

Disease evaluation, timing, and frequency

CPGs are unclear on the timing and mode of HBV disease evaluation during pregnancy.

70.2% (33/47) CPGs addressed the assessment of disease in mothers positive for HBsAg. Among them, seven CPGs recommended testing for HBV DNA alone, while two CPGs recommended testing for both HBV DNA and liver function tests (LFTs). Eight CPGs advised testing for both HBV DNA and hepatitis B e antigen (HBeAg), whereas another six CPGs recommended testing for HBV DNA, LFTs, and HBeAg. Another ten CPGs advised on utilising other tests, including serologic test, creatinine, complete blood count, renal function test, ultrasound scan and clotting profile. 38.3% (18/47) CPGs mentioned the timing of disease evaluation, including first trimester (n = 6), first antenatal care (n = 4), early pregnancy (n = 2), at 28 weeks of gestation (n = 1), during the second (n = 2) and third trimesters (n = 1), in the early second trimester (n = 1), and every 3 months (n = 1).

10.6% (5/47) CPGs addressed the optimal frequency of disease assessment. One CPG suggested that repeating HBV DNA quantification tests in later gestation may be unnecessary, while three CPGs recommended re-assessing HBV DNA and LFTs during the early third trimester (n = 1) and between 26 and 28 weeks of gestation (n = 2), respectively. Another CPG advised that LFTs should be repeated every 2–3 months.

Maternal antiviral prophylaxis

78.7% (37/47) CPGs gave recommendations on utilizing HBV DNA levels to guide initiation of antiviral prophylaxis, and of these 37 CPGs, 94.6% (35/37) agreed that it should be started when HBV DNA levels reach 5.3 $\log_{10}$ IU/mL (200,000 IU/mL). Of which, three CPGs specifically suggested that it can also be started when HBsAg >4 $\log_{10}$ IU/mL, one CPG advised HBV DNA ≥4.3 $\log_{10}$ IU/mL, and one recommended HBV DNA > 6 $\log_{10}$ copies/mL. Thirty two CPGs did not suggest an alternative approach when HBV DNA quantification is not available. Notably, 31.9% (15/47) CPGs explicitly recommended considering a positive HBeAg status as an additional criterion to start antiviral prophylaxis in settings where HBV DNA is not available.

83.0% (39/47) CPGs addressed the selection of antiviral agents. Tenofovir disoproxil fumarate (TDF) was the treatment of choice by all CPGs, while five CPGs also acknowledged the acceptability of Tenofovir Alafenamide (n = 3), Telbivudine (n = 1) and Lamivudine (n = 1).

The timing for initiation of antiviral prophylaxis was mentioned in 76.6% (36/47) CPGs. The recommended periods to start antiviral prophylaxis vary (from after 24 weeks till up to 32 weeks) or are vague in description (second/third trimester), with the most recommended timing points being between 24 and 28 weeks of gestation (n = 9) and 28–32 weeks of gestation (n = 8). Other suggestions included starting from 28 weeks of gestation (n = 6), initiation at the beginning of the third trimester (n = 2), during the third (n = 3) and second trimesters (n = 1), after the first trimester and before third trimesters (n = 2), between 24 and 32 weeks of gestation (n = 1), between 26 and 28 weeks of gestation (n = 1), at around 30 weeks of gestation (n = 1), as soon as possible (n = 1) and starting from 24 weeks of gestation or earlier (n = 1).

70.2% (33/47) CPGs had recommendations regarding the optimal timing for discontinuing antiviral prophylaxis, with suggestions ranging from at birth or continuation up to 12 weeks postpartum (n = 6), continuation up to 12 weeks postpartum (n = 12), discontinuation at birth (n = 2), and continuation until at least delivery (n = 3), between birth and 12 weeks postpartum (n = 1), until at least delivery or completion of the infant HBV vaccination series (n = 1), and

	Screening	Disease evaluation			Viral load to start antiviral	Antiviral if HBeAg positive	Choice of antiviral	Timing to start antiviral	Timing to discontinue antiviral	Prenatal invasive test	Intrapartum invasive test	Mode of delivery
		Tests	Timing	Frequency								
Argentina 2021[7]	All pregnant women	HBV DNA, HBeAg, LFTs, the others	First trimester	Repeat HBV DNA at 26–28 weeks	≥200,000 IU/mL	–	TAF, TDF	26–28 weeks	Continue for 12 weeks postpartum	–	–	–
Asia Pacific 2022[8]	All pregnant women	HBV DNA, HBeAg	–	–	≥200,000 IU/mL	Yes	TDF	24–28 weeks	At birth or up to 12 weeks postpartum	To discuss with the pregnant women and balance the risk and benefit of invasive test in highly viraemic women (≥7 $\log_{10}$ IU/mL)	–	Caesarean section not indicated
Australia 2022[9]	All pregnant women	HBV DNA, HBeAg, LFTs	Early second trimester	–	>200,000 IU/mL	–	TDF	From 28 weeks	Stop between birth and 12 weeks postpartum	To avoid CVS and amniocentesis in women with high viral loads if alternatives are possible	–	Caesarean section not indicated
Bhutan 2020[10]	All pregnant women	HBV DNA, HBeAg, LFTs	Second trimester	–	>200,000 IU/mL	–	TDF	28–32 weeks	Continue for 12 weeks postpartum	–	–	Caesarean section not indicated
Brazil 2020[11]	All pregnant women	HBeAg, anti-HBe, HBV DNA	Third trimester	–	>200,000 IU/mL	Yes	TDF	Third trimester	Continue for 12 weeks postpartum	–	–	–
Canada 1 2018[12]	All pregnant women	HBeAg, anti-HBe, HBV DNA, LFTs	–	–	>200,000 IU/mL	–	TDF	24–32 weeks	At birth or up to 12 weeks postpartum	–	–	Caesarean section not indicated
Canada 2 2020[13]	All pregnant women	HBV DNA, HBeAg	–	–	>200,000 IU/mL	–	TDF	24–28 weeks	Continue for 12 weeks postpartum	To discuss with the pregnant women and balance the risk and benefit of amniocentesis in highly viraemic women (≥7 $\log_{10}$ copies/mL)	–	–
China 1 2020[14]	All pregnant women	HBV DNA, HBeAg, LFTs	–	Repeat LFTs every 2–3 months.	>200,000 IU/mL	Yes	TDF	28–32 weeks	At birth	Amniocentesis can be performed in women with HBeAg negativity or HBV DNA ≤2 × 10^5 IU/mL, To discuss with the pregnant women and balance the risk and benefit of amniocentesis in positive HBeAg or highly viraemic women (>2 × 10^5 IU/mL) Villocentesis, cordocentesis, or intrauterine surgery during pregnant can bring maternal blood components into fetus and thus lead to intrauterine transmission	–	Caesarean section not indicated
China 2 2022[15]	All pregnant women	HBV DNA	–	–	>200,000 IU/mL	Yes	TDF	24–28 weeks	At birth or continue for up to 4–12 weeks postpartum	Avoid amniocentesis	–	–
Czech Republic 2018[16]	All pregnant women	–	–	–	–	–	–	–	–	–	–	–
Europe 1 2021[17]	–	–	–	–	–	–	–	–	–	–	–	Caesarean section not indicated

(Table 2 continues on next page)

	Screening	Disease evaluation			Viral load to start antiviral	Antiviral if HBeAg positive	Choice of antiviral	Timing to start antiviral	Timing to discontinue antiviral	Prenatal invasive test	Intrapartum invasive test	Mode of delivery
		Tests	Timing	Frequency								
(Continued from previous page)												
Europe 2 2023[18]	All pregnant women	Serologic status, HBV DNA, HBeAg, LFTs	First trimester	–	>200,000 IU/mL	Yes	TDF	24–28 weeks	Continue for 12 weeks postpartum	To discuss with HBeAg-positive pregnant women, or those with high HBV DNA levels (>5.3 $\log_{10}$ IU/mL)	–	Caesarean section is not recommended, it may only be recommended in Asian HBeAg-positive women with high HBV DNA titre (>6.14 $\log_{10}$ IU/mL) who have not received antiviral therapy during pregnancy
Fiji 2023[19]	All pregnant women	–	Early pregnancy	–	>200,000 IU/mL in HBeAg positive or > 2000 IU/mL in HBeAg negative	–	TDF	Third trimester	–	–	–	–
Germany 2021[20]	All pregnant women	HBV DNA, LFTs	Every 3 months	–	>200,000 IU/mL	Yes	TDF	Before third trimester but after first trimester	–	–	–	Caesarean section should be discussed when HBV DNA >200,000 IU/mL at the time of birth
HKSAR 2024[21]	All pregnant women	HBV DNA, HBeAg, LFTs	Early pregnancy	Repeat testing is not needed	>200,000 IU/mL	–	TDF	From 28 weeks	Until at least delivery	CVS should be avoided For amniocentesis, the risk of MTCT is low when the viral load is < 7 $\log_{10}$ IU/mL Suggest transamniotic amniocentesis while avoiding transplacental puncture.	Avoid intrapartum fetal scalp blood sampling and fetal scalp electrode	Caesarean section not indicated
Hungary 2019[22]	–	–	–	–	>200,000 IU/mL, HBsAg >4 $\log_{10}$ IU/mL	–	TDF	24–28 weeks	Continue for 12 weeks postpartum	–	–	–
India 1 2018[23]	All pregnant women	–	–	–	>200,000 IU/mL, HBsAg >4 $\log_{10}$ IU/mL	–	TDF	24–28 weeks	Continue for 12 weeks postpartum	–	–	–
India 2 2019[24]	All pregnant women	–	–	–	–	–	TDF	–	–	–	–	–
Indonesia 2023[25]	All pregnant women	HBV DNA, HBeAg	First antenatal visit	–	≥200,000 IU/mL	Yes	TDF	From 28 weeks	Continue for 4 weeks postpartum	–	–	–
Japan 2019[a,26]	–	–	–	–	–	–	–	–	–	–	–	–
Jordan 2022[27]	All pregnant women	Serologic status, HBV DNA	–	–	>200,000 IU/mL, HBsAg >4 $\log_{10}$ IU/mL	–	TDF	24–28 weeks	Continue for 12 weeks postpartum	–	–	–
Malawi 2023[28]	All pregnant women	–	–	–	≥20,000 IU/mL	Yes	TDF	As soon as possible	Continue for 6 weeks postpartum	–	–	–

(Table 2 continues on next page)

	Screening	Disease evaluation			Viral load to start antiviral	Antiviral if HBeAg positive	Choice of antiviral	Timing to start antiviral	Timing to discontinue antiviral	Prenatal invasive test	Intrapartum invasive test	Mode of delivery
		Tests	Timing	Frequency								
(Continued from previous page)												
Maldives 2021[29]	All pregnant women	HBV DNA, HBeAg	–	–	>200,000 IU/mL	–	TDF	24–28 weeks	Continue for 12 weeks postpartum	–	–	Caesarean section not indicated
Mexico 2021[30]	All pregnant women	HBV DNA	–	–	>200,000 IU/mL	–	TDF	At the start of the third trimester	Continue for 4–12 weeks postpartum	–	–	–
Myanmar 2019[31]	All pregnant women	HBV DNA	–	–	–	–	TDF	From 28 weeks	Continue for 12 weeks postpartum	–	–	–
Peru 2018[32]	All pregnant women	HBV DNA, HBeAg, LFTs	First trimester	–	≥200,000 IU/mL	Yes	TDF	After the first trimester	Continue for 16 weeks postpartum	–	–	Caesarean section not indicated
Philippines 2021[33]	–	–	–	–	>200,000 IU/mL	–	TDF	From 28 weeks	Until at least delivery	–	–	–
Rwanda 2019[34]	All pregnant women	–	–	–	–	–	TAF, TDF	–	–	–	–	–
South Africa 2020[35]	All pregnant women	–	–	–	>200,000 IU/mL	–	TDF	28–32 weeks	Continue for 12 weeks postpartum	–	–	Caesarean section not indicated
South Australia 2020[36]	All pregnant women	Hepatitis A/C/D serology, clotting profile, HIV serology, HBV DNA, anti-HBc, LFTs, CBC	–	Repeat LFTs and HBV DNA at 26–28 weeks	≥200,000 IU/mL	–	TDF	28–32 weeks	Continue for 4–12 weeks postpartum	Avoid transplacental amniocentesis For women with high viral loads the transmission risk is increased in both amniocentesis and CVS	Avoid fetal scalp electrode and scalp blood sampling	Caesarean section not indicated
South Korea 1 2021[37]	–	–	–	–	–	–	–	–	–	To discuss with the pregnant women and balance the risk and benefit of invasive test	–	–
South Korea 2 2022[a,38]	–	–	–	–	–	–	–	–	–	–	–	–
Spain 2020[39]	–	HBV DNA	–	–	>200,000 IU/mL	–	TDF	24–28 weeks	At birth or continue for up to 12 weeks postpartum	–	–	–
Sweden 2019[40]	All pregnant women	HBV DNA, HBeAg	–	–	>200,000 IU/mL	Yes	TDF	28–32 weeks	At birth or continue for up to 12 weeks postpartum	–	–	–
Taiwan 2019[41]	–	HBV DNA	–	–	>10^6 copies/mL	–	LdT, TDF	Third trimester	Continue for 4 weeks postpartum	–	–	–
Thailand 2018[42]	All pregnant women	HBV DNA, HBeAg, LFTs, creatinine	First antenatal visit	–	>200,000 IU/mL	Yes	TDF	28–32 weeks	Continue for 4 weeks postpartum	To discuss with the pregnant women and balance the risk and benefit of invasive test	–	–

(Table 2 continues on next page)

	Screening	Disease evaluation			Viral load to start antiviral	Antiviral if HBeAg positive	Choice of antiviral	Timing to start antiviral	Timing to discontinue antiviral	Prenatal invasive test	Intrapartum invasive test	Mode of delivery
		Tests	Timing	Frequency								
(Continued from previous page)												
Uganda 2019[43]	All pregnant women	CBC, LFTs, RFTs, abdominal ultrasound scan, anti-HCV	–	–	>200,000 IU/mL	Yes	–	From 24 weeks or earlier	Continue for 12 weeks postpartum	–	–	–
USA 1 2018[44]	–	HBV DNA, LFTs	At 28 weeks	–	≥200,000 IU/mL	–	TDF	30 weeks	–	To discuss with the pregnant women and balance the risk and benefit of amniocentesis in highly viraemic women (≥7 $\log_{10}$ copies/mL)	–	–
USA 2 2018[45]	All pregnant women	HBV DNA	First trimester	–	>200,000 IU/mL	–	–	–	–	–	–	–
USA 3 2018[46]	All pregnant women	HBV DNA, LFTs, imaging	Second trimester	–	>200,000 IU/mL	–	TDF	28–32 weeks	At birth or continue for up to 12 weeks postpartum	To discuss with the pregnant women and balance the risk and benefit of amniocentesis in highly viraemic women (≥7 $\log_{10}$ copies/mL)	–	Caesarean section not indicated
USA 4 2019[47]	All pregnant women	HBV DNA	First antenatal visit	–	–	–	TDF	–	–	–	–	–
USA 5 2023[48]	All pregnant women	HBV DNA, total anti-HBc, IgM anti-HBc, anti-HBs	–	–	>200,000 IU/mL	–	TDF	At the start of the third trimester	–	To discuss and balance the risk and benefit of amniocentesis in highly viraemic women (≥7 $\log_{10}$ copies/mL)	Insufficient evidence to recommend practice	Caesarean section not indicated
USA 6 2023[49]	All pregnant women	–	First trimester	–	–	–	–	–	–	–	–	–
USA 7 2024[50]	All pregnant women	HBV DNA, HBeAg, LFTs	First trimester	Repeat in early third trimester	>200,000 IU/mL	–	TAF, TDF	28–32 weeks	At birth	To discuss with the pregnant women and balance the risk and benefit of invasive test	Internal monitoring is not contraindicated	Caesarean section not indicated
WHO 1 2020[51]	All pregnant women	HBV DNA, HBeAg	–	–	≥200,000 IU/mL	Yes	TDF	From 28 weeks	Until at least delivery	–	–	–
WHO 2 2024[52]	All pregnant women	HBV DNA, HBeAg	–	–	≥200,000 IU/mL	Yes	TDF	Second trimester	Until at least delivery or upon completion of the infant HBV vaccination series	–	–	–
Zambia 2019[53]	All pregnant women	HBV DNA, HBeAg	First antenatal visit	–	>200,000 IU/mL	Yes	TDF+3TC	–	Continue for 6 weeks postpartum	–	–	–

Abbreviations: Anti-HBc, Hepatitis B core antibodies; Anti-HBs, Hepatitis B surface antibodies; Anti-HBe, Hepatitis B e antibodies; Anti-HCV, Hepatitis C antibodies; CBC, Complete Blood Count; CVS, Chorionic villus sampling; HBeAg, Hepatitis B e Antigen; HKSAR, Hong Kong Special Administrative; HIV, Human immunodeficiency virus; LdT, Telbivudine; LFTs, Liver Function Tests; RFTs, Renal Function Tests; TDF, Tenofovir disoproxil; TAF, Tenofovir alafenamide; TDF+3TC, Tenofovir disoproxil/lamivudine; USA, United State America; WHO, World Health Organization. Region. [a]The guideline discussed the general management of HBV infection but did not address the twelve clinical questions in the scoping review.

Table 2: **Summary of antenatal and maternal recommendations from CPGs.**

	Breastfeeding	Breastfeeding in women taking antiviral	Timing for birth-dose HBV vaccine	Timing for birth-dose HBIG	Post vaccination serological testing	Vaccine non-responder
Argentina 2021[7]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	Within 12 h	Within 12 h	9–12 months of age	–
Asia Pacific 2022[8]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	ASAP, within 24 h	ASAP, within 24 h	9–18 months of age, 1–2 months after the last dose of HBV vaccine	Revaccination with 3 doses
Australia 2022[9]	Should be encouraged after infant is vaccinated	Not contraindicated	ASAP, within 4 h	ASAP, within 4 h	3 months following vaccine	–
Bhutan 2020[10]	Should be encouraged after infant is vaccinated	–	ASAP, within 24 h	ASAP, within 24 h	9–12 months of age	–
Brazil 2020[11]	–	The drug should be taken at least 4 h before feeding	Within 12 h	Within 12 h	1–2 months following vaccine	Revaccination
Canada 1 2018[12]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	9 months of age and 1–4 months after the last dose of the vaccine	–
Canada 2 2020[13]	–	–	–	–	–	–
China 1 2020[14]	Should be encouraged under any circumstances	Not contraindicated	ASAP, within 12 h	ASAP, within 12 h	7–12 months of age, 1–2 months following vaccine	Revaccination with 3 doses
China 2 2022[15]	Should be encouraged after infant is vaccinated	Not contraindicated	ASAP, within 12 h	ASAP, within 12 h	–	Revaccination with 1 or 3 doses
Czech Republic 2018[16]	–	–	–	–	–	–
Europe 1 2021[17]	Should be encouraged under any circumstances	–	Should be vaccinated	Should be vaccinated	–	–
Europe 2 2023[18]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	Within 12 h	Within 12 h	–	–
Fiji 2023[19]	Should be encouraged under any circumstances	–	ASAP, within 24 h (preferable within 12 h)	Within 12 h	After last dose of HBV vaccine	Revaccination with 3 doses
Germany 2021[20]	Should be encouraged under any circumstances	–	ASAP, within 12 h	ASAP, within 12 h	–	–
HKSAR 2024[21]	–	Not contraindicated	ASAP, within 24 h	ASAP, within 24 h	9–12 months of age	–
Hungary 2019[22]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	–	–
India 1 2018[23]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	–	–
India 2 2019[24]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	ASAP, within 24 h	ASAP, within 12–24 h	1 year of age	–
Indonesia 2023[25]	Should be encouraged after infant is vaccinated	Not contraindicated	Within 24 h	Within 24 h	9–12 months of age	Revaccination with 3 doses
Japan 2019[a],[26]	–	–	–	–	–	–
Jordan 2022[27]	Should be encouraged under any circumstances	Not contraindicated	–	–	–	–
Malawi 2023[28]	Should be encouraged under any circumstances	–	Within 24 h	–	9 months of age	–
Maldives 2021[29]	Should be encouraged under any circumstances	Not contraindicated	ASAP, within 12 h	ASAP, within 12 h	9 months of age	Revaccination with 1 dose
Mexico 2021[30]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	9 months of age	Revaccination with 1 or 3 doses
Myanmar 2019[31]	–	–	ASAP, within 12 h	Within 12 h	–	–
Peru 2018[32]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	–	–
Philippines 2021[33]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	Within 24 h	–	–	–
Rwanda 2019[34]	–	–	–	–	–	–
South Africa 2019[35]	Should be encouraged (despite cracked nipples and/or oral ulcers)	Not contraindicated	Within 12–24 h	Within 12–24 h	9–18 months of age	Revaccination with 3 doses

(Table 3 continues on next page)

	Breastfeeding	Breastfeeding in women taking antiviral	Timing for birth-dose HBV vaccine	Timing for birth-dose HBIG	Post vaccination serological testing	Vaccine non-responder
(Continued from previous page)						
South Australia 2020[36]	Should be encouraged under any circumstances	Not contraindicated	ASAP, within 12 h	ASAP, within 12 h	9–12 months of age	–
South Korea 1 2021[37]	–	–	–	–	–	–
South Korea 2[a] 2022[38]	–	–	–	–	–	–
Spain 2020[39]	Should be encouraged under any circumstances	Not contraindicated	Should be vaccinated	Should be vaccinated	–	–
Sweden 2019[40]	Should be encouraged under any circumstances	Not contraindicated	ASAP	ASAP	15–18 months of age	–
Taiwan 2019[41]	–	–	–	–	–	–
Thailand 2018[42]	–	Not contraindicated	Within 12 h	Within 12 h	1 year of age	Revaccination with 3 doses
Uganda 2019[43]	Should be encouraged under any circumstances	–	Within 24 h	ASAP, within 72 h	–	–
USA 1 2018[44]	–	Suggest to stop antiviral for breastfeeding.	Should be vaccinated	Should be vaccinated	–	–
USA 2 2018[45]	Should be encouraged after infant is vaccinated	Not contraindicated	Within 12 h	Within 12 h	9–12 months of age	Revaccination with 1 or 3 doses
USA 3 2018[46]	Should be encouraged under any circumstances	Not contraindicated	Within 12 h	Within 12 h	9–15 months of age	Revaccination with 3 doses
USA 4 2019[47]	–	–	12 h	12 h	9–12 months of age	–
USA 5 2023[48]	Should be encouraged under any circumstances	Not contraindicated	12 h	12 h	–	–
USA 6 2023[49]	–	–	–	–	–	–
USA 7 2024[50]	Should be encouraged after infant is vaccinated	–	12 h	12 h	–	–
WHO 1 2020[51]	–	Not contraindicated	ASAP, 24 h	Should be vaccinated	–	–
WHO 2 2024[52]	–	–	ASAP, 24 h	–	–	–
Zambia 2019[53]	–	–	ASAP, 24 h	–	–	–

Abbreviations: USA, United State America; WHO, World Health Organization; HKSAR, Hong Kong Special Administrative Region; HBIG, Hepatitis B Immune Globulin; ASAP, As soon as possible; Hours, hrs.
[a]The guideline discussed the general management of HBV infection but did not address the twelve clinical questions in the scoping review.

Table 3: **Summary of postnatal recommendations from CPGs.**

continuation to 4–12 weeks (n = 2), 4 weeks (n = 3), 6 weeks (n = 2), and 16 weeks (n = 1) postpartum.

Prenatal and intrapartum invasive testing

29.8% (14/47) CPGs provided recommendations for prenatal invasive testing. Among them, ten CPGs recommended meticulously balancing the risks and benefits of invasive tests in highly viraemic HBsAg-positive pregnant women. Of which, seven CPGs specifically defined higher risks in women with HBV DNA ≥7 $\log_{10}$ copies/mL (n = 4), HBV DNA ≥7 $\log_{10}$ IU/mL (n = 1), HBV DNA >5.3 $\log_{10}$ IU/mL or HBeAg positive (n = 2). Furthermore, four CPGs suggested that chorionic villous sampling (n = 3) and amniocentesis (n = 1) should be avoided.

Only 8.5% (4/47) CPGs addressed intrapartum invasive testing. Two CPGs recommended avoiding intrapartum fetal scalp blood sampling and fetal scalp electrode, another suggested that internal monitoring is not contraindicated. The other said that there are insufficient data to guide clinical practice.

Mode of delivery

Regarding the mode of delivery, 34.0% (16/47) CPGs addressed this issue. Among these, 87.5% (14/16) CPGs advised against performing a caesarean section solely to reduce the risk of MTCT. One document recommended considering a caesarean section exclusively for Asian HBeAg-positive women with high HBV DNA (>6.14 $\log_{10}$ IU/mL) who did not receive antiviral therapy during pregnancy. Another CPG suggested that caesarean section can be discussed when HBV DNA ≥200,000 IU/mL at the time of birth.

Breastfeeding

63.8% (30/47) CPGs addressed breastfeeding recommendations for infants born to HBsAg-positive mothers. Among these, 60% (18/30) CPGs recommended that breastfeeding should be encouraged without any restrictions, while six CPGs advised discontinuing breastfeeding when the mother had cracked nipples or the infant had oral ulcers. The remaining six

CPGs suggested that breastfeeding is recommended if infant is vaccinated.

59.6% (28/47) CPGs discussed the issue of breastfeeding in mothers who continued antiviral prophylaxis postpartum. The majority (n = 26) mentioned that breastfeeding was not contraindicated in women on antiviral treatment. One suggested the drug should be taken at least 4 h prior to breastfeeding. Another document advised against breastfeeding in mothers receiving antiviral therapy due to the potential excretion of these agents in breast milk.

Immunoprophylaxis for the infants

80.9% (38/47) CPGs addressed HBV vaccination of infants. Among these, 42% (16/38) CPGs emphasized that the vaccine should be administered as soon as possible and should be given within 24 h (n = 8), 12 h (n = 6), 4 h (n = 1), and one did not specify a time. Nineteen CPGs only recommended vaccination within 24 h (n = 4), 12 h (n = 14), 12–24 h (n = 1), without emphasizing "as soon as possible". Furthermore, three CPGs advised vaccinating all infants without reporting any specific timeframe.

72.3% (34/47) CPGs addressed the administration of HBIG of infants. Among these, 35.3% (12/34) of these emphasized that HBIG should be administered as soon as possible and should be given within 24 h (n = 3), 12 h (n = 5), 4 h (n = 1), 72 h (n = 1), within 12–24 h (n = 1), and one did not specify a time. Eighteen CPGs advised HBIG administration within 24 h (n = 1), 12 h (n = 16), 12–24 h (n = 1), without highlighting "as soon as possible". Additionally, four CPGs advocated for administering HBIG to all infants, without specifying a particular timeframe.

Timing of post vaccination serologic testing of infants was addressed in 44.7% (21/47) CPGs. The most common recommendation was to test serology between 9 and 12 months of age (n = 7). Various other defined months of age were recommended by 7 CPGs, while 3 CPGs recommended serologic testing at different defined timings after the last vaccine. Four CPGs suggested utilizing a combination of age and timing after the last vaccine.

Follow-up for vaccine non-responders was addressed in 25.5% (12/47) CPGs. Among these, seven CPGs recommended on three-dose revaccinations, while three CPGs suggested revaccination with one or three doses of vaccine. Another CPG advised revaccination with a single dose of vaccine. The other CPG simply mentioned revaccination without specifying doses of vaccine.

Clinical questions	Classification	Total (n = 47) n (%)
Screening for Hepatitis B during pregnancy	Not mentioned	9 (19.1%)
	All pregnant women	38 (80.9%)
Disease evaluation–Tests	Not mentioned	14 (29.8%)
	Addressed	33 (70.2%)
	• HBV DNA	7
	• HBV DNA + LFTs	2
	• HBV DNA + HBeAg	8
	• HBV DNA + HBeAg + LFTs	6
	• The others (Serologic tests; CBC; RFTs; Abdominal ultrasound scan; Creatinine; Clotting profile)	10
Disease evaluation—Timing	Not mentioned	29 (61.7%)
	Addressed	18 (38.3%)
	• First trimester	6
	• Second trimester	2
	• Third trimester	1
	• First antenatal visit	4
	• Early pregnancy	2
	• Early second trimester	1
	• 28 weeks	1
	• Repeat every 3 months	1
Disease evaluation–Frequency	Not mentioned	42 (89.4%)
	Addressed	5 (10.6%)
	• Reassessment not needed	1
	• Reassess between 26 and 28 weeks	2
	• Reassess during early third trimester	1
	• Reassess every 2–3 months	1
Viral load to start antiviral	Not mentioned	10 (21.3%)
	Addressed	37 (78.7%)
	• > 200,000 IU/mL	24
	• ≥ 200,000 IU/mL	8
	• > 10^6 copies/mL	1
	• > 200,000 IU/mL or HBsAg >4 $\log_{10}$ IU/mL	3
	• ≥ 20,000 IU/mL	1
Antiviral if HBeAg positive	• Not mentioned	32 (68.1%)
	• Addressed & suggested initiation of antiviral agents if seropositive HBeAg	15 (31.9%)
Choice of antiviral	Not mentioned	8 (17.0%)
	Addressed	39 (83.0%)
	• Tenofovir disoproxil fumarate	34
	• Tenofovir disoproxil fumarate or Tenofovir Alafenamide	3
	• Tenofovir disoproxil fumarate or Telbivudine	1
	• Tenofovir disoproxil fumarate and Lamivudine	1
Timing to start antiviral	Not mentioned	11 (23.4%)
	Addressed	36 (76.6%)
	• As soon as possible	1
	• During second trimester	1
	• Beginning of the third trimester	2
	• During third trimester	3
	• Before third but after first trimester	2
	• Starting from 28 weeks	6
	• Start from 24 weeks or earlier	1
	• 24–28 weeks	9
	• 28–32 weeks	8
	• 24–32 weeks	1
	• 26–28 weeks	1
	• Around 30 weeks	1

(Table 4 continues on next page)

Discussion

We reviewed 47 CPGs of variable quality regarding the management of hepatitis B during pregnancy across several clinical questions. A universal HBV screening

Clinical questions	Classification	Total (n = 47) n (%)
(Continued from previous page)		
Timing to discontinue antiviral	Not mentioned	14 (29.8%)
	Addressed	33 (70.2%)
	• At birth	2
	• Until at least delivery	3
	• Continue up to 4 weeks postpartum	3
	• Continue up to 6 weeks postpartum	2
	• Continue up to 4–12 weeks postpartum	2
	• Continue up to 12 weeks postpartum	12
	• Continue up to 16 weeks postpartum	1
	• At birth or up to 12 weeks postpartum	6
	• Between at birth and 12 weeks postpartum	1
	• At least delivery or completion of the infant HBV vaccination series	1
Prenatal invasive test	Not mentioned	33 (70.2%)
	Addressed	14 (29.8%)
	• To balance the risks and benefits of invasive tests in highly viremic HBsAg-positive pregnant women	3
	• To balance the risks and benefits of invasive tests (specifically in women with HBV DNA ≥7 $\log_{10}$ copies/mL)	4
	• To balance the risks and benefits of invasive tests (specifically in women with HBV DNA ≥7 $\log_{10}$ IU/mL)	1
	• To balance the risks and benefits of invasive tests (specifically in women with HBV DNA >5.3 $\log_{10}$ IU/mL or HBeAg positive)	1
	• Can be performed in women with HBV DNA ≤2×10^5 IU/mL or HBeAg negative or to balance the risks and benefits of invasive tests in women with HBV DNA >2×10^5 IU/mL or HBeAg positive	1
	• Should be avoided	4
Intrapartum invasive test	Not mentioned	43 (91.5%)
	Addressed	4 (8.5%)
	• Should be avoided	2
	• Insufficient evidence to guide clinical practice	1
	• Internal monitoring is not contraindicated	1
Mode of delivery	Not mentioned	31 (66.0%)
	Addressed	16 (34.0%)
	• Against performing caesarean section solely to reduce the risk of vertical HBV transmission	14
	• Caesarean section can be considered in HBeAg-positive women with high HBV DNA titer (>7 $\log_{10}$ copies/mL; 6.14 $\log_{10}$ IU/mL) who did not receive antiviral therapy during pregnancy	1
	• Caesarean section can be discussed when HBV DNA ≥200,000 IU/mL at the time of birth	1
Breastfeeding	Not mentioned	17 (36.2%)
	Addressed	30 (63.8%)
	• Should be encouraged	18
	• Should be restricted in mothers with cracked nipples and/or oral ulcers	6
	• Recommended if infant is vaccinated	6
Breastfeeding in women taking antiviral	Not mentioned	19 (40.4%)
	Addressed	28 (59.6%)
	• Not contraindicated	26
	• Should be discontinued if receiving antiviral therapy	1
	• Should take drug 4 h before breastfeeding	1

(Table 4 continues on next page)

approach (100%, 38/38) and using maternal HBV DNA above 200,000 IU/mL to guide initiation of maternal antenatal antiviral prophylaxis (94.6%, 35/37) were supported by most CPGs. In addition, vaginal delivery and breastfeeding were encouraged by 87.5% (14/16) and 60% (18/30) CPGs. There was insufficient guidance on the timing and component of HBV assessments, and recommendations on prenatal and intrapartum invasive tests. Controversies were found in the optimal gestation to initiate and the timing to stop antiviral prophylaxis after delivery. More importantly, international CPGs mainly focused on the ideal strategy to prevent HBV MTCT during pregnancy but may have neglected the practicality in resource-limited settings where the burden of the HBV disease is most pronounced. Among CPGs specific for countries where HBV DNA quantification is not available, the alternative of using HBeAg to identify women requiring antiviral prophylaxis or the universal TDF approach was not mentioned in the majority. Taking together, these factors could impede global HBV elimination.

Prompt HBV disease evaluation in early pregnancy is crucial for identifying women who require antiviral prophylaxis to prevent MTCT. Advancing HBV DNA quantification and treatment to the first and early second trimesters could offer several benefits. First, HBV DNA quantification in the first and second trimesters is as effective in predicting MTCT as third-trimester examination, allowing similar viral load cut-offs to be adopted.[57] Early assessment provides sufficient time for pregnant individuals infected with HBV to consider initiating antiviral prophylaxis when they may be reluctant to take antivirals for an asymptomatic condition and worry about potential teratogenicity. Second, seropositive HBeAg hepatitis B-infected individuals have a 34% higher risk of preterm birth before 34 weeks of gestation compared to non-infected women, as demonstrated in a Chinese population-based cohort study.[58] Preterm birth could result in a shortened treatment duration or even delivery before the initiation of antiviral prophylaxis, increasing the risk of MTCT. For instance, this could be problematic in Sub-Saharan Africa where both the preterm birth rate and HBsAg seroprevalence were high at 10.1% and 6.7% respectively.[59,60] Third, a subset of individuals with extremely high viremia may require an extended treatment duration to suppress the viral load at delivery. Despite initiation of TDF treatment at 30 weeks of gestation, a 3.1% (2/65) MTCT rate was observed among women with a mean baseline viral load of 8.25 $\log_{10}$ IU/mL.[61] Earlier administration of antiviral from second trimester of pregnancy could lead to a significantly lower viral load at delivery compared to those who started treatment at third trimester.[62,63] Finally, some women may request prenatal invasive tests after Down syndrome screening and morphology scans, typically performed before 24 weeks of gestation. HBV DNA quantification prior to

the invasive test can inform these women on the additional MTCT risk and identify those with high viral load and thus start antiviral prophylaxis before the invasive procedure. Therefore, assessing HBV DNA in the first trimester and initiating antiviral prophylaxis from 14 to 20 weeks can address these clinical scenarios which might be missed by the current CPGs.

HBV DNA remains a robust predictor of MTCT. HBeAg cannot replace HBV DNA since approximately 12–16% of HBeAg-negative women exhibited HBV DNA levels ≥5.3 $\log_{10}$ IU/mL (200,000 IU/mL), and around 2% demonstrated HBV DNA levels ≥7 $\log_{10}$ IU/mL.[64] However, the wider availability and affordability (ranging from $0.50 to $15.00 per assay) of rapid diagnostic tests and laboratory-based immunoassays for HBeAg detection, compared to HBV DNA testing (which costs $130 per assay), together with the sensitivity of 88.2% and specificity of 92.6% for detecting a viral load of ≥200,000 IU/mL, make it a more viable option than HBV DNA in low- and middle-income countries.[64,65]

Unfortunately, both HBV DNA or HBeAg serology testing may not be available in resource-limited regions, such as sub-Saharan Africa and South and Southeast Asia, due to financial constraints or logistics difficulties, hindering the determination of eligibility for antiviral prophylaxis.[66] The 2024 WHO HBV guideline proposed scaling up antiviral prophylaxis to all pregnant women who test positive for HBsAg, as a potential strategy to mitigate the risk of MTCT when risk stratification by HBV DNA or HBeAg is not possible. This universal TDF prophylaxis approach may increase the number of women receiving antivirals to more than five times, with 75.7 million pregnant women requiring therapy compared to 13.2 million under a targeted strategy.[67] We could not identify studies that examined the clinical impact and feasibility of expanding access to antiviral prophylaxis for all HBsAg-positive women, but the cost-effectiveness was evaluated by modelling studies. A study modelled 110 countries until 2100 and demonstrated that this universal approach may avert around 4.8 million disability-adjusted life-years, compared to the approach of universal birth dose vaccination together with antiviral prophylaxis to women with a high viral load.[67] Incremental cost-effectiveness ratios might be lower for the universal approach at central cost estimates; however, the cost-effectiveness of this approach would be limited to some countries only. Another modelling-based cost-effectiveness analysis also supported that offering antenatal TDF to HBsAg-positive women may be a viable and economically sound strategy for South Africa and other low- or middle-income countries.[68] Overall, cost-effectiveness is influenced by the relative costs of antivirals and HBV DNA/HBeAg tests, so the universal approach could be a more cost-effective strategy in some countries.

Clinical questions	Classification	Total (n = 47) n (%)
(Continued from previous page)		
Timing for birth-dose HBV vaccine	Not mentioned	9 (19.1%)
	Addressed	38 (80.9%)
	• Within 12 h	14
	• Within 24 h	4
	• Within 12–24 h	1
	• ASAP	1
	• ASAP (within 4 h)	1
	• ASAP (within 12 h)	6
	• ASAP (within 24 h)	8
	• Should be vaccinated (without specifying timing)	3
Timing for birth-dose HBIG	Not mentioned	13 (27.7%)
	Addressed	34 (72.3%)
	• Within 12 h	16
	• Within 24 h	1
	• Within 12–24 h	1
	• ASAP	1
	• ASAP (within 4 h)	1
	• ASAP (within 12 h)	5
	• ASAP (within 24 h)	3
	• ASAP (within 12–24 h)	1
	• ASAP (within 72 h)	1
	• Should be vaccinated (without specifying timing)	4
Post vaccination serological testing	Not mentioned	26 (55.3%)
	Addressed	21 (44.7%)
	• After 9 months of age	3
	• 9–12 months of age	7
	• 9–15 months of age	1
	• 12 months of age	2
	• 15–18 months of age	1
	• After last dose of vaccine	1
	• 1–2 months after last dose of vaccine	1
	• 3 months after last dose of vaccine	1
	• 9 months of age or 1–4 months after last dose of vaccine	1
	• 7–12 months of age or 1–2 months after last dose of vaccine	1
	• 9–18 months of age or 1–2 months after last dose of vaccine	2
Vaccine non-responder	Not mentioned	35 (74.5%)
	Addressed	12 (25.5%)
	• Revaccination with 1 dose of vaccine	1
	• Revaccination with 3 doses of vaccine	7
	• Revaccination with 1 dose or 3 doses of vaccine	3
	• Revaccination (without specifying doses of vaccine)	1

Abbreviations: LFTs, Liver function tests; CBC, Complete Blood Count; RFTs, Renal Function Tests.

Table 4: **The proportion of CPGs that addressed each clinical question.**

This universal approach together with the earlier start of antiviral prophylaxis will undoubtedly expose more women to antivirals for longer periods. This potential overtreatment could be considered less problematic than overlooking women with an elevated risk of MTCT, given the favorable safety profile associated with

antenatal antiviral prophylaxis and the potential of drug resistance to TDF treatment is rare due to the short duration.[69] Evidence so far has not suggested antiviral prophylaxis initiated at any time during pregnancy can be associated with fetal death, preterm birth, or congenital anomalies. A meta-analysis found a lower MTCT rate when antiviral prophylaxis was started before 28 weeks compared to after 28 weeks, with no associated safety issues.[63] One potential concern is postpartum hepatic flares after discontinuation of prophylactic antiviral, although these are usually mild and self-liming.[70] More data on this simplified approach is required to assess the feasibility and acceptability in clinical settings.

HBV vaccination can greatly reduce the MTCT rate from 90% to less than 10% depending on the HBeAg status of the women and whether neonatal HBIG is given.[70] Timing of birth dose vaccine is equally important. Delaying the birth dose vaccine beyond 24 h increased the risk of MTCT from 5.6% when administered within 24 h after birth, to 7.0% at 24–47 h after birth, and 16.7% at 48–96 h after birth.[71] In addition, birth dose vaccination within 12 h further reduced the risk of MTCT from 2.4% to 0.6%.[72] Comparing to birth dose vaccination given at 2–12 h, vaccination within 2 h significantly reduced MTCT from 2.73% to 0.32%.[73] Studies demonstrated that the MTCT rate for birth dose vaccines given within 1–2 h was approximately 1–2%, which was lower than the reported rate of 1–9% in the literature.[74,75] It is sensible that prompt administration of birth dose vaccine can neutralize transient intrapartum HBV exposure, resulting in a lower MTCT rate. 58% CPGs did not emphasize the importance of "vaccination as soon as possible after birth". This may potentially delay immediate vaccination or encourage later vaccination to within 12–24 h after delivery. As such, we suggest that the birth dose vaccine should be given as soon as possible and within 2 h after delivery if facilities are available. Regarding the vaccination schedule among infants of hepatitis B infected women, the timing and frequency of vaccination would depend on the type of available vaccine (monovalent versus combination) and could vary based on the country's immunization program. Either a three-dose or four-dose vaccine is considered an acceptable approach by Centers for Disease Control and Prevention and WHO, as the efficacy to achieve protective immunity is similar.[76]

Approximately 5–10% of individuals failed to develop adequate antibodies after the primary series of HBV vaccination.[77] These vaccine non-responders are vulnerable to horizontal HBV transmission. Only twelve CPGs addressed the management of vaccine non-responders and their suggestions varied. Administering three additional doses of HBV vaccine can induce immunity in 85.3% of infant non-responders.[78] Immunogenic response to revaccination could be increased by increasing number of doses, using a higher antigen dose or a more potent adjuvant.[79]

The strengths of this systematic review include the utilization of a comprehensive search strategy (without language restrictions), and rigorous methodology informed by the AGREE instrument. Furthermore, we thoroughly analyzed all recommendations and information to provide a comprehensive picture that may help researchers identify knowledge gaps requiring further research. Our study had limitations. We simply analyzed the guidelines without going through the evidence behind the recommendations individually. We also could not draw conclusions on certain aspects, such as the timing to discontinue antiviral after delivery, the timing of post-vaccination serological testing and the optimal management of vaccine non-responders. In addition, social factors such as stigma and discrimination, social marginalization, poor education, and limited access to healthcare services are possible barriers to prevention of MTCT and were not explored in this review of CPGs. However, our aims were to draw attention on the deficiency of current CPGs to eliminate HBV, highlight the discrepancies among CPGs and identify any research gaps (Table 5).

We highlighted the current insufficiency among CPGs regarding the management of hepatitis B infected pregnant individuals. Current CPGs may miss the opportunity to offer earlier HBV assessment and treatment or suggest an alternative to utilizing HBV DNA to triage women for antiviral prophylaxis. Further evaluation is required on the clinical impact and feasibility of earlier treatment from early second trimester (i.e. 14–20 weeks), expanding the indication of antiviral prophylaxis to all HBV infected pregnant women when triaging investigation is unavailable, and giving the neonatal birth dose vaccination as soon as possible and within 2 h of delivery. These strategies are potential solutions to accelerate the momentum to achieve global elimination of hepatitis B infection.

Further evidence is required to identify the optimal management of hepatitis B infected pregnant individuals to prevent MTCT. The clinical impact and feasibility of earlier initiation and wider application of antiviral prophylaxis, as well as neonatal birth dose vaccination within 2 h should be explored.

1 Effect of prenatal and intrapartum invasive tests to MTCT.
2 Optimal gestation to initiate prophylactic antiviral to better prevent MTCT.
3 Timing to stop prophylactic antiviral after delivery.
4 Clinical impact, feasibility and acceptability of universal antiviral prophylaxis to all pregnant hepatitis B infected individuals.
5 Effect of timely neonatal birth dose immunization (such as within 2 h of birth) to MTCT.
6 Revaccination strategy for vaccine non-responders.

Table 5: **Research gaps arising from deficiencies of CPGs.**

Contributors

KWC conceptualized the study. YRL developed the study protocol. KWC and YRL wrote the first draft of the manuscript. KWC and YRL did the database and the grey literature searches and screened the articles. KWC, YRL, TSTA and MTYS appraised the quality of literature. KWC and YRL extracted the data and led the data analysis, interpretation, and presentation of findings. KWC and YRL accessed and verified the data. KWC and MTYS provided overall supervision, leadership, and advice. All authors reviewed and approved the final version of the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of interests

The authors report no conflicts of interest.

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Nil.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103038.

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