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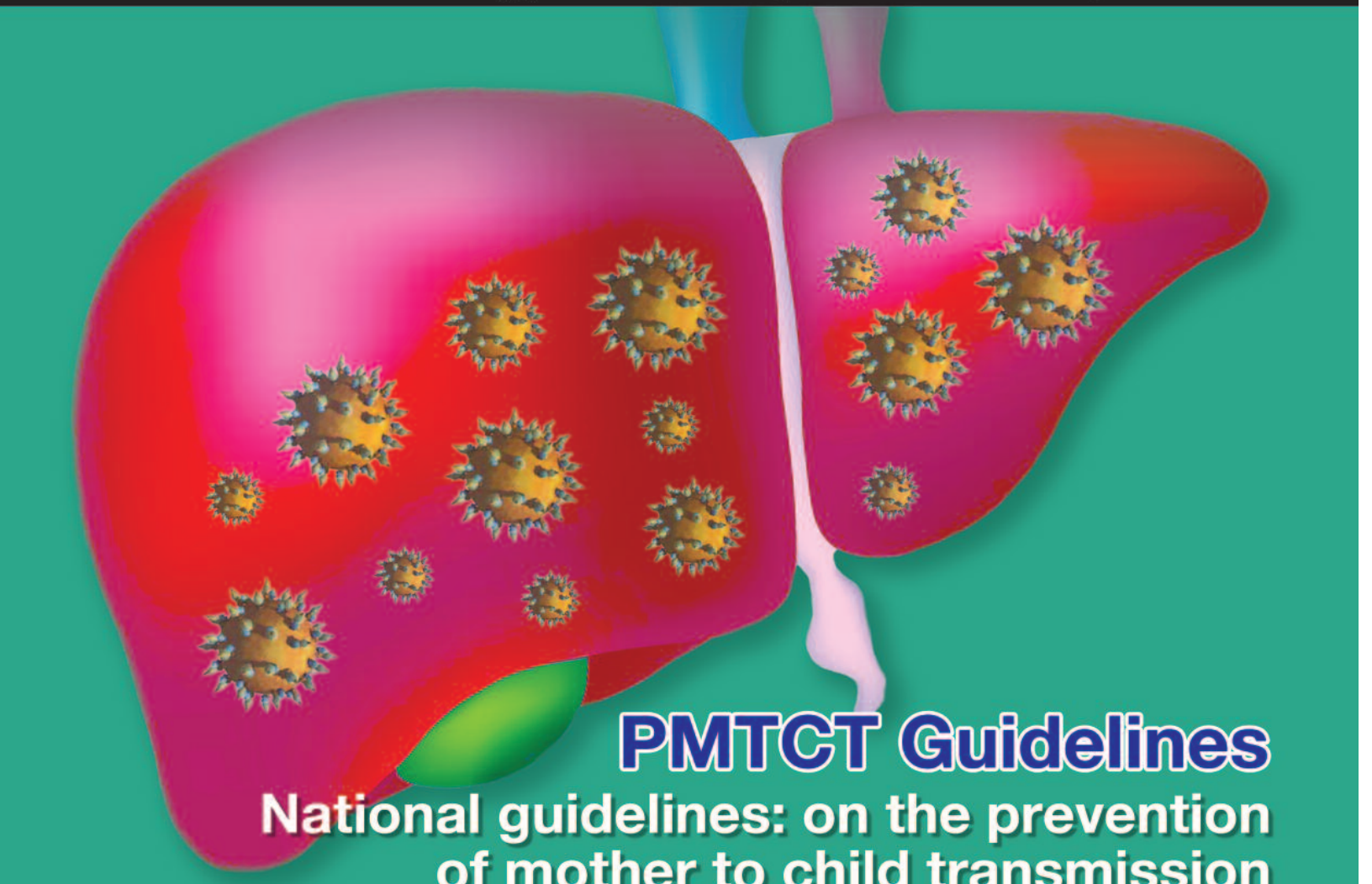

PMTCT Guidelines

National guidelines: on the prevention of mother to child transmission (PMTCT) of hepatitis B virus

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National guidelines: on the Prevention of Mother to Child Transmission (PMTCT) of Hepatitis B virus

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Abstract

Background: Hepatitis B is transmitted from the mother to the new born at the time of delivery. Once infected these children will continue to harbour the virus for life and subsequently present in adulthood as chronic liver disease and its complications. Hepatitis B vaccine given at birth followed by 2-3 additional doses given 4 weeks apart can stop this transmission.

Objective: The guidelines were developed and are being reproduced for wider dissemination to all delivery units and health care providers.

Methods: These guidelines were developed with consultation from all stake holders and technical working groups.

Recommendations: Monovalent hepatitis B birth dose vaccine should be given to all new born babies within 24 hours of birth to prevent mother-to-child transmission of HBV. Mothers having HBsAg and high viral count or detected HBeAg should be given tenofovir prophylaxis from 7th month of pregnancy till delivery. The drug is effective and safe in pregnancy and peri partum period.

Keywords: Mother to child transmission, hepatitis B immunoglobulin, hepatitis B vaccine, tenofovir, entecavir

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Executive Summary

Hepatitis B is a vaccine preventable disease which is mostly transmitted from the mother to the child at the time of birth or during first five years of life. The infection perpetuates in the liver of these infected children and subsequently presents in adulthood as chronic HBV related liver disease and its complications. As of 2015, according to global HBV data reported by WHO, there were approximately 257 million cases that had chronic hepatitis B virus (HBV) infection and about 0.9 million had died due to the disease and its complications like cirrhosis or hepatocellular carcinoma[1] To eliminate viral hepatitis by 2030, there is a need to reduce the prevalence of hepatitis B surface antigen (HBsAg) to below 0.1% in children five years of age. This can be achieved through universal immunization of new-borns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV.

In, Pakistan the, National prevalence of HBsAg in children less than five years of age in 2008 was 1.3%.[2] The serosurveys done by two larger provinces (Punjab in 2018 and Sindh in 2019) showed that the HBsAg prevalence has dropped to 0.3 in children less than five years of age.[3,4] As almost all children infected with hepatitis B virus in early childhood progress to chronic liver disease in adulthood, therefore in Pakistan, there are 500,000 people living with cirrhosis and 25,000 having HCC with yearly deaths in 12,000 cases.[5]

Use of Hepatitis B birth dose to prevent mother-to-child transmission of HBV

WHO recommends 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.[6]

In Pakistan, hepatitis B is given as a pentavalent vaccine at 6th,10th and 14th weeks of birth by the vaccinators through EPIs fixed vaccination sites. The current coverage of 3rd dose of hepatitis B is 84%. The birth dose of hepatitis B is not yet included in the EPI. There is no clarity on who

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will procure the HBV birth dose and who will give it. Since 2021, Punjab and Sindh provinces have procured hepatitis B monovalent dose from their own budget and given it to the MNCH services/PPHI for giving it at birth to all newborns in all health facilities.

Use of antivirals in peripartum period to prevent mother-to-child transmission of HBV:

The use of nucelos(t)ide analogues/ antiviral prophylaxis is effective and safe in pregnant women and in the peri partum period.

Introduction

The Situation Analysis on HBV Elimination

Globally the viral hepatitis disease burden is high with 257 million people having hepatitis B (HBV) and almost 900, 000 died due to its complications. In the Eastern Mediterranean Region (EMR) 21 million cases have HBV.[7,8] Over 85% of the HBV burden lies with Egypt, Pakistan, Somalia, Yemen and Sudan.[9] In most of these countries chronic HBV infection comes from infection acquired soon after birth or during early childhood.[10] Persons infected after the age of five years rarely develop chronic infection.[11]

Recognizing the burden of viral hepatitis in the world, in 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis. This strategy proposes the elimination of viral hepatitis as a public health threat by 2030.[12] Elimination is further defined as 90% reduction in incidence and a 65% reduction in mortality, compared with the 2015 baseline. The prevalence of HBsAg in children aged less than five years is taken as a surrogate indicator of the cumulative incidence of chronic HBV infections.[13] Using these as targets for Pakistan, we need to work on reducing HBsAg prevalence to less than 1% in children five years of age by 2020 and to less than 0.1% by 2030. To reduce the incidence of HBsAg, the hepatitis B vaccine is already included in the Pakistan's Expanded Programme on Immunization (EPI) since 2009.[14] Initially Pakistan had a monovalent hepatitis B birth dose which was replaced with the pentavalent vaccine which is given at 6th,10th and 14th weeks without a birth dose of hepatitis B vaccine. In 2017, WHO made new recommendation of 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).[15] The additional 3- 4 doses of hepatitis B vaccinations, including a timely birth dose, is the foundation on which other interventions to reduce perinatal transmission have been built (Figure).

In Pakistan, a major progress in global response to HBV infection has been made through the expansion of routine hepatitis B vaccination (2018 third dose coverage: 84%).[16]

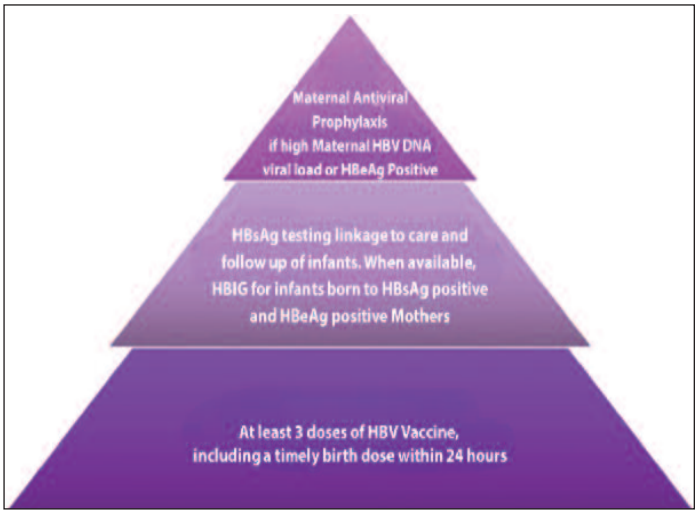

Figure: Incremental approach for prevention of HBV infection at birth and in the first years of life.

The hepatitis B birth dose coverage is 3% .[17] The HBsAg positivity in less than five years age was 1.8% in 2008 survey,[2] which has now reduced to 0.3% as reported in Punjab and Sindh surveys.[3,4] The combined prevalence therefore now is 1.6%. As majority of children less than five years of age, when infected with hepatitis B virus progress to chronic liver disease in adulthood, therefore in Pakistan, there are assumptions that 173,000 people are living with cirrhosis, 10,400 have decompensated cirrhosis, 13,500 have HCC. The incidence of cirrhosis is 16,000, decompensated cirrhosis 2500, HCC 8400. Yearly deaths due to the liver complications are 10,000 cases.[18]

The prevention of mother-to-child transmission (PMTCT)

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).[18] A timely hepatitis B birth dose given to the infant in one leg along with hepatitis B immune globulin (HBIG) prophylaxis in the other leg shortly after birth can prevent HBV MTCT in over 95% children. Maternal peripartum prophylaxis with antivirals can provide additional protection.[15] Giving HBIG to the mother does not provide any protection to the infant.[19] Very high levels of maternal HBV DNA are seen in HBeAg-positive women. These high levels are associated with high risk of HBV transmission (20% in Asia), despite vaccine prophylaxis and HBIG.[20,21] Such a transmission is less than 1% in Asia among HBeAg-negative women.[22,23] There is now evidence that the use of antivirals by mothers during pregnancy suppresses the HBV DNA levels and thus reduce the transmission of HBV to infants from HBsAg-positive women.[24] Using this evidence, it is now recommended that pregnant women with high HBV DNA levels may be considered for antiviral

prophylaxis during pregnancy to prevent perinatal HBV infection.[25,26] 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 can be used as opportunity for integrated triple elimination of mother-to-child transmission of all pathogens.[27] Almost 6.1% of women with HIV infection have co-infection with HBV,[28] therefore treating these women with Tenofovir-based antiretroviral therapy (ART) provides an additional opportunity to simultaneously treat the HBV co-infection and reduce mother-to-child transmission of HBV along with HIV.

The routine use of antiviral therapy to prevent mother-to-child transmission of HBV is not recommended. All pregnant women should first be assessed for eligibility for long-term treatment based on their health needs before initiation of prophylaxis.[29] Prophylaxis with antivirals during the third trimester of pregnancy has been found to be effective in reducing mother-to-child transmission of HBV in women having high viral load or positive HBeAg.

Objectives

The objective of these guidelines is to provide guidance on the prevention of mother to child transmission of hepatitis B virus and the use of peripartum antiviral prophylaxis in HBVDNA positive/HBeAg-positive pregnant women for the prevention of mother-to-child transmission (PMTCT) of HBV.

Target audience

The key audience for these guidelines is the officials in the Ministry of Health who are responsible for the development of national policy and guidelines related to prevention of mother-to-child transmission of HBV in Pakistan. The guidelines would also be helpful for physicians who treat persons infected with HBV as well as gynaecologists, obstetricians and paediatricians.

Related guidelines

The other guidelines on HBV prevention published by WHO have been consulted to develop these guidelines along with the materials published in Pakistan. The Pakistan society of gastroenterology (PSG) published the hepatitis B testing and treatment guidelines.[30] The Prime Minister's programme developed its guidelines[31] using the PSG guidelines and also consulting the other international guidelines. At that time apart from the prophylactic use of hepatitis B vaccine in the high risk groups there was recommendation to use oral antivirals (Lamivudine) in selected chronic HBV cases for one year. Pakistan society for the study of liver diseases (PSLD) developed management of HBV guidelines[32] and later with the support of WHO, Pakistan's National Guidelines on hepatitis B testing were developed in 2017.[33] From 2005 till 2021 there was no revision of the guidelines despite many new developments that had taken place in the diagnosis, treatment and prophylaxis of HBV. In 2021, the Punjab hepatitis programme developed their hepatitis B testing and treatment guidelines using a consultative process. These guidelines are not made public but their review show that they are made for use by the specialists and not for the hepatitis programme or the general physicians and the OBGYN consultants.

The AASLD,[34] APASL,[35] EASL[36] guidelines are more intended for use by the upper to middle income countries where testing and treatment facilities are available across the board and where access and affordability is not an issue. The WHO guidelines for the testing and treatment of persons having hepatitis B infection[29] along with the hepatitis B guidelines for the testing and treatment of pregnant women have been developed for use by all countries and they focus on LMIC where access and affordability is an issue.[33] These WHO guidelines are simple and are intended for use by the ministries of health to develop their country specific guidelines and also for use by general practitioners and the doctors in delivery units and the paediatricians. The WHO guidelines were found most appropriate for Pakistan therefore these have been used as the base with tailoring done as per country need.

These guidelines also use the WHO guidelines (2017) on hepatitis B and C,[33] guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection[29] and the WHO Guidelines on prevention of mother to child hepatitis B and C testing[35] which recommend that all pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible.

Material and methods

To develop these guidelines Provincial technical working groups (TWGs) and National TWGs were notified by the concerned ministries and nominations were received. These guidelines have been developed by the TAG through the consultation with the National hepatitis TWG, which included gastroenterologists, hepatologists, public health experts, gynaecologists, paediatricians, gynecologists, researchers, clinicians and individuals with relevant expertise. The TAG oversaw the entire guidelines development process.

The guidelines were developed through a consultative process. Federal and Provincial Technical Working Groups (TWGs) were formulated by the Federal and Provincial Health departments to work on the guidelines. The TWGs were composed of the experts from hepatitis control

programmes, expanded programme on immunization, gynaecology, paediatrics, epidemiology and representatives from federal and provincial health departments.

All published material on hepatitis B in pregnant mothers, neonates and mother to child transmission was searched on the internet. Local published reports were searched from the ministries while scientific reports were retrieved from the gastroenterology and the hepatology societies of Pakistan. Local literature was searched using the Pub med and the grey literature from news reports and presentations was also collected. AASLD, APASL and WHO guidelines were also used as a reference in 2021. As WHO guidelines were found to be more suitable for Pakistan, therefore their recommendations were used as the base for Pakistan's national hepatitis B guidelines for the prevention of mother to child transmission and for the use of antivirals in the peripartum period. The draft guidelines were shared with the Federal and Provincial TWGs for their input and feedback in a series of consultative meetings. Based on the feedback received from TWGs, the final draft was developed. The final draft was shared and approved in a consultative (online) meeting by the TWGs in 2022.

Recommendations
Immunization:

- ❖ All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.;
- ❖ Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for EPI, and reporting and monitoring systems should be strengthened to improve the quality of data on the hepatitis B birth dose.;
- ❖ The birth dose should be followed by 2 or 3 doses to complete the primary series.

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

- ❖ Pregnant women testing positive for HBsAg with an HBV DNA ≥5.3 log10 IU/mL (≥ 200,000 IU/mL) should receive Tenofovir prophylaxis from 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.

Costs of Tenofovir and diagnostics
Tenofovir is available for PKR 800-1000/month. The current market price for quantitative HBV DNA testing varies from PKR 13,000- 15,000/test. The best current market price for laboratory based HBeAg testing is PKR 1200-1800 (ELISA) and there is no WHO prequalified HBeAg rapid test available in Pakistan.

In settings where 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

- ❖ In settings where 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*3
- ❖ Compared to HBV DNA, HBeAg has high sensitivity but lower specificity for predicting the risk of mother-to-child transmission.

*3The performance of HBeAg testing suggests that is an acceptable alternative to diagnosing HBV DNA≥5.3IU/mL

Key Recommendations on

1. Infant Vaccination:

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.

2. Testing of pregnant women for HBsAg, HIV and syphilis:

a) All pregnant women should be tested for hepatitis B surface antigen (HBsAg)*1 HIV and syphilis at least once and as early as possible in the pregnancy.

3. Tenofovir prophylaxis to prevent mother-to-child transmission of HBV:

a) Pregnant women testing positive for HBsAg and having HBV DNA≥ 5.3 log10 IU/mL*2 should 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.

4. 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:

a) Settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative

Table: Monitoring and indicator framework for the prevention of mother-to-child transmission of HBV through peripartum prophylaxis by WHO.

Level	Type of Indicator	Definition of the indicator for HBV PMTCT				Equivalent for HIV Indicator and Syphilis	
		Indicator	Numerator	Denominator	Source of Data	HIV	Syphilis
Context	ANC Care	Coverage of first ANC visit	Number of women attending at last one ANC	Number of pregnant women	Maternal and child health program	Yes	Yes
	Deliveries	Coverage of assisted deliveries	Number of deliveries attended by a health care worker	Number of deliveries	Maternal and child health program	Yes	Yes
Processing/ output of Services	Testing	Proportion of women tested for HBsAg	Number of women tested for HBsAg	Number of women attending at least of 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
	Management of the Mother	Proportion of HBsAg + mothers eligible for prophylaxis	Number of women tested for HBVDNA or HBeAg	Number of women testing positive for HBsAg	Monitoring of ANC register, in vitro diagnostics registers	Yes	Yes
		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
	management of the infants	Proportion of exposed newborns receiving a timely birth dose	Number of exposed newborns receiving hepatitis B vaccine within 24 hours of life	Number of newboms born to HBsAg positive mothers	Maternity registers immunization	No	No
		Proportion of exposed newborns receiving HBIG	Number of newboms receiving HBIG	Number of newboms born to HBsAg positive mothers	Maternity registers	No	No
		Proportion of all newborns receiving a timely birth dose	Number of newboms receiving Hepatitis B Vaccine within 24 hours of life	Number of newboms	Maternity registers Immunization registers	No	No
		Proportion of infants tested for infection at 7- 12 months of age *a	Number of infants tested at 7-12 months of age	Number of infants born to HBsAg positive mothers	Program records	Yes	Yes
Outcome	Rate of mother to child transmission	Incidence of HBV infection in children bom to HBsAg positive mothers	Number of HBsAg positive infants 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 *b	Number of HBsAg positive children	Number of children tested	Biomarker survey Mathematical modelling	No	No

ANC = Antenatal Care, HBIG = Hepatitis B Immunoglobulin, HBeAg = Hepatitis B Surface Antigen, HBeAg – Hepatitis B Envelop Antigen.

*a Children can be tested after completion of the third dose.

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

to HBV DNA testing to determine eligibility for Tenofovir prophylaxis to prevent mother-to-child transmission of HBV. *3

*1. Particularly in settings with a ≥ 2% seroprevalence in general population; *2.HBV DNA ≥ 5.3 log10 IU/mL is equivalent to ≥ 200,000 IU/mL; *3. The performance of HBeAg testing suggests that is an acceptable alternative to diagnosing HBV DNA ≥ 5.3 log10 IU/mL

WHO recommendations: WHO recommends that for countries that implement the PMTCT may use the following monitoring and indicator framework for the prevention of mother to child transmission of HBV through peripartum prophylaxis. (Table)

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