World Health Organization

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: GUIDELINES ON ANTIVIRAL PROPHYLAXIS IN PREGNANCY

JULY 2020

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Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy

ISBN 978-92-4-000270-8 (electronic version)
ISBN 978-92-4-000271-5 (print version)

Suggested citation. Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Printed in Switzerland.

Design and layout: 400.co.uk

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ACKNOWLEDGEMENTS

Many individuals from a range of backgrounds and specialties have contributed to the development of this guidance. WHO is sincerely grateful for their time and support.

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Modelling

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Funding

Funding for the development of these guidelines was provided by the Government of Germany and by the United States Centers for Disease Control and Prevention.

ABBREVIATIONS AND ACRONYMS

ART	antiretroviral therapy
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
DALY	disability-adjusted life year
EPI	Expanded Programme on Immunization
EMTCT	elimination of mother-to-child transmission
GHSS	Global Health Sector Strategy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	(WHO) Guidelines Review Committee
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
ICER	incremental cost–effectiveness ratio
NAT	nucleic acid test
OR	odds ratio
PICO	Population, Intervention, Comparison, Outcomes
PMTCT	prevention of mother-to-child transmission
RDT	rapid diagnostic test
SAGE	(WHO) Strategic Advisory Group of Experts (on Immunization)
TDF	tenofovir disoproxil fumarate
UK	United Kingdom
UNICEF	The United Nations International Children's Emergency Fund
USA	United States of America
WHO	World Health Organization

GLOSSARY OF TERMS

Chronic HBV infection	Persistence of HBsAg for six months or more after initial infection with HBV
Clinical/diagnostic sensitivity	Ability of a test to correctly identify those with the infection or disease
Clinical/diagnostic specificity	Ability of a test to correctly identify those without the infection or disease
Cirrhosis	Extensive liver scarring secondary to prolonged inflammation of the liver (F4 in the METAVIR scoring system)
HBV DNA	Hepatitis B virus (HBV) viral genomes that can be detected and quantified in serum*
Tenofovir prophylaxis	Use of tenofovir disoproxil fumarate (TDF) to prevent mother-to-child transmission of HBV
Peripartum prophylaxis	Initiation of prophylaxis from 28 weeks of pregnancy until at least birth

* HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL. 1 IU/mL ~ 5.3 copies/mL, and so values given as copies/mL can be converted to IU/mL by dividing by a factor of 5. (i.e. 10 000 copies/mL = 2000 IU/mL; 100 000 copies/mL = 20 000 IU/mL; 1 million copies/mL = 200 000 IU/mL).

EXECUTIVE SUMMARY

Background

WHO estimates that in 2015, 257 million people were living with chronic hepatitis B virus (HBV) infection worldwide, and that 900 000 had died from HBV infection, mostly as a result of cirrhosis or hepatocellular carcinoma. Most HBV-associated deaths among adults are secondary to infections acquired at birth or in the first five years of life. In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy on viral hepatitis, which calls for the elimination of viral hepatitis as a public health threat by 2030 (defined as a 90% reduction in incidence of new infections and a 65% reduction in mortality). Elimination of HBV infection as a public health threat requires a reduction in the prevalence of hepatitis B surface antigen (HBsAg) to below 0.1% in children 5 years of age. This can be achieved through universal immunization of newborns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV.

Rationale for updating the recommendations on prevention of mother-to-child transmission of HBV to address peripartum prophylaxis with antivirals

The WHO position papers on immunization recommend that all infants receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, and that the birth dose be followed by two or three doses of hepatitis B vaccine at least four weeks apart to complete the primary series. Immunization against hepatitis B starting at birth is the foundation of the prevention of perinatal and horizontal transmission of HBV. In 2015, in the WHO *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection*, no recommendation was made for the additional use of antiviral therapy to prevent mother-to-child HBV transmission. This was because of the still limited and low quality evidence base with several ongoing trials, and the lack of consensus as to the programmatic implications of a policy for more widespread use of antivirals in pregnancy. Three key developments prompted the consideration to now include the use of antiviral prophylaxis for pregnant women with HBV infection as an additional measure to prevent mother-to-child transmission of HBV. First, further evidence has become available on the efficacy and safety of antiviral prophylaxis in pregnant women and their children. Second, WHO has received requests from countries and regions with already high birth dose and infant vaccination coverage for updated guidance on the use of peripartum prophylaxis. Third, data from epidemiological studies and modelling suggest that infant vaccination alone would be insufficient to reach the 0.1% HBsAg prevalence goal in children by 2030, and that peripartum prophylaxis may also be needed.

Methods

In accordance with the procedures established by its Guidelines Review Committee (GRC), WHO commissioned systematic reviews, impact modelling and a cost–effectiveness analysis. A regionally representative and multidisciplinary Guidelines Development Group (GDG) met in September 2019 to formulate the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Evidence to inform the recommendations included two commissioned systematic reviews and meta-analyses, impact and cost–effectiveness modelling, an assessment of the overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resource use, cost–effectiveness, considerations on equity and human rights, and feasibility across the different WHO regions.

Summary of recommendations

Existing recommendations on immunization from the WHO position paper 2017 *(6)*

a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours;

b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose;

c) The birth dose should be followed by two or three doses to complete the primary series.

Existing recommendation on testing of pregnant women for HIV and syphilis from the 2019 *Consolidated guidelines on HIV testing services (22)*, and for hepatitis B from the 2017 WHO *Guidelines on hepatitis B and C testing (23)*

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)* at least once and as early as possible in the pregnancy (HIV standing recommendation since 2007; syphilis: *strong recommendation, moderate-quality evidence;* HBsAg*: *strong recommendation, low-quality evidence*).

* Particularly in settings with a ≥2% seroprevalence in the general population.

Tenofovir prophylaxis to prevent mother-to-child transmission of HBV

New recommendation

WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL)[1] receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose *(conditional recommendation, moderate quality of evidence).*

Use of HBeAg testing, where HBV DNA testing is not available, to determine treatment eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV

New recommendation

WHO recommends that in settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV[2] *(conditional recommendation, moderate quality of evidence).*

Implementation considerations

- Universal immunization of infants with hepatitis B vaccine, including a timely birth dose, is the foundation of programmes to prevent HBV infection at birth and in the first years of life. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among children aged 5 years through vaccination need to focus their efforts on increasing their vaccination coverage, including timely birth dose.
- The clinical trials that evaluated the efficacy and safety of tenofovir prophylaxis also included hepatitis B immune globulin (HBIG) as an additional preventive strategy in both trial arms. In a number of settings (mostly in high income countries) where it is available, HBIG is used in

1 HBV DNA ≥5.3 $\log_{10}$ IU/mL is equivalent to ≥200 000 IU/mL.

2 The performance of HBeAg testing suggests that it is an acceptable alternative to diagnosing HBV DNA ≥5.3 $\log_{10}$ IU/mL.

addition to hepatitis B vaccination, including birth dose, to reduce the risk of mother-to-child transmission of HBV. However, HBIG is a blood product that has to be screened for infectious diseases. The costs are high, a cold chain is required and HBIG can be in short supply. In low and middle-income setting, it may only be available when purchased by individuals.

- As many countries are working towards dual elimination of perinatal HIV and syphilis infection, there are opportunities for efficiency gains and integration to also include elimination of mother-to-child transmission of HBV. Two WHO regions (Region of the Americas and the Western Pacific Region) already have plans and a framework for triple elimination.

- Programmes to test and treat eligible pregnant women for HBV infection need to be implemented in the context of universal health coverage, aiming for covering the highest proportion of women while reducing financial hardship.

- Testing of pregnant women needs to take place under circumstances that prevents stigma and discrimination and provides post-test counselling and education on measures to reduce the risk of transmitting HBV to the infant, encourage partner testing and ensure linkage to care of HBsAg positive women.

- Clinical assessment should include an evaluation of whether HBsAg-positive pregnant women would be eligible for antiviral treatment for their own health. However, in accordance with criteria in the 2015 WHO *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (20)*, only a small proportion of women of childbearing age would be eligible for long-term treatment.

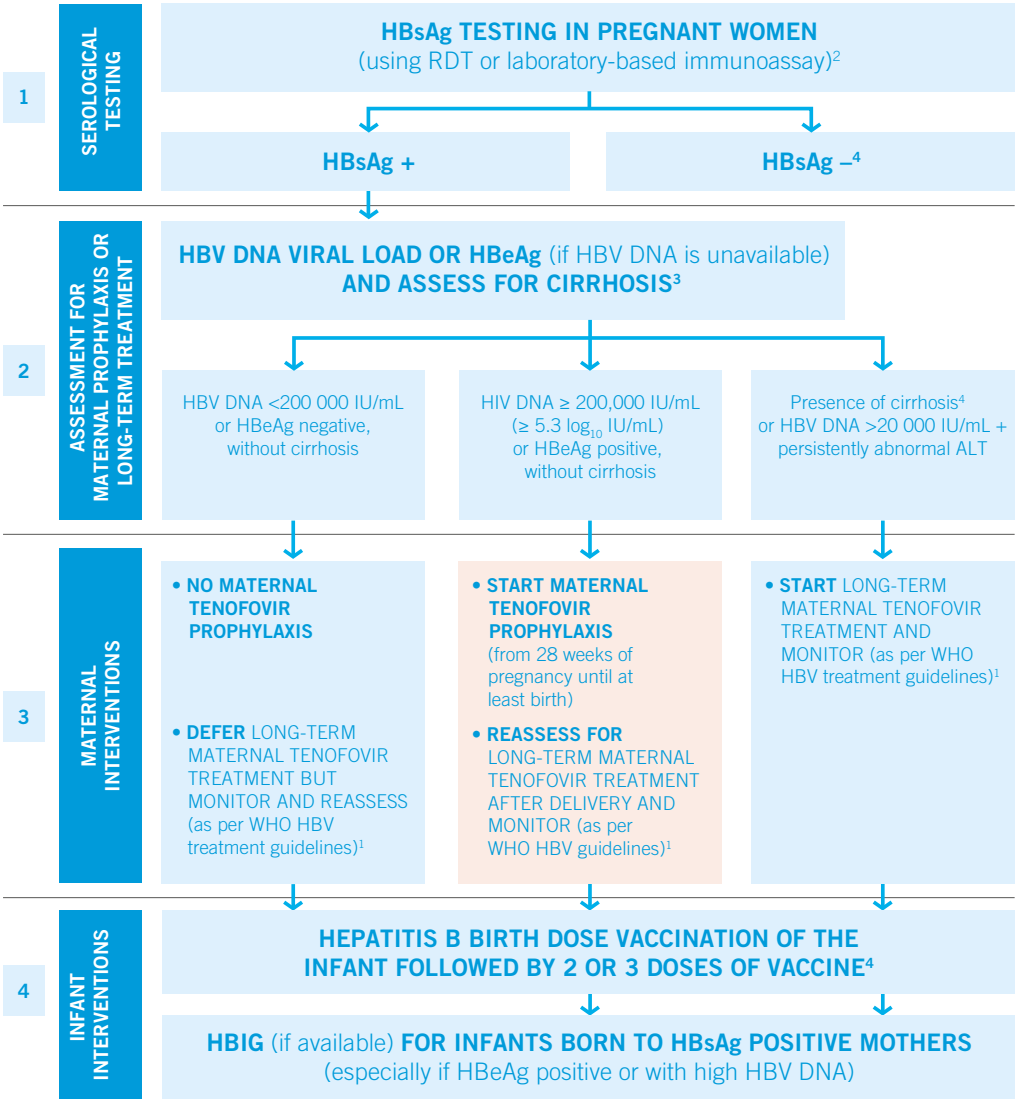
- HBV DNA quantification is the reference method to identify those HBsAg-positive pregnant women with a high viral load most at risk of transmitting HBV to their infants. Access to HBV DNA quantification (in terms of costs and availability of testing platforms) remains limited in low-income settings. Continuing efforts are needed to increase access to HBV DNA testing and reduce costs.

- Diagnostic tests used need to meet quality, safety and performance standards (with regard to analytical, diagnostic and clinical sensitivity and specificity).[3]

3 Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use and, where possible, at testing sites enrolled in a national or international external quality assessment scheme.

Algorithm on maternal and infant interventions for prevention of mother-to-child transmission, and assessment of eligibility of mother for treatment for her own health

(Based on these guidelines and the 2015 Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection[1].



Abbreviations: ALT: alanine aminotransferase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma: HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; RDT: rapid diagnostic test

[1] Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection; https://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/

[2] At least once and as early as possible in the pregnancy

[3] Using clinical criteria and non-invasive tests (APRI score > 2 in adults or Fibroscan)

[4] Hepatitis B timely (within 24 hours) birth dose vaccination of the infant followed by 2 or 3 doses of hepatitis B vaccine should be given regardless of HBsAg status of the pregnant mother.

CHAPTER 1. INTRODUCTION

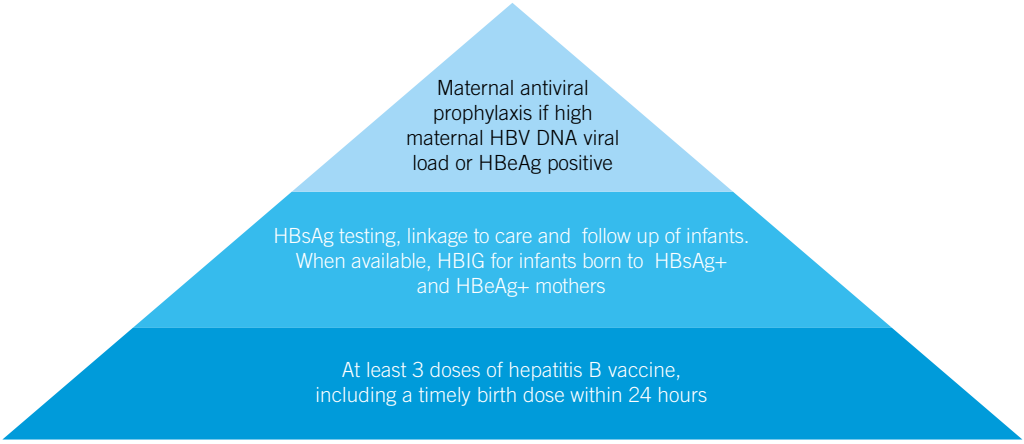
1.1 Progress in and challenges to HBV elimination

WHO estimates that in 2015, hepatitis B virus (HBV) infection caused 900 000 deaths, mostly through the development of cirrhosis and hepatocellular carcinoma (HCC) *(1)*. WHO also estimated that in 2015, 257 million people were living with chronic HBV infection worldwide, placing them at risk of serious illness and death from cirrhosis and HCC *(1)*. The burden of HBV infection remains disproportionately high in low- and middle-income countries. Approximately 70% of the 257 million people living with HBV infection live in areas where HBV infection is highly endemic, particularly in parts of Asia and Africa. In highly endemic regions, most of the burden of chronic HBV infection comes from infection acquired soon after birth or during early childhood *(2)*. Persons infected after the age of 5 years rarely develop chronic infection.

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which proposes the elimination of viral hepatitis as a public health threat by 2030 *(3)*. Elimination is defined as a 90% reduction in incidence and a 65% reduction in mortality, compared with the 2015 baseline. The prevalence of hepatitis B surface antigen (HBsAg) in children 5 years of age is considered a surrogate indicator of the cumulative incidence of chronic HBV infections *(4)*. In accordance with the GHSS on viral hepatitis, the pathway to the impact target of a reduction in incidence includes a prevalence of HBsAg under 1% in children 5 years of age by 2020 and under 0.1% by 2030. To reduce the incidence of chronic HBV infection, WHO has recommended inclusion of the hepatitis B vaccine in the Expanded Programme on Immunization (EPI) since 1992 *(5)*. In 2017, the latest update of the WHO position paper recommended universal immunization of infants, with three or four doses of hepatitis B vaccine, and the first dose of hepatitis B vaccine given as soon as possible after birth (within 24 hours) *(6)*. The birth dose of hepatitis B vaccine constitutes post-exposure prophylaxis to prevent transmission to infants exposed to HBV during birth and initiates the first dose of a series of immunizations that will confer long-term protection against HBV infection.

The three- or four-dose hepatitis B vaccination series, including a timely birth dose, is the foundation on which other interventions to reduce perinatal transmission can be built (*see* Fig. 1). Major progress in the global response to HBV infection has been made through the expansion of routine hepatitis B vaccination (2018 third dose coverage: 84%) *(7)*. However, birth dose coverage remains heterogeneous (2018 coverage: 42% globally, 4% in the WHO African Region) *(8)*.

FIG. 1. Incremental approach to prevention of HBV infection at birth and in the first years of life



HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen

1.2 The role of prevention of mother-to-child transmission (PMTCT) in HBV elimination

Transmission of HBV from mother to child is more common in children born to women who have a high viral load and/or are positive for the hepatitis B e antigen (HBeAg) *(9)*. Infant hepatitis B immune globulin (HBIG) prophylaxis shortly after birth and maternal peripartum prophylaxis with antivirals can provide additional protection to that provided by a timely birth dose of hepatitis B vaccine *(6)*. In contrast, maternal HBIG administration does not provide additional protection to the infant *(10)*. Very high maternal concentrations of HBV DNA, typically observed in HBeAg-positive women, are associated with an elevated risk of transmission (ranging from 20% in Asia to 32% in Africa), despite vaccine prophylaxis and HBIG *(9, 11, 12)*. This compares to less than 1% transmission in Asia and Africa among HBeAg-negative women *(12, 13)*. Evidence suggests that the use of antivirals may suppress HBV DNA levels and reduce transmission of HBV to infants of HBsAg-positive women. Therefore, pregnant women with high HBV DNA levels may be considered for antiviral prophylaxis during pregnancy to prevent perinatal HBV infection (*see* Fig. 1) *(14–17)*. The use of antiviral

prophylaxis in addition to infant immunization is consistent with approaches used to prevent mother-to-child transmission of HIV and syphilis (and Chagas disease in the Americas). This provides opportunities for integrated triple or quadruple elimination of mother-to-child transmission of all pathogens *(18)*. In addition, 6.1% of women with HIV infection have coinfection with HBV *(19)*. HIV treatment with tenofovir-based antiretroviral therapy (ART) for women living with HIV provides an opportunity to simultaneously treat those with HBV coinfection, and reduce mother-to-child transmission of HBV alongside that of HIV.

In the WHO 2015 *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (20),* the Guidelines Development Group had concluded that a formal recommendation could not be made on the routine use of antiviral therapy to prevent mother-to-child transmission. However, since the indications for treatment in HBV-infected pregnant women are the same as that for other adults, all pregnant women should first be assessed for eligibility for long-term treatment based on their own health needs before initiation of prophylaxis *(20)*. While prophylaxis with antivirals during the third trimester of pregnancy was known to be effective in reducing mother-to-child transmission of HBV, at the time there was insufficient information available on the programmatic implications.

1.3 Objectives

The objective of these guidelines is to provide evidence-based guidance on the use of peripartum antiviral prophylaxis in HBsAg-positive pregnant women for the prevention of mother-to-child transmission (PMTCT) of HBV.

1.4 New developments and rationale for an update of the guidelines

Since the publication of the WHO 2015 HBV treatment guidelines *(20)*, three key developments prompted reconsideration of the use of peripartum antiviral prophylaxis to prevent mother-to-child transmission of HBV.

1. Additional evidence has become available on the efficacy and safety of antiviral prophylaxis with tenofovir in HBsAg-positive pregnant women. In regards to safety, there is a low risk of exacerbation or postpartum flare after cessation of prophylaxis, and there appears to be minimal effect on infant bone mineral density with maternal use of tenofovir prophylaxis. This can contribute to the overall reassessment of the balance of benefits and harms of antiviral prophylaxis in eligible pregnant women.

2. WHO has received requests from countries and regions (i.e. the Americas and the Western Pacific) with high birth dose coverage for updated guidance on the use of antiviral prophylaxis in pregnant women, in order to further reduce the risk of mother-to-child transmission of HBV.

3. Data from epidemiological studies and modelling indicate that high coverage of three- or four-dose infant vaccination, including timely birth dose, would not be sufficient to reach the incidence elimination goals by 2030 (HBsAg prevalence of <0.1% in children five years of age) *(21)*. Antiviral prophylaxis of pregnant women with high viral load may need to be added *(18)*.

1.5 Target audience

The key audience for these guidelines includes Ministry of Health officials responsible for the development of national policy and guidelines related to prevention of mother-to-child transmission of HBV in all countries, but particularly in low- and middle-income countries. The guidelines may also be helpful for health workers who treat persons infected with HBV as well as those providing care for pregnant women and infants.

1.6 Scope of the guidelines

These guidelines update the recommendations section on PMTCT of the WHO 2015 *Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (20),* with a focus on the use of antiviral prophylaxis in pregnancy to prevent mother-to-child transmission of HBV.

1.7 Related guidelines

These guidelines are intended to complement existing guidance on HBV prevention. WHO has published several guidelines focusing on various aspects of the treatment and care of people living with HBV infection.

Updated WHO position paper on hepatitis B vaccines (2017) (6). This WHO position paper reflects the recommendations as endorsed by the Strategic Advisory Group of Experts (SAGE) on immunization and updates the 2009 position paper *(5)*. It includes the following recommendations:

a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.

b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.

c) The birth dose should be followed by two or three doses to complete the primary series.

Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection (20) were published in 2015, but did not make a recommendation on the use of antivirals for the PMTCT of HBV.

Consolidated guidelines on HIV testing services for a changing epidemic: policy brief (22), published in 2019, includes a recommendation on testing of pregnant women for HIV and syphilis from the 2019 *Consolidated guidelines on HIV testing services for a changing epidemic: policy brief (22),* and for hepatitis B from the WHO *Guidelines on hepatitis B and C testing (23).* It is recommended that all pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)[1] at least once and as early as possible.

1.8 Guiding principles

The following principles informed the development of these guidelines and should guide the implementation of the recommendations.

- These guidelines will contribute to realizing the Sustainable Development Goals (SDGs) through achieving key global and national hepatitis goals; SDG indicator 3.3.4: Hepatitis B incidence per 100 000 population *(24)*, and achieve the highest attainable standard of health for all women, children and adolescents *(25)*.
- The guidelines are based on a public health approach, which seeks to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches.
- Implementation of the guidelines needs to be accompanied by efforts to promote and protect gender equality and the human rights of people who need hepatitis services. In addition, it should ensure informed consent and prevention of stigma and discrimination in the provision of services, as well as engagement of civil society in the decision-making process.
- Implementation of the recommendations in these guidelines should be informed by the local context, availability of resources, organization and capacity of the health system and anticipated cost–effectiveness.

1 Particularly in settings with a ≥2% seroprevalence in the general population.

CHAPTER 2. METHODOLOGY

2.1 WHO guidelines development process

These guidelines were produced in accordance with the recommendations for standard guidelines, as described in the *WHO Handbook for guideline development (26)*. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was followed *(27)*. The Global Hepatitis Programme constituted a WHO Steering Committee, which included individuals with relevant expertise from different WHO departments and regions. The Steering Committee oversaw the entire guidelines development process.

The Global Hepatitis Programme constituted a Guidelines Development Group to ensure representation from various stakeholders, including patients' groups, advocacy groups, researchers and clinicians. Group members were also selected to achieve geographical representation and gender balance.

The Global Hepatitis Programme commissioned work to guide decision-making. First, a systematic review and meta-analyses estimated (i) the safety and efficacy of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission, and (ii) the performance of HBeAg tests to determine eligibility for antiviral prophylaxis. Second, WHO commissioned modelling to estimate the impact and cost–effectiveness of antiviral prophylaxis.

The Guidelines Development Group met at WHO headquarters in Geneva, Switzerland on 9–10 September 2019.

2.2 Formulations of recommendations

The Guidelines Development Group reviewed the results of the systematic reviews and meta-analysis, modelling and complementary information. It also examined the draft decision-making tables to ensure that there was understanding and agreement on the scoring criteria (*see* Web annexes 1 and 2 for the reviews and meta-analyses, and decision-making tables, and Web annex 3 for the modelling).

The Guidelines Development Group used the GRADE methodology to rate the certainty of the evidence and determine the strength of the recommendations. The strength of the recommendations was rated as either strong (the panel was confident that the desirable effects of the intervention outweighed the undesirable effects and most or all patients would benefit from following the recommended strategy) or conditional (the panel determined that the desirable effects of the intervention probably outweighed the undesirable effects and the decision to perform the recommended strategy may vary for individual patients and situations). The certainty of evidence supporting each recommendation was graded as high, moderate, low or very low.

The Guidelines Development Group then formulated recommendations following discussion based on the certainty of the evidence, the balance of benefits and harms, consideration of values and preferences, equity and human rights, resource use and the feasibility of carrying out the intervention. The chairs and methodologist helped the Guidelines Development Group to reach consensus during the meeting. After addressing all the comments and questions from members of the Guidelines Development Group, the chairs asked group members whether they agreed with the recommendations to document consensus. All group members agreed with all the recommendations. Implementation considerations were subsequently discussed, and areas and topics requiring further research identified.

2.3 Roles

The WHO steering group formulated the questions on Population, Intervention, Comparison, Outcomes (PICO). The Guidelines Development Group reviewed the evidence profiles and decision-making tables, composed and agreed upon the wording of the recommendations and reviewed drafts of the guidelines document.

The guidelines methodologist ensured that the GRADE framework was appropriately applied throughout the guidelines development process. This included formulation of the PICO questions, ensuring the comprehensiveness and quality of the systematic reviews, and preparation of the evidence profiles and decision-making tables. The methodologist also provided guidance to the Guidelines Development Group in formulating the wording and strength of the recommendations.

The External Review Group reviewed the draft guidelines document and provided critical feedback.

2.4 Declarations of interest and management of conflicts of interest

In accordance with WHO policy, all external contributors to the guidelines, including members of the Guidelines Development Group and External Review Group, completed a WHO declaration of interest form (*see* Web annex 6). A brief biography of each member of the Guidelines Development Group was posted on the WHO website. The biographies of the group members are available on https://www.who.int/hepatitis/news-events/gdg-pmtct-hbv/en/.

The Steering Committee reviewed and assessed the declarations submitted by each member and agreed on an approach to assess potential conflicts of interest, which they discussed with a staff member of the WHO Office of Compliance, Risk Management and Ethics. At the meeting, declarations of interest were reported according to WHO standard requirements. Individuals from organizations that had received significant funding from private (pharmaceutical) companies for research grants were considered to have a conflict of interest, and their participation in the Guidelines Development Group was classified as restricted. The Group members whose participation was restricted were Su Wang and Gonzague Jourdain. These individuals provided technical expertise in reviewing the decision-making tables but were excluded from participation in the discussion and formulation of the recommendations.

The declarations of interest forms from members of the External Review Group were reviewed in accordance with the WHO guidelines development policy. Any conflict of interest identified was considered when interpreting comments from External Review Group members during the external review process. The external reviewers could not and did not make changes in the recommendations (*see* Web annex 6).

2.5 Dissemination and monitoring of implementation

The guidelines will be made accessible on the WHO website with links to other United Nations and related websites. The Global Hepatitis Programme secretariat will disseminate the guidelines through WHO regional offices to WHO country offices and ministries of health, as well as to key international, regional and national collaborating centres, civil society organizations and national programmes. WHO will assist Member States to adapt the guidelines to their national context.

Implementation of these guidelines can be measured by the number of countries that incorporate them into their national programmes.

2.6 Evidence and information that guided the recommendations

2.6.1 Systematic review and meta-analysis

WHO commissioned a systematic review and meta-analysis on the safety and efficacy of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission. English and Chinese databases were searched. Duplicate studies were removed and randomized controlled trials as well as observational studies were included, resulting in 129 eligible studies. Data were extracted to provide a summary estimate of the efficacy and overview of the safety of antiviral medicines administered during pregnancy to prevent mother-to-child transmission of HBV. Following a suggestion made at the meeting of the Guidelines Development Group, the pool of studies was re-analysed to identify the threshold at which peripartum prophylaxis should be used.

WHO commissioned another systematic review and meta-analysis on the use of HBeAg testing as an alternate measure to identify those with high viral load and so to determine the eligibility for antiviral prophylaxis to prevent mother-to-child transmission of HBV. English and Chinese databases were searched. Duplicate studies were removed and randomized controlled trials as well as observational studies were included, resulting in 82 eligible studies. Data were extracted to provide a summary estimate of the performance of HBeAg tests in pregnant women with HBV infection to diagnose those with high HBV DNA levels eligible for antiviral prophylaxis to prevent mother-to-child transmission.

Complete search strategies are provided in two reports and are available in Web annexes 1 and 2. Decision-making tables are also available in Web annexes 1 and 2.

2.6.2 Modelling and cost–effectiveness analysis

A modelling analysis was commissioned to predict the expected impact on HBV infections averted and disability-adjusted life years (DALYs) averted with antiviral prophylaxis during pregnancy. An existing global model was adapted to evaluate the global and regional impact of a strategy of antiviral prophylaxis for pregnant women with HBV infection *(21)* (*see* Web annex 3). The model was also used to estimate the cost–effectiveness of antiviral prophylaxis in HBV-infected pregnant women in addition to three doses of hepatitis B vaccine, including a timely birth dose with and without the use of HBIG in different WHO regions (*see* Web annex 3).

2.6.3 Feasibility, values and preferences

The Global Hepatitis Programme conducted an online stakeholder consultation to gather the perspectives of programme managers, health-care workers and civil society organizations on introducing antiviral prophylaxis to prevent mother-to-child transmission of HBV. Following consultation with the Guidelines Steering Group, three online consultations were designed using an online survey tool. Respondents were engaged through members of the Guidelines Development Group and WHO regional advisors, who distributed the consultations within their networks. Data were analysed to estimate the frequency of various responses by categories, and charts were created by the online analysis tool (*see* Web annex 4).

The literature was reviewed to assess knowledge and acceptability of measures to prevent mother-to-child transmission of HBV. MEDLINE™ was searched using terms for HBV infection, mother-to-child transmission, antiviral therapy, patient preferences, patient values, acceptability and knowledge. We selected studies that used consultations/questionnaires to ask participants (pregnant women) to indicate their knowledge and willingness to use interventions to prevent mother-to-child transmission. Three studies were identified, and available data was summarized in tables (*see* Web annex 4).

CHAPTER 3. RECOMMENDATIONS

3.1 Tenofovir prophylaxis to prevent mother-to-child transmission of HBV

Existing recommendations on immunization from the WHO position paper 2017 *(6)*

a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours;

b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose;

c) The birth dose should be followed by 2 or 3 doses to complete the primary series.

Existing recommendation on testing of pregnant women for HIV and syphilis from the 2019 *Consolidated guidelines on HIV testing services (22)*, and for hepatitis B from the WHO *Guidelines on hepatitis B and C testing (23)*

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)[1] at least once and as early as possible in the pregnancy (HIV standing recommendation since 2007; *syphilis: strong recommendation, moderate-quality evidence; HBsAg[1]: strong recommendation, low-quality evidence).*

New recommendation

WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL[2]) receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose *(conditional recommendation, moderate quality of evidence).*

1 Particularly in settings with a ≥2% seroprevalence in the general population.

2 HBV DNA ≥5.3 $\log_{10}$ IU/mL is equivalent to ≥200 000 IU/mL.

3.1.1 Summary of the evidence

WHO commissioned a systematic review and meta-analysis to evaluate the efficacy and safety of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission. The efficacy analysis was based on data from tenofovir disoproxil fumarate (TDF), lamivudine and telbivudine prophylaxis. Lamivudine and telbivudine have low genetic barriers to drug resistance mutations, which may lead to the emergence of drug-resistant strains of HBV *(28)*. TDF has a high barrier to drug resistance *(20)*. WHO recommends nucleos(t)ide analogues with a high barrier to resistance to treat HBV infection *(20)*. Thus, TDF is the medicine of choice for PMTCT. The safety and subgroup analyses only considered TDF.

Efficacy of maternal tenofovir prophylaxis to prevent mother-to-child transmission of HBV

A WHO-commissioned systematic review and meta-analysis identified 129 studies that evaluated the efficacy of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission. All studies in the meta-analysis included HBIG in both trial arms, with the exception of six studies, in which the use of HBIG was not reported. Most studies were performed in the Western Pacific Region. There were no studies available from the African Region or from the Americas. The meta-analysis indicated a protective effect regardless of the antiviral used to prevent mother-to-child transmission (TDF 300 mg: odds ratio [OR] 0.16, 95% confidence interval [CI]: 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI: 0.13–0.22; telbivudine 600 mg: OR 0.10, 95% CI: 0.08–0.13, *see* Web annex 1).

Safety of maternal tenofovir prophylaxis to prevent mother-to-child transmission of HBV

The safety of TDF has been documented in the context of PMTCT of HIV *(29)*. In addition, safety was examined in the specific context of peripartum prophylaxis of HBV PMTCT.

Maternal safety. Six studies were included in a meta-analysis that reported the risk of maternal HBV flare after TDF discontinuation. Across these studies, 35 of 418 mothers (8%) who received TDF during pregnancy experienced a flare after discontinuation, compared with 23 of 382 mothers (6%) who did not receive the medicine at a matched time-point. The absence of significant differences between the groups suggests that discontinuation of tenofovir prophylaxis might not increase the risk of flare (weighted pooled risk difference in the meta-analysis: 0.00 [95%CI: 0.04–0.04]) (*see* Web annex 1).

Infant safety. One randomized controlled trial examined the effect of tenofovir

prophylaxis on infant bone mineral density. There were no differences reported between 62 infants in the maternal prophylaxis group and 53 infants in the maternal placebo group in terms of lumbar spine bone mineral density measured at 1 year of age (mean: 0.324 (SD ± 0.036) and 0.330 (SD ± 0.036), respectively, *see* Web annex 1).

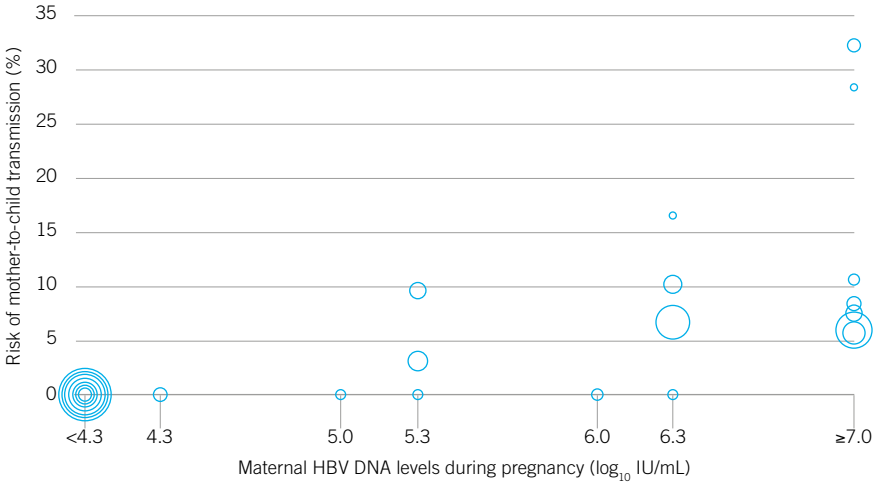
Pregnancy duration and start of tenofovir prophylaxis

Pooled OR estimates were similar for tenofovir prophylaxis starting at a median pregnancy duration of <28 weeks (OR 0.10, 95% CI 0.04–0.25), 28 weeks (OR 0.24, 95% CI 0.13–0.44), or >28 weeks (OR 0.09, 95% CI 0.02–0.32, *see* Web annex 1). An analysis of seven studies from China compared second versus third trimester start of prophylaxis with antiviral medication. This analysis indicated that starting prophylaxis during the second trimester was more efficacious than starting during the third trimester. However, this observation was based on a small number of events and most trials evaluated telbivudine or lamivudine (*see* Web annex 1).

HBV DNA threshold in pregnant women with HBV infection to predict the risk of mother-to-child transmission

Although this element was not part of the original PICO question, the studies identified in the context of the first systematic review allowed the conduct of a meta-analysis to assess the risk of perinatal infection according to the maternal HBV viral load (measured by $\log_{10}$ IU/mL) among infants who received a timely birth dose and HBIG. Studies with a small sample size (<10 subjects) were excluded. When timely birth dose and HBIG were used, there was no breakthrough infection reported when the maternal HBV DNA viral load was below 5.3 $\log_{10}$ IU/mL (*see* Fig. 2 and Web annex 2).

FIG. 2. Risk of mother-to-child transmission of HBV according to maternal HBV DNA levels during pregnancy



Resistance to tenofovir prophylaxis

Only one study performed resistance testing following the use of tenofovir prophylaxis in women. This study, with 120 participants, reported no HBV mutations related to the use of tenofovir prophylaxis. Two other studies evaluated antiviral resistance in women defaulting from prophylaxis or where infants were infected with HBV. In both cases, no resistant mutations were identified (*see* Web annex 1).

Population-level impact of interventions for PMTCT of HBV

An existing model of the global HBV epidemic was adapted to evaluate the impact of a strategy to use tenofovir prophylaxis for eligible pregnant women with HBV infection. Worldwide, scaling up vaccination incrementally to a 90% coverage of the three-dose hepatitis B vaccine, including timely birth dose, would prevent an additional 14 million new neonatal HBV infections and 38 500 DALYs over the next 10 years. Adding HBsAg testing and tenofovir prophylaxis of eligible pregnant women to the scenario of three-dose vaccination coverage including timely birth dose would prevent an additional 2.9–3.0 million neonatal infections over the same period (*see* Web annex 3).

3.1.2 Rationale for the recommendation

The Guidelines Development Group recognized that universal immunization of infants with hepatitis B vaccine, including a timely birth dose, is the most effective intervention to prevent HBV infection at birth and in the first years of life.

The Guidelines Development Group made an overall conditional recommendation to use tenofovir prophylaxis to prevent mother-to-child transmission. The Group acknowledged that most clinical trials that evaluated the efficacy of tenofovir prophylaxis had also included the use of HBIG in both arms. However, it was concluded that the efficacy of antiviral prophylaxis could reasonably be extrapolated to settings in which HBIG is not available. The Group noted that trials are under way to provide an evidence base for the efficacy of tenofovir to prevent mother-to-child transmission among women whose infants did not receive HBIG.

The Guidelines Development Group determined a viral load threshold of HBV DNA ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL) at which pregnant women are eligible to receive tenofovir prophylaxis. Meta-analysis indicated that a pregnant woman with a viral load ≥5.3 $\log_{10}$ IU/mL may transmit HBV to her infant even when the infant receives the timely birth dose vaccine, HBIG and completes the hepatitis B vaccine series (*see* Fig. 1).

Balance of benefits and harms

Benefits

Maternal tenofovir prophylaxis may prevent HBV infection in infants born to HBV-infected women. This may protect these children from the risk of developing serious disease complications later in life. On a population level, prevention of transmission of HBV may reduce the reservoir for further transmission.

Harms

The main potential harm is the risk of liver flare after discontinuation of prophylaxis. Although the risk of flare is low, reactivation has been reported in patients treated for hepatitis B after antiviral prophylaxis had been withdrawn *(30)*. There is also the risk that a recommendation could lead to the false perception that tenofovir prophylaxis in HBV-infected pregnant women could replace the use of timely birth dose vaccination.

Values and preferences and acceptability

Three published studies *(31–33)* and two unpublished studies were identified that assessed the preferences of pregnant women related to interventions to prevent mother-to-child transmission. These studies indicated that most women were willing to have their infant given a timely birth dose, varying from 66% (251/380) of women in Viet Nam, to 93% (195/209) in Ghana *(31, 32)*. In Ghana, 93% of the surveyed women were willing to take antiviral prophylaxis *(31)*. In a study in Burkina Faso, 100% of eligible women agreed to take antiviral prophylaxis (A. Guingane, unpublished data). In a programme to prevent mother-to-child transmission of HBV in China (the SHIELD project), 97% of women eligible for prophylaxis were willing to receive it (Dr Hou, unpublished data). In contrast, one study conducted in Guangdong China found that only 17% (125/737) of women surveyed were willing to take antiviral prophylaxis *(33)*.

Of 153 health-care workers, 56 programme managers and 81 civil society representatives who responded to an online consultation carried out by WHO prior to the Guidelines Development Group meeting, 50–60% reported that a programme to prevent mother-to-child transmission of HBV is in place in their country or place of work. Advantages of tenofovir prophylaxis mentioned by respondents included prevention of HBV infection in the infant, and opportunity to both provide care and treatment of the mother, and to build on and promote integrated HBV, HIV and syphilis services. While there is support for the use of prophylaxis in pregnant women to prevent mother-to-child transmission, around one third of respondents

expressed concerns about costs and the risk tenofovir prophylaxis poses to the mother's and infant's health. While prophylaxis is cost effective, the willingness to pay may vary. Safety concerns underscore the need for education of health-care workers and pregnant women to increase knowledge and reduce misperceptions when the payer is the mother because of health systems factors that lead to out of pocket expenses (*see* Web annex 4).

Feasibility

Experience from the elimination of mother-to-child transmission (EMTCT) of HIV and syphilis suggests that it is feasible to provide testing for pregnant women followed by prophylaxis for eligible women to prevent infection. By the end of 2018, around 79% of pregnant women knew their HIV status, and of those identified as infected, 82% received treatment *(34)*. Worldwide, in 2016, an estimated 66% of pregnant women were tested for syphilis, and, among those identified as infected, 78% of women were treated *(35)*.

An online consultation among health-care workers, programme managers and civil society representatives indicated that 77% of respondents felt that it was feasible to offer HBV testing and provide eligible pregnant women with tenofovir prophylaxis. Challenges reported by stakeholders included costs and availability of HBV DNA tests and TDF, training of health-care workers, education of women living with HBV infection, and lack of capacity and infrastructure to test and treat pregnant women (*see* Web annex 4).

Equity and human rights

HBV-infected pregnant women from groups that are marginalized or stigmatized (e.g. people who inject drugs, sex workers) or minority populations (migrants, indigenous populations), in general have a higher prevalence of HBV infection than the general population and have poor access to health care. Integrated antenatal services for HBV, HIV and syphilis provide an opportunity to reach out to marginalized groups and minority populations. However, additional measures are required to ensure that these populations have access to health services without stigma and discrimination to reduce health inequities.

Use of tenofovir prophylaxis to prevent mother-to-child transmission in addition to timely birth dose could reduce health inequities in low-income settings where HBIG is not available or affordable. However, interventions based on testing of pregnant women followed by tenofovir prophylaxis cost more than hepatitis B vaccination of infants alone. Therefore, tenofovir prophylaxis in addition to vaccination may not be feasible in low-income countries in the short term.

The Guidelines Development Group raised concerns that routine testing of pregnant women may lead to challenges in maintaining confidentiality as well as stigma and discrimination against those testing positive. This highlights the importance of health-care worker training and rights-based frameworks that facilitate access to testing and treatment.

The use of tenofovir prophylaxis for eligible pregnant women might also lead to initiation of prophylaxis for prevention of infection of the infant taking precedence over consideration of health issues of the mother. However, few women of childbearing age are likely to have clinical or laboratory signs of liver disease and so be eligible for long-term treatment after pregnancy for their own health. Recommendations in the 2015 HBV guidelines include the specific criteria for who to treat with long-term antiviral therapy *(20)*. Programmes that would implement these guidelines on PMTCT of HBV need to ensure that women infected with HBV are assessed for eligibility for treatment for their own health and that those found eligible are placed on treatment, in accordance with the 2015 HBV treatment guidelines *(20)*.

Resource considerations

Cost–effectiveness of scaling up timely birth dose. The global cost of adding 90% timely birth dose coverage to a scenario of 90% coverage of three-dose hepatitis B vaccination is estimated at US$ 1.6 billion for 2020–2030. The incremental cost–effectiveness ratios (ICERs) for this strategy vary by WHO region, ranging from US$ 133 to US$ 952 per DALY averted and eight world regions have ICERs of <US$ 300 per DALY averted (*see* Web annex 3).

Cost–effectiveness of antenatal testing and prophylaxis for eligible pregnant women. The global cost of adding antenatal testing of pregnant women for HBsAg and providing tenofovir prophylaxis for those at increased risk of mother-to-child transmission (over scaled up timely birth dose) would be an extra US$ 2.2–2.7 billion over 10 years. The ICERs of this testing and prophylaxis strategy guided by HBV DNA, in addition to timely birth dose, varies between US$ 890 and US$ 7355 per DALY averted, depending on the world region. The regions with the lowest ICERs for antiviral scale up are East Asia, West Africa, Central Europe, Central Africa and East Africa with ICERs of US$ 890, US$ 1066, US$ 1069, US$ 1106 and US$ 1250 per DALY averted, respectively (*see* Web annex 3).

In summary, compared to the status quo, scaling up timely birth dose is the most cost-effective option that delivers the most health benefit for the lowest cost. However, in countries that have already scaled up the timely birth dose, adding antenatal testing of pregnant women and tenofovir prophylaxis is an additional opportunity to prevent perinatal infections and may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented.

Costs of tenofovir and diagnostics in different WHO regions

TDF is no longer patent protected and is available for US$ 27 or less per year of treatment. The current market price for HBV DNA testing varies from US$ 15–50 in the Region of the Americas to US$ 30–100 in the Western Pacific Region and the African Region. The best current market price for laboratory-based HBeAg testing is US$ 7.5. The price of rapid diagnostic tests (RDTs) to detect HBeAg ranges between US$ 0.5 and US$ 1.3.

3.1.3 Implementation considerations

- Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among children aged 5 years through vaccination would need to focus their efforts on increasing their vaccination coverage, including timely birth dose.

- Temporary immunity may be obtained by administering HBIG for post-exposure prophylaxis. HBIG prophylaxis in conjunction with hepatitis B vaccination may be of additional benefit for newborn infants whose mothers are HBeAg-positive *(6)*.

- The clinical trials that evaluated the efficacy and safety of tenofovir prophylaxis also included hepatitis B immune globulin (HBIG) as an additional preventive strategy in both trial arms. In a number of settings (mostly in high income countries) where it is available, HBIG is used in addition to hepatitis B vaccination, including birth dose, to reduce the risk of mother-to-child transmission of HBV. However, HBIG is a blood product that has to be screened for infectious diseases. The costs are high, a cold chain is required and HBIG can be in short supply. In low and middle income countries, it may only be available when purchased by individuals.

- As many countries are working towards dual elimination of perinatal HIV and syphilis infection, there are opportunities for efficiency gains and integration to also include elimination of mother-to-child transmission of HBV.

- Programmes to test and treat eligible pregnant women need to be implemented in the context of universal health coverage, aiming for covering the highest proportion of women while reducing financial hardship.

- Testing of pregnant women needs to take place under circumstances that prevent stigma and discrimination. Post-test counselling and education should be conducted on measures to reduce the risk of transmitting HBV to the infant, encouragement for partner testing and ensuring linkage to care of HBsAg-positive women to assess for eligibility for treatment for the mothers own health *(23)*.

- Clinical assessment should include an evaluation of whether mothers would be eligible for treatment for their own health. However, in accordance with criteria in the 2015 WHO treatment guidelines, only a small proportion of women of childbearing age would be eligible for long-term treatment *(20)*.
- All eligible pregnant and breastfeeding women living with HBV infection can safely use tenofovir *(36)*.
- The diagnostic tests used need to meet quality, safety and performance standards (with regard to both analytical, diagnostic or clinical sensitivity and specificity).[3]
- In women with HIV/HBV infection, treatment with ART that contains TDF should be continued after pregnancy.
- Tenofovir has no drug–drug interactions with HIV medications. Renal toxicity needs to be monitored when used with sofosbuvir/ledipasvir or sofosbuvir/velpatasvir. Other potential drug–drug interactions can be checked on the internet site of the University of Liverpool (https://www.hep-druginteractions.org).

3.1.4 Research gaps

- Effectiveness of testing and prophylaxis with antivirals of pregnant women to prevent mother-to-child transmission in different regions, especially the African Region. New data on effectiveness could have an impact on cost–effectiveness.
- Efficacy of TDF to prevent mother-to-child transmission of HBV among women whose infants did not receive HBIG. Given the limited access to HBIG and the need to screen for infectious diseases, the use of HBIG-free regimens could be a cheaper and safer option when using HBIG. A range of trials are now under way to provide an evidence base for this consideration and more may be needed.
- Efficacy of TDF to prevent mother-to-child transmission among women whose infants did not receive a timely birth dose.
- Evaluation of different service delivery models for provision of integrated HIV, syphilis and hepatitis B testing, care, prophylaxis and treatment services.
- Evaluation of continuing treatment after delivery as (i) HBV treatment guidelines may evolve towards broadening treatment eligibility criteria, and (ii) subsequent pregnancies in HBV-infected women will also be associated with the risk of mother-to-child transmission.

3 Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use and, where possible, at testing sites enrolled in a national or international external quality assessment scheme.

- Evaluation of different strategies to prevent mother-to-child transmission of HBV in the context of the evolving research agenda towards a cure for HBV infection.
- Evaluation of tenofovir alafenamide (TAF) and entecavir for PMTCT.
- Additional strategies for PMTCT of HBV in HCV- or HDV-coinfected women.
- Evaluation of tenofovir prophylaxis in women in multiple subsequent pregnancies to prevent mother-to-child transmission.

3.2 In settings in which antenatal HBV DNA testing is not available, use of HBeAg testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV

New recommendation

WHO recommends that in settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis, to prevent mother-to-child transmission of HBV[4] *(conditional recommendation, moderate quality of evidence).*

3.2.1 Summary of the evidence

Performance of HBeAg tests to diagnose high HBV DNA levels in pregnant women with HBV infection

WHO commissioned a systematic review and meta-analysis to assess the performance (sensitivity and specificity) of HBeAg tests in pregnant women with HBV infection in identifying women with high HBV DNA levels (≥5.3–6.2 $\log_{10}$ IU/mL). There were 27 studies included from the Western Pacific Region, seven from the African Region, five from the European Region, one from the South-East Asia Region and one from the Region of the Americas. The overall sensitivity and specificity of HBeAg for diagnosis of HBV viraemia based on a DNA threshold ≥5.3–6.2 $\log_{10}$ IU/mL was 88.2% (95% CI: 83.9–91.5) and 92.6% (95% CI: 90–94.5), respectively (*see* Web annex 2).[5]

4 The performance of HBeAg testing suggests that it is an acceptable alternative to diagnosing HBV DNA ≥5.3 $\log_{10}$ IU/mL.

5 HBV DNA ≥5.3 $\log_{10}$ IU/mL is equivalent to ≥200 000 IU/mL

In two studies that evaluated HBeAg RDTs, there was a pooled sensitivity of 70.1% (95% CI: 58.2–79.9) and a pooled specificity of 95.7% (95% CI: 93.3–97.3) for diagnosis of HBV viraemia based on a DNA threshold ≥5.3–6.2 $\log_{10}$ IU/mL (*see* Web annex 2).

Performance of HBeAg tests in pregnant women with HBV infection to predict the risk of mother-to-child transmission

The above-described systematic review and meta-analysis also assessed the performance (sensitivity and specificity) of HBeAg positivity to predict the risk of mother-to-child transmission. The analysis was stratified by different preventive interventions. In nine eligible studies that used HBeAg to predict the risk of mother-to-child transmission, the overall sensitivity and specificity was 99.1% (95% CI: 61.8–100) and 55.7% (95% CI: 34.0–75.5), respectively. When restricted to children who received birth dose vaccine plus HBIG, the sensitivity was 98.8% (95% CI: 52.0–100) and specificity was 49.2% (95% CI: 25.1–73.7, *see* Web annex 2).

Performance of different HBV DNA thresholds in pregnant women with HBV infection to predict the risk of mother-to-child transmission

The above-described systematic review and meta-analysis estimated the performance (sensitivity and specificity) of different HBV DNA thresholds in pregnant women with HBV infection to predict the risk of mother-to-child transmission. HBV DNA viral load threshold of ≥5 $\log_{10}$ IU/mL was associated with a sensitivity of 97.7% (95% CI: 42.9–100) and a specificity of 68.4% (95% CI: 48.6–83.2) for predicting mother-to-child transmission.

In conclusion, compared to HBV DNA, HBeAg has high sensitivity but lower specificity for predicting the risk of mother-to-child transmission.

3.2.2 Rationale for the recommendation

The Guidelines Development Group made an overall conditional recommendation to use HBeAg testing to determine eligibility for tenofovir prophylaxis in settings where HBV DNA is not available. The Group recognized that HBV DNA quantification is the reference method to determine eligibility for tenofovir prophylaxis in pregnant women to prevent mother-to-child transmission. However, based on the available evidence, it was decided that the performance of HBeAg is acceptable, and therefore can be used as an alternative test in settings where access to HBV DNA quantification is limited.

Balance of benefits and harms

Benefits

The use of HBeAg testing may increase access to testing and tenofovir prophylaxis for HBV-infected pregnant women, thereby reducing the incidence of mother-to-child transmission in low-income settings.

Harms

Potential harms include the overuse (use of prophylaxis in women at low risk of mother-to-child transmission of HBV) or underuse (no prophylaxis in women at high risk of mother-to-child transmission of HBV) of tenofovir prophylaxis depending on the setting. The recommendation may lead to the perception that HBeAg is the preferred or optimal method for the assessment of eligibility for tenofovir prophylaxis, which may reduce efforts to increase access to HBV DNA testing. The recommendation may also lead to the misconception that HBeAg to determine eligibility for tenofovir prophylaxis in pregnant women could be used to determine eligibility for treatment among all persons with HBV infection. However, the Guidelines Development Group determined that the benefits are likely to outweigh any potential harms.

Values and preferences and acceptability

Some pregnant women value highly the use of antivirals for HBV PMTCT over risks related to unnecessary exposure to TDF and potential adverse events *(31)* (*see* section 3.1.2 Values and preferences).

One hundred fifty-three health-care workers, 56 programme managers and 81 civil society representatives expressed their views in an online consultation carried out by WHO. Respondents viewed testing of pregnant women to guide use of tenofovir prophylaxis with HBeAg as an acceptable intervention. Identified advantages included reduction in costs, increased access to testing for pregnant women and increased equity for disadvantaged groups (*see* Web annex 4).

Feasibility

Respondents to the online consultation among health-care workers, programme managers and civil society representatives indicated that it was feasible to use HBeAg tests to determine eligibility for tenofovir prophylaxis. Challenges mentioned included the costs and availability of HBeAg tests, training of health-care workers, and education of women living with HBV infection.

Equity and human rights

HBV DNA quantification is the reference test to determine eligibility for tenofovir prophylaxis in HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV. However, some settings have poor access to HBV DNA quantification, especially remote rural areas where many antenatal clinic visits take place. Emphasizing the need to increase access to cheaper HBV DNA tests and endorsement of HBeAg as an alternative marker for HBV DNA quantification could result in increased availability of affordable testing and subsequent access to tenofovir prophylaxis. This would reduce inequities in access for pregnant women in settings with poor access to testing and prophylaxis.

Resource considerations

The financial implications of the choice between HBV DNA and HBeAg testing depends on the relative prices of these tests and would vary across countries, but the cost–effectiveness ratios of an HBV viral load-guided strategy or an HBeAg-guided strategy are largely similar (*see* Table 1).

3.2.3 Implementation considerations

- HBV DNA quantification is the reference method to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV in pregnant women. Access to HBV DNA quantification (in terms of costs, availability of tests, availability of testing platforms and quality of tests) remains limited in some settings. Efforts need to continue to increase access to HBV DNA testing and reduce prices.

- The tests being used need to meet quality, safety and performance standards (with regard to both analytical and clinical sensitivity and specificity).[3]

3.2.4 Research gaps

- Evaluation of measures to ensure that vulnerable populations have access to health services without stigma and discrimination.

- Evaluation of service delivery models to offer testing and tenofovir prophylaxis, including for vulnerable populations.

- Development of RDTs for HBeAg with higher diagnostic accuracy.

- Evaluation of the performance of HBeAg tests in the presence of coinfection with HCV and HDV and in different genotypes.

- Evaluation of the performance of HBeAg tests available in different WHO regions.

3 Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use and, where possible, at testing sites enrolled in a national or international external quality assessment scheme.

CHAPTER 4. IMPLEMENTATION CONSIDERATIONS

4.1 General considerations and principles

Several parameters are key to planning for an approach to prevent mother-to-child transmission of HBV in different countries and settings. These include the epidemiology of HBV infection (prevalence of chronic HBV infection and of high HBV DNA levels or HBeAg positivity in persons with HBV infection), service coverage of immunization, including the birth dose of hepatitis B vaccine, availability of commodities for diagnosis and treatment, experience with testing and peripartum prophylaxis with antivirals.

4.1.1 Prevalence of HBV infection

WHO recommends universal immunization of infants against hepatitis B starting with a timely birth dose in all settings *(6)*, regardless of HBV endemicity. Where the prevalence of HBV infection is intermediate (2–8%) or high (>8%), universal immunization of infants has had a large impact and is cost effective *(37)*. The results of the impact model and cost–effectiveness analysis that was conducted for these guidelines suggest that in settings with high endemicity, high coverage with a timely birth dose followed by two or three additional doses of vaccine would lead to the greatest impact at the lowest cost (*see* Web annex 3). Some countries with low endemicity have, however, chosen selective strategies to prevent mother-to-child transmission that are based on testing pregnant women to identify those infected. These countries have already been implementing interventions similar to the peripartum prophylaxis recommended in these guidelines, even though they did not implement universal use of hepatitis B immunization in accordance with WHO recommendations.

4.1.2 Prevalence of HBeAg positivity in HBV-infected women of childbearing age

Among women of childbearing age with chronic HBV infection, the prevalence of HBeAg positivity that correlates with high HBV DNA viraemia varies across regions *(38)*. As a result, the risk of perinatal transmission also varies *(11, 12)*. Historically, the African and the Western Pacific regions have the highest prevalence of HBV infection *(1)* but differ in the prevalence of HBeAg positivity. The prevalence of HBeAg positivity in HBV-infected women of childbearing age is generally higher in the Western Pacific Region compared to other regions,

while the African Region has a lower prevalence *(38, 39)*. The introduction of hepatitis B vaccine as part of the Expanded Programme on Immunization (EPI) has led to improved prevention of horizontal transmission in the past decades. As a result, the proportion of chronic HBV infections attributable to horizontal transmission has decreased. Perinatal infection now accounts for a higher proportion of the remaining transmission, both in the Western Pacific and African regions.

4.1.3 Infant immunization coverage

In 2018, the global coverage of the third dose of hepatitis B vaccine was high (84%) *(8)*. However, there were outliers and some countries still struggle to reach high coverage. Where the third dose coverage remains low, increasing coverage is key to eliminating horizontal transmission. Of the six WHO regional offices, three (Western Pacific, Europe and South-East Asia) have mechanisms in place to verify achievements of the better to use hepatitis B control goal through immunization *(40, 41)*. The Eastern Mediterranean Region is still establishing their process. The African Region, however, is first working on the establishment of birth dose policies. In the Region of the Americas, pilot testing of verification of the 0.1% elimination goal has started.

4.1.4 Timely birth dose coverage

In 2018, the coverage of the timely birth dose remained heterogeneous (from 4% in the African Region to 83% in the Western Pacific Region). Where coverage of the timely birth dose remains low, increasing coverage is a priority for two reasons. First, a timely birth dose followed by two or three additional doses is the intervention that leads to the greatest impact at the lowest cost (*see* Web annex 3). Second, studies demonstrating the efficacy of antiviral prophylaxis have been conducted only in the setting of routine use of infant vaccination (including a timely birth dose) (*see* Web annex 1). At present, the efficacy of peripartum antiviral prophylaxis in the absence of a timely birth dose is unknown. However, future research in the field could address this knowledge gap.

4.1.5 Availability of commodities

The availability of medicines and diagnostics needed for peripartum antiviral prophylaxis varies. TDF is no longer protected by any patent, and therefore should be available for procurement in any country of the world for US$ 2.5/month or less *(42)*. In practice, in some countries, the absence of national programmes may lead to fragmented procurement, high in-country mark-ups and higher overall prices. HBV DNA testing can be procured for as little as US$ 15/test. The best current market price for laboratory-based HBeAg testing

is US$ 7.5 and for RDTs to detect HBeAg, the price ranges between US$ 0.5 and US$ 1.3. However, the in vitro diagnostic infrastructure differs from country to country. Finally, HBIG availability and prices vary. In sub-Saharan Africa, availability is particularly limited. It is mostly available in the private sector at high prices.

4.1.6 Experience with peripartum prophylaxis

Several countries that used to be highly endemic for HBV infection have achieved major progress in hepatitis B control through high coverage of infant hepatitis B vaccination, including timely birth dose *(43)*. Because breakthrough infections in children born to women with high HBV DNA and who received a timely birth dose followed by two or three additional doses now constitute a source of residual perinatal infections *(43, 44)*, programmes for peripartum prophylaxis have been initiated in most regions *(15, 45)*. In some regions, however, particularly the African Region, experience with peripartum prophylaxis is still limited.

4.2 Regional considerations

The various WHO regions are faced with different scenarios with respect to these parameters. As a result, the implementation of these guidelines may vary by region. The situation assessment provided below is based on interactions of the WHO regional offices with ministries of health of the Member States.

4.2.1 African Region

The African Region is characterized by high endemicity of HBV infection, but lower prevalence of HBeAg positivity among women of childbearing age than in the South-East Asia Region, suboptimal routine infant vaccination coverage, low hepatitis B birth dose vaccine coverage, and limited availability of in vitro diagnostic infrastructure and commodities (including HBIG). In this context, initial efforts to implement hepatitis B vaccine birth dose policies would lead to the greatest impact at the lowest cost (*see* Web annex 3). Initially, efforts to introduce a timely birth dose may start in women delivering in health-care facilities (in 2019, 59.5% of pregnant women delivered in a health-care facility) *(46)*. Additional efforts will be needed to reach women who deliver in the community. From 2021, the support of Gavi, the Vaccine Alliance, should facilitate introduction of a birth dose of hepatitis B vaccine in the EPI schedule *(47)*. The cost of a mono-dose of hepatitis B vaccine is low (US cents 13), under the threshold of national co-payment for Gavi-sponsored vaccines *(47)*. Therefore, financial support from Gavi under the current policy will be primarily directed at operations rather than at vaccine procurement. While efforts to

prevent mother-to-child transmission of HBV in the African Region should focus on timely birth dose, implementation of pilot projects for peripartum prophylaxis would also allow experience to be gained in the field. Research projects examining the efficacy of peripartum prophylaxis in the absence of HBIG and/or timely birth dose could also open new programmatic options in the future.

4.2.2 Region of the Americas

The Region of the Americas is characterized by low endemicity of HBV infection, with pockets of high endemicity, particularly among indigenous populations. The estimated regional prevalence of HBsAg in children at 5 years of age is <0.1%. The prevalence of HBeAg among women of childbearing age varies. By 2018, 26 countries and territories had introduced universal hepatitis B birth dose vaccine into their national immunization schedules with an estimated regional coverage of 72%. In 2019, four additional countries introduced a universal birth dose, representing nearly 92% of the total birth cohort in the Region. In 2016, the Pan American Health Organization endorsed "EMTCT Plus", a Framework for elimination of mother-to-child transmission of HIV, Syphilis, Hepatitis B, and Chagas *(48)*. In recent years, the national context allowed initial experiences of peripartum prophylaxis in a few countries. In 2017, 24 countries were routinely testing pregnant women for HBsAg, while 22 countries provide HBIG for exposed newborns. Implementation of the present guidelines for peripartum prophylaxis would facilitate the prevention of more perinatal HBV infections.

4.2.3 Eastern Mediterranean Region

The Eastern Mediterranean Region is characterized by intermediate endemicity of HBV infection and low prevalence of HBeAg among HBV-infected women of childbearing age. Overall, third dose coverage with the hepatitis B vaccine is high (82%) and the birth dose coverage is low (33%). Experience with peripartum prophylaxis is limited. In this context, efforts to increase timely birth dose coverage should be prioritized.

4.2.4 European Region

The European Region is characterized by low-to-intermediate endemicity of HBV infection in most of its Member States, and low prevalence of HBeAg among HBV-infected women of childbearing age. However, several countries in the south Caucasus and central Asia, and a few countries in eastern and central Europe had high endemicity profiles before universal immunization was introduced. In addition, migrants born in high-endemicity countries have a higher prevalence of HBV infection. Overall, vaccination coverage with the

third dose of hepatitis B vaccine is high (84%) but in 2019, four Member States had not implemented universal immunization of infants against hepatitis B nationally because of their low endemicity *(1)*. Some Member States of the WHO European Region (mostly high-income countries with low baseline prevalence of HBV infection) do not implement universal hepatitis B vaccination but rely on targeted prevention of perinatal transmission through testing all pregnant women and providing the birth dose to children born to HBsAg-positive mothers.

Implementation of the present guidelines for peripartum prophylaxis would further facilitate the prevention of perinatal HBV infections, particularly in countries that are not using universal hepatitis B immunization.

4.2.5 South-East Asia Region

The South-East Asia Region is heterogeneous with respect to the epidemiology of HBV infection. Some countries have intermediate or low endemicity for HBV infection (e.g. Sri Lanka). Some countries have high endemicity for HBV infection with a high prevalence of HBeAg positivity among HBV-infected women of childbearing age (e.g. Democratic People's Republic of Korea, Indonesia, Thailand). Also, in intermediate-endemicity settings, there are indigenous people with a higher prevalence of HBV infection *(49)*. The 2018 coverage of the third dose of hepatitis B vaccine was high (89%) and the coverage of the birth dose was intermediate (48%). Eight out of 11 Member States provide a universal birth dose. However, two of the four Member States that have already reached the 1% goal of HBsAg prevalence in children 5 years of age did not have a timely birth dose in their immunization schedule *(50)*. There is experience of peripartum prophylaxis where HBV is highly endemic and perinatal transmission common, as in Thailand *(15)*. Implementation of the present guidelines for peripartum prophylaxis would facilitate the prevention of perinatal HBV infections, especially in Member States that may decide against adoption of birth dose vaccine in view of the low prevalence of HBsAg that has already been achieved with existing three doses of hepatitis B vaccine.

4.2.6 Western Pacific Region

In the Western Pacific Region, an estimated 115 million people were living with HBV infection in 2015 and the regional prevalence of chronic HBV infection was estimated at 6.2% *(1)*. When hepatitis B vaccination was introduced in the 1990s, most Member States had a high endemicity of HBV infection and a high prevalence of HBeAg positivity *(51)*. The Region was the first to decide on a target for the control of HBV infection through immunization, aiming at

2% prevalence of HBsAg in children aged 5 years by 2012 *(52)*. In 2018, the coverage of the birth dose and third dose of hepatitis B vaccine was high overall (83% and 90%, respectively), though a number of Member States still had challenges in achieving high coverage *(53)*. In 2018, nine out of 25 reporting Member States and areas had achieved 95% coverage for the timely birth dose while 13 of 27 Member States and areas had achieved 95% coverage of the third dose of vaccination. As a whole, the Region achieved the 2017 target of 1% prevalence of HBsAg in children 5 years of age. However, as a result of large populations and with some Member States having a very high HBV prevalence in the general population, breakthrough infections still account for a large number of perinatal infections. In 2017, the Regional Committee for the Western Pacific Region endorsed the Regional Framework for the Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B and Syphilis in Asia and the Pacific, 2018–2030 *(54)*. The Framework proposes a coordinated approach towards achieving triple elimination of mother-to-child transmission of HIV, HBV and syphilis through access to quality reproductive, maternal, newborn and child health services. A number of Member States in the Western Pacific Region have spearheaded efforts to further reduce mother-to-child transmission, including through the use of antiviral prophylaxis and follow up of exposed infants *(55, 56)*. In China, universal antenatal testing for HIV, hepatitis B and syphilis have been offered since 2011, and modelling studies in 2015 to estimate the impact of interventions on the HBV epidemic catalysed discussions on the possibilities of enhancing tightening the HBV prevention strategy toward elimination. In 2017, comprehensive interventions for EMTCT of HBV were established in three provinces as part of pilot projects on triple elimination. In 2018, Malaysia initiated pilot projects for EMTCT of HBV in four states. In 2019, Mongolia updated its national guidelines for EMTCT to include HBV and HCV. Cambodia and Viet Nam have developed national action plans for triple elimination and Philippines and Papua New Guinea are in the process of developing national frameworks. The present guidelines will support countries in introducing and scaling up antiviral prophylaxis to further reduce mother-to-child transmission of HBV.

TABLE. 1. Key elements of the context to guide policies for the prevention of mother-to-child transmission of HBV in the six WHO regions

	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region
2015 HBsAg prevalence in the population (%)[a]	3% (2–4.7%)	0.2% (0.1–0.5%)	1.6% (1.2–2.1%)	0.4% (0.2–0.8%)	0.7% (0.5–1.6%)	0.9% (0.6–1.3%)
2017 HBsAg prevalence in under-5 children (%)[b]	2.34%	0.07%	0.69%	0.21%	0.26%	0.38%
HBeAg positivity (%) in women of childbearing age[c]	26% (21.2–30.6%)	28.3% (24.1–33.9%)	27.3% (21.6–33.9%)	27.3% (22.2–31.9%)	29.3% (21.7–36.1%)	29.3% (24.1–34.9%)
3rd dose hepatitis B vaccine coverage (range in countries)[d]	76% (25–99%)	81% (60–99%)	82% (42–99%)	84% (52–99%)	89% (78–99%)	90% (44–99%)
Coverage of timely birth dose (range in countries)[d]	4%	72% (55–95%)	33% (18–89%)	39% (60–99%)	48% (7–99%)	83% (25–100%)
ANC coverage at least once (%) their own health[e]	52.5%	89%	70%	100%	49%	80%
Births assisted by skilled birth attenådant (%)[f]	59.5%	96.5%	89%	99%	77%	96%

a Global hepatitis report. Geneva: World Health Organization; 2017

b London School of Tropical Medicine & Hygiene; 2017

c Ott JJ, Stevens GA, Wiersma ST. The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions; 2012

d WHO/UNICEF joint reporting process; 2019

e UNICEF antenatal care; EPI: Expanded Programme on Immunization; https://data.unicef.org/topic/maternal-health/antenatal-care/#status

f In the European Region, almost half of the countries do not implement universal birth dose vaccination but instead rely on targeted prevention of perinatal transmission through testing of all pregnant women and providing birth dose to children born to HBsAg-positive mothers.

ANC: antenatal care; HBIG: hepatitis B immune globulin; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; NAT: nucleic acid test; PWID: people who inject drugs; RDT: rapid diagnostic test

	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region
Country experience with peripartum prophylaxis	Very limited	6 countries	Limited	High-income countries	3 countries	9 countries
HBsAg prevalence in minority populations (indigenous, PWID, migrants)	NA (high endemicity)	Indigenous: 2–7% to >8%	-	Migrants born in high-endemicity countries	PWID: 0.8–14%	Selected key populations
Price of HBIG	US$ 150–200	US$ 18	No data	No data	US$ 70–110	US$ 10–50
Availability of HBIG	Limited in private market. Provided in tertiary care in South Africa and Namibia	Used in 22/28 countries	No data	28/43 countries reporting to WHO/ Europe survey	Available in the private sector in a few Member States	Varies across countries
Price of HBV DNA test	US$ 30–100	US$ 14–50	No data	US$ 20–70	US$ 30–50	US$ 30–100
Availability of diagnostics	RDTs available but of variable quality, some limited access to GeneXpert HBV DNA	No data on HBeAg, 19 out of 29 have access to HBV DNA, some through private sector			Available in both public and private sectors	HBV DNA available in many countries but often through centralized laboratories
EPI verification process in place	Not yet	Pilot testing	In progress	Yes	Yes	Yes

CHAPTER 5. MONITORING AND EVALUATION

5.1 Core indicators from the Global Health Sector Strategy on viral hepatitis

Prevention of mother-to-child transmission of HBV is a core intervention of the GHSS on viral hepatitis *(3)*. This core intervention consists of the timely birth dose of hepatitis B vaccine and other additional interventions, including peripartum prophylaxis. The monitoring and evaluation framework of the GHSS *(3)* includes a number of indicators that are relevant to this core intervention. Service coverage indicators include:

- third dose coverage of hepatitis B vaccine (Indicator C.3.b); and
- coverage of interventions to prevent mother-to-child transmission of HBV (Indicator C.3.a).

The impact indicator is the cumulative incidence of chronic HBV infection in children 5 years of age (Indicator C.9.a), which is also an indicator of the Sustainable Development Goals *(24)*. As chronic infection with HBV is mostly asymptomatic, the prevalence of HBsAg among children 5 years of age is a surrogate marker for the cumulative incidence of chronic HBV infection *(4)*. The reference measurement method is a biomarker survey *(4)*. However, the statistical power of biomarker surveys decreases as the prevalence decreases.

5.2 Additional indicators that can guide programme implementation

In addition to the core indicators (C.3.a, C.3.b and C.9.a), a number of indicators can facilitate programme implementation (*see* Table 2). Most of these indicators have equivalents in the monitoring and evaluation frameworks of the EMTCT of HIV and syphilis *(57)*. This would provide opportunities for synergies in data systems to improve monitoring and evaluation efforts.

Context indicators

Two indicators monitored through the Maternal and Child Health programme can provide important contextual information on the feasibility of peripartum prophylaxis to prevent mother-to-child transmission of HBV.

1. **The coverage of antenatal care** can provide information on the capacity of the health system to reach pregnant women to initiate testing for HBV infection.

2. **The proportion of deliveries attended by skilled birth attendants** can provide information on the capacity of the health system to reach infants with interventions at birth, including birth dose and HBIG.

Process/output indicators

A number of indicators can capture the sequence between initial testing, referral to care and initiation of peripartum prophylaxis. The source of information for these indicators are programme records, including antenatal care registers, in vitro diagnostics registers, maternity registers and immunization records.

1. Indicators for the testing of mothers. These include the proportion of mothers tested for HBsAg, the proportion of mothers testing positive for HBsAg and the proportion of HBsAg-positive mothers tested for HBV DNA or HBeAg.

2. Indicators for the management of mothers. These include the proportion of HBsAg-positive mothers eligible for prophylaxis and the proportion of eligible women who receive antivirals.

3. Indicators for the management of infants. These include the proportion of exposed infants receiving a timely birth dose, the proportion of exposed infants receiving HBIG, the proportion of all infants receiving a timely birth dose and the proportion of exposed infants tested for infection at 7–12 months of age.

Outcome indicator

The rate of mother-to-child transmission is the incidence of HBV infection in infants born to HBsAg-positive mothers. It is calculated by dividing the number of HBsAg-positive infants at post vaccination serological testing by the number of infants tested at 7–12 months of age (1–2 months after completion of the last dose of vaccine according to the WHO position paper on immunization). The data source is the follow up of infants born to HBsAg-positive mothers *(55)*.

Impact indicator

The impact indicator is the cumulative incidence of chronic HBV infection among children 5 years of age (Indicator C.9.a). The prevalence of HBsAg among children 5 years of age is measured in biomarker surveys *(4)*.

5.3 Measuring progress towards elimination

Service coverage indicators

Mathematical models that were developed to inform the GHSS on viral hepatitis suggested that to reach a 0.1% prevalence of HBsAg in children 5 years of age, it is necessary to attain 90% coverage for both the third dose of hepatitis B vaccine (C.3.a) and 90% coverage for the PMTCT of HBV, which can include timely birth dose with or without peripartum prophylaxis (C.3.b) *(3)*. These coverage targets should be reached by 2030.

Impact indicators

As per the GHSS on viral hepatitis, the 2020 global milestone will be a prevalence <1% of HBsAg in children 5 years of age. This can be achieved through vaccination, including a birth dose, and measured through biomarker surveys that estimate the prevalence of HBV infection among children *(4)*. Web annex 5 of these guidelines outlines the framework of an approach that can be used in regions to validate the attainment of the 1% control goal through hepatitis B immunization by 2020. This framework was developed on the basis of the verification protocols from the South-East Asia Region *(40)* and the Western Pacific Region *(41)*. It could be used in regions that do not yet have a verification framework. Achievement of the 2020 target will then pave the way for the more ambitious 2030 target of reducing the prevalence of HBV infection to 0.1%. The present guidelines define the interventions needed to achieve the 2030 target. Methods that will be used to validate elimination require additional work. As the prevalence of HBsAg in children 5 years of age decreases, the capacity to use biomarker surveys will be increasingly limited because of costs and a lack of statistical power to measure very low prevalence. Methods for validation of elimination will give a greater emphasis on the prospective follow up of children born to HBV-infected mothers. Mathematical modelling techniques could then be used to combine data from the prospective follow up of children born to HBV-infected mothers with biomarker survey data to estimate the prevalence of HBsAg in children 5 years of age.

5.4 Dissemination of the monitoring and evaluation framework

In addition to these guidelines, this monitoring and evaluation framework will be disseminated in the next version of the hepatitis strategic information guidelines, and in future guidance related to the triple elimination of mother-to-child transmission of HIV, syphilis and HBV.

TABLE. 2. Monitoring and indicator framework for the prevention of mother-to-child transmission of HBV through peripartum prophylaxis

Level	Type of indicator	Definition of the indicator for HBV PMTCT				Equivalent indicator for HIV and syphilis	
		Indicator	Numerator	Denominator	Source of data	HIV	Syphilis
Context	**ANC care**	Coverage of first ANC visit	Number of women attending at least one ANC	Number of pregnant women	Maternal and child health programme	Yes	Yes
	Deliveries	Coverage of assisted deliveries	Number of deliveries attended by a health-care worker	Number of deliveries	Maternal and child health programme	Yes	Yes
Process/ output of services	**Testing**	Proportion of women tested for HBsAg	Number of women tested for HBsAg	Number of women attending at least one ANC	Monitoring of ANC registers, in vitro diagnostics registers	Yes	Yes
		Proportion of women testing positive for HBsAg	Number of women testing positive for HBsAg	Number of women tested for HBsAg	Monitoring of ANC registers, in vitro diagnostics registers	Yes	Yes
		Proportion of HBsAg + women tested for HBV DNA or HBeAg	Number of women tested for HBV DNA or HBeAg	Number of women testing positive for HBsAg	Monitoring of ANC registers, in vitro diagnostics registers	Yes	Yes
	Management of the mother	Proportion of HBsAg + mothers eligible for prophylaxis	Number of HBsAg + women eligible for prophylaxis	Number of HBsAg + women tested for HBV DNA or HBeAg	Monitoring of ANC registers, in vitro diagnostics registers	Yes	Yes
		Proportion of eligible women who receive antivirals for prophylaxis	Number of eligible women receiving antivirals	Number of HBsAg + women eligible for prophylaxis	Monitoring of ANC registers	Yes	Yes

Level	Type of indicator	Definition of the indicator for HBV PMTCT				Equivalent indicator for HIV and syphilis	
		Indicator	Numerator	Denominator	Source of data	HIV	Syphilis
	Management of the infant	Proportion of exposed newborns receiving a timely birth dose	Number of exposed newborns receiving hepatitis B vaccine within 24 hours of life	Number of newborns born to HBsAg positive mothers	Maternity registers Immunization registers	No	No
		Proportion of exposed newborns receiving HBIG	Number of newborns receiving HBIG	Number of newborns born to HBsAg positive mothers	Maternity registers	No	No
		Proportion of all newborns receiving a timely birth dose	Number of newborns receiving hepatitis B vaccine within 24 hours of life	Number of newborns	Maternity registers Immunization registers	No	No
		Proportion of infants tested for infection at 7–12 months of age[g]	Number of infants tested at 7–12 months of age	Number of infants born to HBsAg positive mothers	Programme records	Yes	Yes
Outcome	**Rate of mother-to-child transmission**	Incidence of HBV infection in children born to HBsAg positive mothers	Number of HBsAg positive infants at post-vaccination serological testing	Number of infants tested at 7–12 months of age	Follow up of infants born to HBsAg positive mothers	Yes	Yes
Impact	**Cumulative incidence in children 5 years of age**	Cumulative incidence of HBV infection in children 5 years of age[h]	Number of HBsAg positive children	Number of children tested	Biomarker survey Mathematical modelling	No	No

ANC: antenatal care; HBIG: hepatitis B immune globulin; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus

g Children can be tested after completion of the third dose.

h The prevalence of HBsAg in children 5 years of age is a surrogate indicator of the cumulative incidence of chronic HBV infection.

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978 92 4 000270 8