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WORD COUNT 8918
TIME SUBMITTED 19-AUG-2024 03:08PM
PAPER ID 111151389

Name of Journal: *World Journal of Experimental Medicine*

Manuscript NO: 95960

Manuscript Type: REVIEW

Exploring the impact of Hepatitis B Immunoglobulin and antiviral interventions to reduce vertical transmission of Hepatitis B Virus

HBV vertical transmission

Abstract

Hepatitis B Virus (HBV) infection is a major public health burden. In HBV endemic regions, high prevalence is also correlated with the infections acquired in infancy through perinatal transmission or early childhood exposure to HBV, the so-called mother-to-child transmission (MTCT). Children who are infected with HBV at a young age are at higher risk to develop chronic HBV infection than those infected as adults, which may lead to worse clinical outcome. To reduce the incidences of HBV MTCT, several interventions for the infants or the mothers, or both, are already carried out. This review explores newest information and approaches available in literature regarding HBV MTCT prevalence and its challenges, especially in high HBV endemic countries. It covers HBV screening in pregnant women, prenatal intervention, infants' immunoprophylaxis, and post-vaccination serological testing for the children.

Key Words: hepatitis B virus; hepatitis B immunoglobulin; mother-to-child transmission; vertical transmission; antiviral prophylaxis

Core Tip: Mother-to-child transmission (MTCT) of the Hepatitis B Virus is still a problem in HBV endemic countries. This review explores newest information and approaches available in literature to overcome MTCT and its challenges, including screening of pregnant women, prenatal intervention, infant's immunoprophylaxis, and post-vaccination serological testing.

INTRODUCTION

Hepatitis B Virus (HBV) infection continues to be a leading cause of morbidity and mortality worldwide. HBV infection causes a wide range of disease manifestations and clinical outcomes from acute asymptomatic to chronic hepatitis B (CHB). Despite the availability of safe and effective vaccines to control the viral transmission, more than two billion people in the world are estimated to be affected by HBV infection[1]. CHB leads to long-term inflammation and liver damage that can progress to serious liver

diseases, including liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[2]. Currently, over 292 million people globally are chronically infected with hepatitis B. Additionally, an estimated 58 million people have occult hepatitis B infection (OBI). This CHB causes significant health problems, leading to over 880,000 deaths annually from cirrhosis and HCC[3].

CHB is estimated to affect 4.1% of people worldwide across all age groups. CHB prevalence varies notably in different regions according to the Global Burden Disease Study 2019[4]. In Africa, the HBV infection rate is particularly high, with estimated 6.5% of the population affected. The Eastern Mediterranean and Southeast Asia regions also face considerable challenge, with 3.1% of its population living with CHB. Meanwhile, in the European and Americas regions, the prevalence is relatively lower at 1.1% and 1.2%, respectively[4].

As home of more than half of the global population, the Asia-Pacific region has the highest number of deaths due to HBV. CHB was a major cause of death from cirrhosis in the Asia-Pacific region in 2015. Also, in that year, more than two-thirds of all cases of acute viral hepatitis in the world occurred in this region[5]. Most of the burden of HBV-related diseases in the Asia-Pacific region is mainly due to the infections acquired in infancy *via* perinatal transmission or early childhood exposure. Children who are infected with HBV at a young age are much more likely to develop CHB than adults. The risk of CHB infection is highest in infants who are infected in the first year of life (80–90%) compared to children infected between 1 and 5 years of age (30–50%) and people who are infected as adults (< 5%)[6,7].

There is limited accurate and large-scale data on the prevalence of hepatitis B surface antigen (HBsAg) in pregnant females in the Asia-Pacific region[7]. Varying rates of HBsAg positivity in pregnant women have been reported, from 0.1–1.0% in Japan, 3% in South Korea, 4% in Mongolia, and up to 6% in China. In the Western Pacific region, perinatal transmission is estimated to cause 180,000 new HBV infections in infants each year[8]. A study in Indonesia found that 2.76% of nearly 70,000 pregnant women across 12 provinces had HBV infection in 2015. The prevalence was found lowest in West

Sumatra (1.6%) and highest in West Papua (8.0%)[9]. In addition, a study of pregnant women conducted in 37 midwifery clinics and one private obstetric clinic from July 2018 to April 2019 in Bandung, West Java, Indonesia found that 6.1% were HBsAg seropositive[10]. A review of studies conducted across Southeast Asia and the Western Pacific regions between 1983 and 2016 found that the prevalence of HBsAg in children born to mothers who were also hepatitis B e antigen (HBeAg) seropositive ranged from 2.7% to 53.0%[11].

Managing hepatitis B in pregnant women requires careful consideration for both the mother's health and the risk of viral transmission to the infant. The World Health Organization (WHO) has established global targets to eliminate viral hepatitis as a significant public health threat by 2030. These goals include (1) reduction of new chronic HBV infections by 90% (which means less than 0.1% of 5-year-olds with HBsAg seropositive); (2) increase the coverage of the hepatitis B vaccine birth-dose (HepB-BD) within 24 hours of birth (to protect the newborns) by 90%, and (3) increase completion of the full hepatitis B vaccine series (HepB3) in infant by 90%[12].

HBV VERTICAL TRANSMISSION ROUTE

Mother-to-childtransmission (MTCT) of HBV involves the transfer and reproduction of HBV fromthe mother to the child, resulting in the generation of new viral particles[7].The HBV vertical transmission is defined as thetransfer of infection from mother to child either during pregnancy, childbirth,or after delivery[1], as depicted in **Figure 1**.

While thespecific prevalence of transmission routes remains uncertain, delivery-relatedtransmission appears to be the primary cause of vertical transmission. Notably,the presence of HBeAg and high HBV DNA viral load (VL) in mothers aresignificant risk factors for mother-to-infant transmission[13]. After theavailability of hepatitis B immunoglobulin (HBIG) and effective hepatitis B vaccine (HepB), the rates of MTCT inchildren born from mothers with CHB, whether they are HBeAg

seropositive or seronegative,have decreased dramatically to approximately 4–10% and less than 0.1%,respectively [14,15].

Prenatal transmission

HBV transmission during pregnancy refers tointrauterine transmission. The risk factors for HBV intrauterine transmissionare still poorly understood. Various reports have identified potential factors associated with intrauterine transmission of HBVincluding method of delivery, prior abortion history, antepartum hemorrhage,and maternal HBV DNA load, although with conflicting results [16–18].The intrauterine HBV infection rate is found to be linearwith the maternal serum HBsAg titers and HBV DNA concentrations[17]. There areseveral mechanisms that would allow for intrauterine HBV transmission, theseinclude viral infection of the placenta, maternal HBeAg positivity,extrahepatic reservoirs, transplacental leakage and the impact of medicalprocedures.

Viral infection of the placenta

The placenta typically protects against thetransmission of blood-borne pathogens to the fetus. However, several studieshave reported the presence of HBV particles, HBsAg, and HBV DNA, in the fourdistinct layers of placenta, with varying rates of HBVinfection among the different layers[21]. The rate of HBV infection diminishes gradually withinthe maternal-to-fetal placental layer, with HBV detection rate in deciduacells, trophoblastic cells, villous mesenchymal cells, and villous capillaryendothelial cells was 55.4%, 51.0%, 46.5%, and 29.9%, respectively [21].HBV was also present in both the endothelial cells of the villous capillariesand the trophoblasts within the placenta, supporting the theory that the breachof the placental barrier as one of the pathways for intrauterine infection[17,22].Thus, HBV has the potential to breach the placental barrier, leading to viral infectionand replication across various types of placental cells prior to reaching thefetus[23].The rates of HBVinfection in the placentas increase following the age of pregnancy. The HBV infection rates

during the first trimester,second trimester, and full-term were found to be 4.2%, 16.6%, and 44.6%,respectively [24].

Maternal HBeAg positivity

More recent research hasidentified maternal HBeAg positivity and high HBV DNA VL as the most criticalrisk factors for HBV vertical transmission. In a study by Xu *et al.*,maternal HBeAg positivity, HBsAg titer, and HBV DNA level were observed to bethe risk factors for transplacental HBV transmission[17].A more recent study had also shown that the placentalinfection rate is higher in HBeAg-positive mothers compared to theHBeAg-negative group (odds ratio (OR) 15.56, 95%CI 2.5-95.7), in addition,placental infection is significantly related to intrauterine transmission ofHBV (OR 4.6, 95%CI 2.29-9.4)[25]. Thus, HBeAgpositivity in mothers might indicate for increase intrauterine transmissionrisks for the infant. However, Chalid *et al*. noteda noteworthy discovery of 3.1% occurrence of high HBV DNA level (> 5.3 Log_{10}copies/mL) in cord bloods of HBeAg seronegative mothers, indicating for thelimited effectiveness of HBeAg detection in predicting intrauterinetransmission [26].Thus, relying solely on HBeAg status to predict intrauterine transmission isnot sufficient. Other factors, such as HBV DNA levels and placental infectionrates, also play a crucial role in transmission risk, indicating the need for amore comprehensive approach to assessing and managing HBV transmission riskduring pregnancy.

Extrahepatic reservoirs

Extrahepaticreservoirs and germlines infection also increase the risk of HBV prenataltransmission. Peripheral blood mononuclear cells (PBMCs) might serve asextrahepatic reservoirs since HBV DNA has been detected in these cells. A 2015study showed that infants born to HBV DNA-seronegative but HBV DNA-positivePBMCs mothers have a 5-fold higher risk for HBV infection compared to thoseborn to mothers with HBV DNA-negative PBMCs[27]. HBV presence in germline cells has also been shown[20]. In CHB male patients, HBV may be present as either freeviral particles in

the seminal plasma or as integrated DNA in the genome ofspermatozoa[28]. This HBV presence has been associated with adverseeffects on the motility and fertilizing abilities of sperms and may even inducechromosome aberration during embryo development due to the high incidence ofintegrated viral DNA[29]. In CHB female patients, HBV has been shown to infectovum at different stages of development and may even replicate within the ovum[30]. HBV expression in the oocyte has been associatedwith HBV DNA level and infection status of the mother[31]. Despite all these findings, there is still limitedunderstanding on whether HBV-infected germlines from the parent can be passeddown directly to the infant.

Transplacental leakage and the impact ofmedical procedures

Transplacentalleakage may occur when the placental barriers are ruptured, which allows fordirect exchange between the fetal and maternal blood. This might occur in theperiod of early pregnancy due to the immaturity of placenta. Thetransfer of HBeAg-positive maternal blood across the placenta, which can betriggered by uterine contractions during pregnancy or disruptions in placentalbarriers (such as threatened preterm labor or spontaneous abortion), is aprobable pathway for HBV intrauterine infection.

Invasive medical procedures, such as amniocentesis and chorionicsampling during pregnancy have also been reported to increase the risk of HBVprenatal transmission[20]. Amniocentesis has been shown to significantlyincrease the rate of MTCT (OR 21.3, 95%CI 2.90-153.775) on studies in HBsAg-and HBeAg-positive mothers with very high HBV DNA level (³ 7 Log_{10} copies/mL)[32]. Needle penetration during amniocentesis can damagechorionic villi, leading to the mixing of maternal and fetal blood, and maycause bleeding from fetal-maternal capillaries within the fetal membranes[23]. These studies indicated that in pregnant motherswith high HBV DNA VL, amniocentesis procedures should not be encouraged or onlybe considered after proper risk and benefit assessment to reduce viraltransmission rate to the infants[19,33].

A recent case reportstudy assessing the impact of fetal blood sampling during pregnancy on MTCTrate showed that, like amniocentesis, fetal blood sampling in HBsAg-positivewomen also increased the risk of MTCT. Performing fetal blood sampling forprenatal diagnosis prior to postnatal immunoprophylaxis could heighten thelikelihood of intrauterine HBV infection because of potential placentaldisruption and maternal blood contamination[34,35]. This was evident by persistent HBsAg positivity upto 12 months in the infants born from untreated, HBeAg-positive, and high HBVDNA VL mothers. Meanwhile, the infants born from antiviral-treated,HBeAg-positive, and high HBV DNA VL mothers showed HBsAg seronegative and antibodyto HBsAg (anti-HBs) seropositive status until the end of the follow-up period[36]. More studies are warranted to verify these findingssince the study has a very low sample count.

Perinatal transmission

Infection duringchildbirth may arise due to micro transfusion between the mother and fetus oringestion of infectious fluid[37].A previous study had shown the presence of HBsAg in a significant proportion inboth vaginal epithelial cells (55–98%) and cervicovaginal cells (12%), alongwith detectable HBV DNA[38].Moreover, HBsAg was detected in amniotic fluid samples (26%) and vaginal fluidsamples (96%)[39].These findings suggest that direct exposure to infective fluids in the maternalgenital tract could be a possible route of HBV transmission to infants[38,39].

Several studies have exploredthe impact of delivery mode on HBV transmission risk. Findings from a 1988 studyin China showed that among 447 infants born to HBsAg-positive women, around 25%of those delivered vaginally were infected with HBV at birth, compared to lessthan 10% of those delivered *via* cesarean section[40].However, a later study found that the incidence of CHB among infants who were bornby spontaneous vaginal delivery, either with the use of forceps or vacuumextraction, and by cesarean section and who had received HBIG dan HepB vaccinationdid not differ significantly, at 7.3%, 7.7%, and 6.8%, respectively. Thesefindings indicate that the

cesareansection mode of delivery was not sufficient to decrease the MTCT rate,particularly in the occurrence of possible immunoprophylaxis failure [16].However, performing elective cesarean sections for HBeAg seropositive mothers withpre-delivery HBV DNA levels of ≥ 6 Log_{10} copies/mL might decrease the risk of viral transmissionfrom mother to child [41].

Post-natal transmission

In late 1980, Wong *etal*. first reported that breastfeeding poses a significant concern forpostpartum HBV transmission, with detected HBsAg in 72% of breast milk samples [39].However, a more recent study by Chen *et al*. suggests that while HBsAg,HBeAg, and HBV DNA are present in both colostrum and breast milk, there is no concreteevidence that breastfeeding increases the risk of HBV MCTC. Their study also foundthat the prevalence of HBsAg in breastfed infants was 1.5%, compared to 4.7% informula-fed infants, with no significant statistical difference[42].These findings suggest that the risk of viral transmission through breast milkis minimal, compared to the risk posed by direct exposure to maternal blood orfluids during delivery. Several hepatitis experts have also evaluated thepotential danger posed by a significant daily intake of breast milk for theinfant, given the delicate condition of the gastrointestinal mucosa and theincomplete development of the digestive tract[43].However, as of now, there has not been any evidences showing an elevated riskof viral transmission through direct contact with bleeding nipples or opensores on the breast, especially when appropriate immunoprophylaxis has been administeredat birth[33,44,45].

CURRENTSTRATEGIES TO REDUCE MTCT RATE

Strategy of MTCT elimination differsbetween different geographical regions, thus, it is important to understand thespecific circumstances on each region to find solutions in local context toeliminate HBV infection[46,47]. Differentstrategies may be adopted to reduce and prevent risks of HBV MTCT. Theseapproaches may include targeted intervention only for the infants or the mothers.However, concerted actions for both the

infants and the mothers are believed tobe more effective in reducing the vertical viral transmission rate. There are fourgeneral approaches that need to be included in any HBV MTCT prevention program,especially in high HBV endemic countries: (1) screening of pregnant women; (2) prenatalintervention on the pregnant women; (3) timely infant's immunoprophylaxis, and(4) post-vaccination serological testing for the children[46,47].

Screening of pregnant women

Screening for HBV infection duringpregnancy would be necessary to identify mothers whose infants are at risk ofperinatal transmission. Detection of HBsAg has been demonstrated to be an economicalapproach and easily applicable even in areas with limited resources. Indeed,HBsAg detection by qualitative rapid detection test is commonly used for HBVscreening programs in pregnant women in Asia and Africa [48–50]. Detection of HBVDNA VL, by quantitative PCR assay, however, can provide a more accurate pictureof the maternal HBV infection status. In addition, HBV DNA VL can also be usedto identify which mothers need antiviral prophylaxis since high maternal HBVDNA level has been identified as a significant risk factor for HBV MTCT[51,52].

Since HBV DNA VL quantification is morecostly and needs a proper instrument set-up, the method is inefficient to use particularlyin areas with few resources, thus not many HBV screening programs recommend forits use[53]. Alternatively, detectionof other HBV serological markers, HBeAg and quantitative HBsAg levels, have beenidentified as possible surrogate markers for HBV DNA level detection inpregnant women. HBeAg is a marker for viral replication, thus HBeAg detectioncan help to identify high-risk pregnant women in a resource-limited setting. Inaddition, a meta-analysis study has shown that HBeAg detection was accurate inclassifying women with high HBV DNA titers (> 5.3 Log_{10} IU/mL),with sensitivity of 99.5% (95%CI 91.7-100) and specificity of 62.2% (95%CI 55.2-68.7),respectively[54].

Additionally, the use of quantitative HBsAgdetection in areas of limited resources is also encouraged. A 2016 study hasshown a positive correlation between maternal

serum quantitative HBsAg level withHBV DNA VL, which can accurately predict maternal HBV DNA level, particularlyin those having high VL levels (6–8 Log_{10}IU/mL)[55]. A more recentstudy showed that maternal serum quantitative HBsAg level was also stronglycorrelated with HBeAg status, with higher quantitative HBsAg level in the HBeAgseropositive group compared to the HBeAg seronegative (3.88 *vs* 2.86 Log_{10}IU/mL). Serum quantitative HBsAg level can also be used to predict HBVinfection in the placenta (with 90% sensitivity and 83% specificity) andumbilical blood cord (with 82% sensitivity and 96% specificity). Therefore, maternalserum HBsAg level can be used as a surrogate test for HBeAg and HBV DNA VLtests in pregnant women with HBV infection[25].

Prenatal intervention

HBIG is a purified solution of humanimmunoglobulin containing high titers of anti- HBs. HBIG is widelyadministered to neutralize hepatitis B viruses rapidly by activating thecomplement system and strengthening the humoral immunity. Prenatal injection ofHBIG to pregnant women, theoretically could prevent intrauterine infection bytransferring maternal antibodies to the fetus. HBIG injection to the CHBmothers (either HBsAg seropositive or HBeAg seropositive) will offer protectionto the infants through passive diffusion of the antibody through the placenta.The effect of this antibody passive diffusion is found greatest during the lasttrimester of the pregnancy[63].

A meta-analysis study in 2017 showed thatHBIG administration was effective in preventing hepatitis B occurrence innewborn infants born from mothers with HBsAg- and HBV DNA-positive[63]. However,another study found that HBIG administration alone could not prevent MTCT,especially in mothers with high HBV DNA viral load[64]. Since there is anadditional potential risk of immune complex disease due to the specific bindingof HBIG to HBsAg, the European Association of the Study of The Liver (EASL)still does not consider the use of HBIG in HBsAg-positive mother[65].

Instead of administering HBIG in the third trimesterof pregnancy, antiretroviral therapy (ART) might be a better choice to preventMTCT. The use of ART has been widely accepted and applied in clinical practice settingsand shows a good result in blocking HBV vertical transmission from mother toinfant. It has been reported that antiviral therapy on mothers with high HBVDNA VL (³ 7 Log_{10} IU/mL) significantly reducedthe rate of MTCT from 14.3% to 0%[66]. Several typesof nucleos(t)ide analogue (NA) drugs including lamivudine (3TC), telbivudine (LdT),and tenofovir disoproxil fumarate (TDF) have been used in CHB pregnant women tostudy the safety and efficacy of these antiviral prophylaxes for the mothersand the infants to reduce HBV MTCT rate [60–62].

Antiviral prophylaxisfor CHB pregnant women has now been recommended by the three major liver studyassociations, the Asia Pacific Association for the Study of the Liver (APASL), EASL, and theAmerican Association for the Study of the Liver (AASLD). The APASL hasrecommended that pregnant females with HBV DNA levels ³5.3 Log_{10} IU/mL should receive antiviral prophylaxis to preventMTCT. TDF is the recommended antiviral prophylaxis, which should be initiatedat 24-28 weeks of the gestation period, in addition to appropriateimmunoprophylaxis for the infants[7].Similarly, the EASL also advised for TDF treatment as antiviral prophylaxis forpregnant women with HBV DNA levels of ³5.3 Log_{10} IU/mL or HBeAg-positive at week 24-28 of gestation period whichshould be continued for up to 12 weeks after delivery[65].The AASLD specifically recommend the use of TDF to prevent the risk of MTCT inHBsAg-positive pregnant women with high HBV DNA levels (³5.3 Log_{10} IU/mL) and to minimize the risk of emergence of viralresistance during the treatment. However, AASLD discouraged the use of ART toreduce the risk of perinatal HBV transmission in HBsAg-positive pregnant womenwith low HBV DNA levels (< 5.3 Log_{10} IU/mL)[33].

In line, WHO had justreleased their new guidelines for CHB infection prevention, diagnosis, care,and treatment, and updated their recommendation for antiviral prophylaxis forpregnant women. To prevent MTCT of HBV, TDF treatment is

recommended for highHBV VL (³5.3 Log_{10} IU/mL) or HBeAg-positive, HBsAg-positive pregnant women, starting from thesecond trimester of pregnancy until delivery or until completion of vaccinationin the infants. In the case where testing of HBV DNA and/or HBeAg is lacking,TDF treatment for all HBV-infected (HBsAg-positive) pregnant women isrecommended[59].

A 2019 meta-analysis study had compared theeffectiveness between 3TC, LdT, and TDF in reducing MTCT rate. They showed thatonly LdT treatment was associated with reduced rate of HBsAg positivity ininfants; and higher rates of HBeAg loss, reduced HBV DNA levels, andnormalization of ALT levels in mothers. None of the NA drugs treatment wereassociated with any preterm birth, congenital malformation, or low birthweight. Furthermore, LdT treatment also significantly lowered both the MTCT rateand infants' HBV DNA positivity at birth, and increased HBV DNA level suppressionin mothers[67]. A 2020real-world study had also compared the efficacy and safety of 3TC and LdTtreatment in more than 2,000 pregnant mothers with high HBV DNA levels (> 6 Log_{10} IU/mL) in China to preventMTCT. They found that antiviral treatment, either with 3TC or LdT, which wasinitiated in the third trimester, greatly reduced the MTCT rate compared tountreated mothers. There were also no differences in perinatal complicationsfor the mothers and growth parameters for the infants[68]. These resultsindicate for the recommended use of LdT treatment for CHB pregnant mothers toprevent MTCT. However, there are raised concerns regarding the low geneticbarrier of LdT, which may allow for the emergence of viral resistance-associatedmutations[7]. As such, NAdrugs treatment history in pregnant women is crucial to determine which type ofdrugs can be administered. In treatment-naïve pregnant mothers, 3TC or LdTtreatment is preferred, since antiviral resistance to 3TC or LdT is rare due tothe brief length of the drug exposure. However, in treatment-experienced subjects,TDF treatment is more advisable due to its favorable resistance profile.Furthermore, TDF has demonstrated a good long-term fetal safety profile[65].

Recently, more studies are comparing theefficacy and safety of TDF treatment in pregnant mothers. A 2020 observationalstudy in 644 pregnant women with HBeAg-

positive and high HBV DNA VL (≥ 5.3 Log_{10} IU/mL), showed that treatmentwith LdT and TDF significantly lowered maternal HBV DNA level at times of delivery,with an average decrease of two log_{10} IU/mL, thus consequently reducedthe MTCT rate. No adverse events were observed, thus both NA drugs are safe formothers and newborns. In addition, pregnant women that were treated with TDF inthe second trimester showed an even more significant reduction of HBV DNA levelcompared to those treated in the third trimester. This study showed that TDF hasbetter efficacy than LdT in reducing maternal HBV DNA levels[69]. Regarding HBVgenetic diversity, a 2022 Chinese study had demonstrated that HBV genotype maybe associated with response to antiviral treatment in pregnant women, asmeasured by changes in the HBV DNA level. HBV genotype has been identified asan independent factor related with the change of HBV DNA level, but not HBV RNAlevel, after antiviral treatment (either with LdT or TDF)[70].

Despite the good safety profile of TDF, theuse of TDF has been correlated with kidney and bone loss problems. Therefore,another form of tenofovir, tenofovir alafenamide fumarate (TAF) is alsocurrently used to manage HBV infection. However, there are still limited dataon the effect of TAF treatment in pregnant mothers with CHB. Early prospectiveobservational study had studied the effect of TAF treatment during pregnancy in232 CHB mothers with high HBV DNA VL (≥ 5.3 Log_{10}IU/mL) in preventing MTCT. In comparison with TDF, TAF treatment waswell tolerated with similar safety profiles for the mothers and infants.Overall, both TAF and TDF treatment in the study cohort resulted in a reducedrate of MTCT to 0%[71]. These results indicate that TAF can also besafely used for antiviral prophylaxis in CHB-pregnant mothers.

Additionally, a systematic review study in2023 had found that there is no significant difference in the safety andefficacy of TDF and TAF treatment in highly viremic CHB pregnant women. Both NAdrug treatments resulted in significant reductions of maternal HBV DNA levelsduring delivery and MTCT rate to 0%[72]. Another recentmeta-study has also concluded that TAF treatment showed good efficacy as

otherantiviral prophylaxis in reducing MTCT rates with good safety profiles in bothmothers and infants[73].

Infants' immunoprophylaxis

Infants are more vulnerable to HBVinfection. Infants who contracted HBV infection during their first year of lifeare more likely to develop CHB. Several prevention strategies, such as activeand passive immunoprophylaxis, can protect the infants from HBV infection. Activeimmunoprophylaxis is given through HBV vaccination, while passiveimmunoprophylaxis is obtained through HBIG injection shortly after birth. Overall,the percentage of children under five years old with CHB has now decreased,from 5% in the pre-vaccination era (1980s–2000s) to around 1% in 2019[74]. These numbers representa noteworthy progress in the global effort to reduce HBV infection in children.

Some studies have shown that infantimmunization can effectively prevent MTCT. Regardless of the mother's HBVstatus, the WHO guideline advises that all newborns should receive HepB-BDwithin 24 hours after birth, followed with additional doses at months one and sixof age. HBIG is also recommended to be given to infants of HBsAg-positivemothers[46,47]. However, the implementationof the guidelines may differ regionally, based on the HBV prevalence in thatregion. In China, with high prevalence of HBV infection, the implementation ofthree doses of HepB vaccination for infants born to HBsAg-positive mothers isreported to result in significant decrease of MTCT risk up to 95%[75]. Meanwhile, inlow-prevalence HBV regions in Europe including Germany, Ireland, theNetherlands, and the United Kingdom, the HepB-BD is typically administered toinfants between the ages of six to nine weeks[76].

Theeffectiveness of HepB-BD vaccine can be seen in the Americas and Europeancountries. In the Americas region, 57% of the countries have a national plan in place forviral hepatitisprevention, treatment, and control.They have alsoimplemented infant vaccination programs for over 20years. The region is considered successful in eliminatingMTCT of HBV, as evidenced by the very low prevalence (< 0.1%) of

hepatitis B in children under five years old.In addition, thethree-doses vaccination coverage rate for below one-year-old children was 87%, with birth dose vaccination coverage rate of76% in 2017[77].

Europeancountries also made significant progress toward hepatitis B control between year2016 and 2019. Out of the 53 countries in the European region, the number of countries that have achieved the coveragetargets for Hep-BD, all three doses of the hepatitis B vaccine, and HBV screeningin pregnant women are 35, 19, and 17, respectively. Italy and the Netherlandsare the first two countries in Europe who are validated by WHO as being successfulin their hepatitis B control program, with HBsAg prevalence £ 0.5% among the vaccinatedcohort [77,78].

The efficacy of HBIG injection in preventingHBV infection in infants remains controversial. HBIG administration was shownto reduced MTCT in infants of HBsAg seropositive women compared to nointervention (6% *vs* 21%, risk ratio (RR) 0.30, 95%CI 0.20-0.52)[46,47,63]. However, severalstudies in infants born to both HBsAg seropositive and HBeAg seronegativemothers had shown that addition of HBIG injection to HBV vaccination dose didnot provide additional protective effect compared to HBV vaccination alone[79,80]. Another studyhas also corroborated these findings, where they found that in infants bornfrom HBeAg seronegative mothers, HBV vaccination alone is sufficient andeffective in reducing the rate of MTCT without the addition of HBIG injection[58]. Since HBeAg isnot routinely tested in HBsAg seropositive pregnant women, HBIG injection wouldstill be beneficial for infants born of these women, especially in high HBVprevalence area, to reduce cases of infantile fulminant hepatitis[81]. In Taiwan, thegovernment still encourages for HBIG injection in infants of HBsAg seropositivemothers, regardless of the maternal HBeAg status, since the cost of HBIG isconsidered as cheaper than HBeAg testing[81].

The protective effect of HBIG injection mayalso relate to the time of administration. A few studies had demonstrated thatearlier immunoprophylaxis administration may provide a greater protectionagainst MTCT. In a 2021 study in China where both HBIG and HepB-BD wereinjected in newborns within an hour after delivery, the overall

MTCT rate was0.9%[82]. Similarly, arecent study also confirmed the vital role of the administration time ofcombined immunoprophylaxis (both HBIG and HepB-BD) for infants born to CHBmothers. Infants that were administered combined immunoprophylaxis within twohours of birth have an MTCT rate of 0.32% (1/308) compared to 2.73% (8/293) inthose who received theirs between two and 12 hours after birth[83].

A raised concern about the use of HBIGimmunoprophylaxis in infants is the rate of occult HBV infection (OBI). OBIcases, defined as HBsAg seronegative but HBV DNA seropositive, were morecommonly found in neonates who received both the HepB vaccination and HBIGdoses, possibly due to the added immune pressure induced by the HBIG injection[79,80]. A study inChina looking at the status of HBV infection in neonatal HepB- and HBIG-vaccinatedinfants born from HBsAg seropositive mothers found that 3.9% (3/77) of the infantswere HBsAg-positive and 36.4% (28/77) were identified as OBIs. Further, infantswith OBI had lower levels of anti-HBs but higher levels of antibody againsthepatitis B core antigen (anti-HBc). However, this high anti-HBc level was foundto diminish beyond the 18-month follow-up period followed with HBV DNA seronegativity.This study concluded that the detected OBI in these vaccinated infants was notlikely an established OBI, but a transient persistence of HBV DNA accompanied bypassive transference of anti-HBc from the CHB mothers[84].

Passive transferenceof HBV antibodies from mothers to infants has also been observed in a 2020prospective cohort study in China. They found that despite the zero MTCT rate(shown as HBsAg seronegativity in infants) and anti-HBs seropositivity in theinfants (with high antibody titers), a small proportion of the infants stillexpressed anti-HBc and anti-HBe (antibody to HBeAg) during follow up period of7-month after birth[85]. Thus, these findings indicated that even thoughperinatal transmission did not occur, HBV antibodies may still be able to enterthe infants due to passive transfer from the mothers through intrauterinetransmission[85].

Post-vaccination serological testing

The effectiveness of MTCT prevention can bedetermined in post-vaccination serological testing (PVST). This test should bedone after the last dose of the infants' HBV vaccine to determine the outcomeof the given immunoprophylaxis.

The WHO recommended that PVST is performedfor all HBV-exposed HepB vaccinated infants around 1 to 2 months after thecompletion of the HepB vaccination series, when the antibody response isusually greatest. The infants will be tested for (1) HBsAg, to determinechronic HBV infection, and (2) anti-HBs, to detect immunity against HBV, whereanti-HBs titer of ≥ 10 mIU/mL indicates for protective immunity[5].The PVST is needed to monitor the outcomes and impact of MTCT interventionstrategy, by determining the proportion of infants who are (1) infected withHBV; (2) uninfected and have protective immunity against HBV, and (3)uninfected but not responding to HepB vaccination[6,7].

A 2017 retrospective study in Chinaidentified that, in 438 pairs of mother and infant, 5.3% infants who hadreceived complete HepB doses were HBsAg seropositive, with PVST time around 1to 8 months after the last HepB dose[86]. Similarly,another 2017 PVST study in China reported that HBsAg positivity rate was 3.7%with anti-HBs positivity rate of 90.9% in 1,025 maternal-infant pairs. Theyalso identified that maternal HBeAg status was correlated with infant'spositivity for both HBsAg and anti-HBs. Additionally, the highest anti-HBslevels in the infants were detected in PVST assessed at 1 to 2 months followingthe final HepB dose, and prolonged PVST intervals resulted in decreased theanti-HBs geometric mean concentration[75].

The time of PVST may influence theproportion of the non-responders. Huang *et al.* showed that when PVST was assessed at an intervalof 1, 2, 3, 4, 5, 6, and 7 to 8 months after the last HepB dose, the non-responserate were 1.6%, 1.1%, 0.9%, 0.7%, 1.1%, 0.7%, and 5.7%, respectively, withsignificantly higher non-response rate in PVST at 7 to 8 months. In addition,anti-HBs titres also declined significantly in infants with medium anti-HBsresponses when PVST is performed at a longer interval since the final HepBdose. These results indicate that the optimal PVST interval for infants bornfrom

HBsAg-positive mothers is at seven months of age or around one month aftercomplete HepB vaccination doses[87].

A more recent prospective observationalPVST study in China confirmed the previous findings. Among 2,120 mothers andinfants pairs, the HBsAg positive rate was 0.77%, anti-HBs positive was 96.84%,and both HBsAg and anti-HBs seronegative rate was 2.39%. Among 34 infants with thedouble seronegative results, 15 had received the complete HepB doses[88]. A recent studyanalysing PVST results among at-risk babies born to HBV positive mothers from2008 to 2022 in China showed that the MTCT rate between infants born toHBsAg-positive/HBeAg-negative and HBeAg-positive mothers was significantlydifferent (0.75% *vs* 6.33%). In addition, the MTCT rate for infants born toHBeAg-positive mothers receiving antiviral prophylaxis was 1.72%[89].

The PVST is important to determine MTCTrate in at-risk infants born from HBV-infected mothers, however there is also arisk of low compliance for PVST. In a retrospective cohort study in Fujian,China, only 4,988 infants out of 8,474 at-risk infants were eligible for PVST.Twenty-percents of infants (n = 994) were loss to follow-up for the testingcascade, with 55% of parents refusing venous blood sample collection or failureof field sample collection, 16% transferred out of region, and 10% of parentschose to performed independent PVST without reporting the results. They alsoidentified that the high PVSTnoncompliance rates was associated with infants born from HBeAg-positivemothers (OR 1.2, 95%CI 1.1-1.4)[90].

The vaccine non-responder cases mayinfluence the effectiveness of HepB vaccination in HBV-exposed infants. For at-riskinfants who were still negative for HBsAg and anti-HBs even after receiving thecomplete HepB doses, WHO recommended that they received a revaccinationfollowed by a repeat PVST 1 to 2 months after the last vaccination dose[6,7]. A 2012 study inChina had demonstrated the effect of revaccination to the vaccine non-responderinfants. From 1,814 infants, 3.1% were identified as non-responders (anti-HBstiters < 10 mIU/mL) and 28.4% were low-responders (anti-HBs titers ≥ 10 and < 100 mIU/mL). After HepB revaccination, 14.7% became low-responders and 85.3%became responders in the 34 non-responder infants.

On the other hand, in the 74low-responder infants, 78.4%shifted into responders while 21.6% remained as low-responders[91].

A recent retrospective study had shown that,for the non-responders, an additional fourth vaccine booster dose may bebeneficial to improve the anti-HBs response. They found that a fourth dose vaccineinjection resulted in detectable anti-HBs levels in 52.2% (105/201) of HepB vaccinenon-responders[92]. Additionally,another study had shown that those with pre-booster anti-HBs levels of 2 to 9.9mIU/mL had a higher possibility of responding to an additional vaccine boosterdose compared to those with anti-HBs levels of < 2 mIU/mL[93].

Another issue that is associated with HBVvaccination is vaccine escape mutations (VEMs). The appearance of VEMs has notbeen intensively studied, however detecting the emergence, rate, and clinicalsignificance of these variants is important for HBV management, especially inhigh HBV prevalence regions. There is lacking viral genetic data on VEMs in thepopulation, although current genomic data indicates for a low prevalence ofindividual vaccine escape mutations[47,94]. A phylogeneticanalysis showed that VEMs may arise independently of antiviral treatment or HBVvaccine exposure, but these variants can be found across different HBVgenotypes, with the highest prevalence identified in genotype C[94]. As such,emergence of VEMs remains a potential challenge in association with infants HBVvaccination program[46,47].

COMBINATION OFANTIVIRAL AND IMMUNE PROPHYLAXIS TO REDUCE MTCT

Research had shownthat the combination of passive and active immunization in infants born toHBsAg-positive mothers reduced the rate of MTCT. However, this immunizationapproach cannot fully eradicate the risk of MTCT, since incidence ofimmunoprophylaxis failure has been reported in the vaccinated infants[95]. Delayed vaccination and inadequate initialinjections in the infants, along with high maternal HBV DNA levels, have beenassociated with these immunoprophylaxis failures[96]. In addition, epidemiological and modeling studieshave also shown that HBV

immunization alone would not be sufficient in reducingthe WHO's target of 0.1% HBsAg prevalence goal in children by the year 2030[7,45]. Therefore, additional approaches are needed toachieve zero MTCT rate. Many trial studies in the last decade have shown thepromising use of antiviral prophylaxis in CHB pregnant women, in combination withimmunoprophylaxis for the infants, to reduce risk of MTCT, as the antiviraltreatment in pregnant women had shown good safety and efficacy profile inlowering HBV DNA level[95].

A 2020 study hadcompared the MTCT rate in neonatal HBV-vaccinated infants born fromantiviral-treated and non-treated CHB pregnant women. Antiviral treatment inmothers (either with LdT, TDF, or 3TC) reduced the MTCT rate in infants to 0%(0/60) from 0.1% (3/30) in the infants born from the non-treated mothers and39.2% (11/28) in the control group[97]. Accumulating evidences from randomized-controlledtrials (RCTs) have also shown the effectiveness of combined intervention toprevent HBV MTCT[46,47]. Data from 15 RCTs with 2,706 infants from HBsAgseropositive mothers showed that reduced MTCT risk is higher in HBIG- andHepB-vaccinated infants born of highly viremic mothers (HBV DNA ^{3}5.3 Log_{10} IU/mL) who received antenatal NA prophylaxis (RR 0.47, 95%CI 0.29-0.75), compared to (1) the vaccinated infants born from highly viremic but untreated mothers (RR 0.31, 95%CI0.10-0.99); (2) infants receiving combined HBIG and HepB vaccination (RR 0.37,95%CI 0.210-0.67), and (3) infants receiving only HepB vaccination (RR 0.32,95%CI 0.21-0.50) [98].

A meta-analysis study in 2022 analyzed300 studies worldwide to determine the rate of HBV MTCT incidence underdifferent prophylaxis regimens. The overall MTCT incidence rate withoutprophylaxis is 31.3%, which varies in different regions. Infants' vaccinationreduced the MTCT risk in HBeAg seropositive mothers from 82.9% to 15.9% andfrom 10.3% to 2.3% in HBeAg seronegative mothers. Further reduction of MTCTrate to 0.3% (95%CI 0.1%-0.5%) was achieved by combination of maternalperipartum NA prophylaxis and infants' vaccination. In addition, the risk of HBVtransmission can be stratified based on the maternal HBV DNA VL, with observed occurrenceof MTCT

incidence when the maternal HBV DNA level viral load is higher than4.29 Log_{10} IU/mL[46,47,99].

CHALLENGES AND EFFORTS

There are severalchallenges that may occur in implementing antiviral and immune prophylaxis approachfor MTCT prevention in HBsAg seropositive pregnant women. These include the costsand availability of antiviral and immune prophylaxis, ideal time to initiatethe antiviral prophylaxis, lack of access to HBV DNA tests, cases ofimmunoprophylaxis failure in infants, in addition to the lack of trainedhealth-care workers, lack of capacity, and limitation of infrastructure in someHBV endemic countries[7,45].

The cost and accessto antiviral prophylaxis

The cost and access to antiviral prophylaxis couldpose a serious issue for HBV MTCT prevention program in pregnant mothers. TDFis now listed on the WHO list of essential medicines and considered as lowcost, however access to TDF in some HBV prevalent regions remains poor[46,47]. In China, the lowered cost of TDF to less than USD1.50 per month and ensuring its availability in most hospitals in the country,greatly supported the success of their SHIELD HBV MTCT prevention program[46]. In African countries, access to TDF for HBV patientsmay be possible through the existing HIV program, since TDF is also used forHIV treatment with an already well-established supply chains[100]. In addition, it is estimated that 6.1% of women withHIV infection were also coinfected with HBV[7,45], thus TDF treatment in pregnant women in Africa willbe beneficial for prevention of both HIV and HBV transmission in the region.

In case of lowaccessibility to TDF for pregnant mothers, a combined antivirals use (forexample TDF with other anti-HBV agent) or more reliance on immunoprophylaxis programmay be considered for MTCT prevention[46,47][101]. A 2018 clinical trial performed in 331 pregnant womenin Thailand showed that administration of neonatal HBIG and full doses of HBVvaccination in infants born from HBeAg seropositive

women were sufficient toreduce the MTCT rate. Further, they found that additional TDF treatment in themothers did not result in a significantly lower rate of HBV transmission[101]. A 2023 retrospective study in Thailand had performedcost-effectiveness analyses of different TDF-based intervention strategies: (1)TDF to eligible mothers and HBIG for all infants; (2) TDF to eligible mothersand HBIG for infants from HBeAg-positive mothers, and (3) TDF to eligiblemothers without HBIG for infants. Their analyses showed that the HBIG-freestrategy was the most cost-saving intervention, with 0 to 1.4% transmissionrates, making it an ideal strategy for high HBsAg seropositive prevalence butresource-constrained population[102].

The ideal time toinitiate the antiviral prophylaxis

Another issue relatedto antiviral prophylaxis for pregnant women is when to start the treatment. Therecommended initiation time for antiviral prophylaxis is after the 24 gestationweeks period. However, it was unclear whether the antiviral treatment in CHBpregnant women can be initiated before the 24 weeks of gestation. A study hasshown that reduction of HBV DNA level was more significant in pregnant womenthat started treatment in the second trimester (< 27 weeks) compared to thethird trimester (> 28 weeks)[69]. A significant reduction of HBV DNA level was also observedin pregnant women that were treated with TDF in the second trimester comparedto those treated in the third trimester[69]. A network meta-analysis study comparing the efficacyand safety of antiviral therapy on pregnant mothers also concluded thattreatment administered during the early or middle pregnancy period had a betterefficacy for HBeAg seropositive pregnant mothers with high HBV DNA VL (6.3 Log_{10} IU/mL). Further, this particular effect is shownconsistently, regardless of the used NA drugs[103].

A 2020 prospectivecohort study in China enrolled 136 CHB women to assess the safety and efficacyof antiviral treatment before and during pregnancy. A small proportion of thewomen with active CHB was treated with either TDF or LdT prior to pregnancy tonormalize their liver enzymes, and continued with TDF or LdT

consumptionthroughout the entire pregnancy. The study showed that these women showed nodifferences in obstetrical-related complications compared to the other threegroups, pregnant women who received antiviral therapy (1) in early pregnancy(< 24 weeks); (2) in late pregnancy (> 24 weeks), or (3) in latepregnancy, but with high HBV DNA VL (³ 6 Log_{10} IU/mL). In addition, all theirinfants' (which had received neonatal HBIG dose and complete HepB doses) showednegative HBsAg status after a 7-month follow-up period, with no differences inthe infants' rate of congenital malformation and other growth indicators[85].

Current evidences onthe use of antiviral prophylaxis in HBsAg seropositive mothers were positive,as there were no observed adverse events for the mothers and the infants[69,85]. So far, no NA drugs were associated withobstetrical-related complications for the mothers and congenital malformationfor the infants[67],[69,85], thus all NA drugs are considered safe for mothersand newborns. However, there are still limited long-term safety data on theeffect of antiviral prophylaxis use during pregnancy[103], and whether antiviral prophylaxis is safe to use inmultiple pregnancies. Thus, more data are needed to fully understand the effectof this treatment for the mothers and the infants.

The costs of immuneprophylaxis

Despite thesatisfactory effect of infants' immunoprophylaxis, the vaccine delivery includingmaintenance of the cold chain logistics, consistency and equity of supply,timely administration may hinder MTCT elimination[46,47]. One strategy to improve feasible implementation of HBIGand HepB for infants of HBV-positive mothers within one hour of birth is toensure the vaccine supply both in the delivery room and postnatal ward[82,104].Current monovalent HBV vaccine is considered as low cost, however, the total healthcarecost also includes the cost for the infrastructure and personnel. Therefore,the total cost for the patient might actually be higher than the cost ofvaccine dose itself[46,47]. Regardless, the rate of infants receiving theappropriate HepB dose at birth has increased in areas where local healthcarepolicies mandate for

HBV vaccination shortly after birth with constant supplyof available vaccine in the labor and maternity wards[105,106].

Taiwan serves as a success story for infants'HBV vaccination program. As the first nation that implemented HBV vaccinationprogram for infants in 1984, they gradually expanded their vaccination targetto increase the vaccination coverage, from only infants with high-risk mothersto all infants regardless of the maternal HBsAg status. Now, they are targetingall infants who missed their vaccination as newborns and adolescents. After 30years of implementation, Taiwan has successfully decreased the prevalence ofHBsAg from 9.8% to 0.5% in individuals ≤ 30 years old and to ≤ 1% among5-years-old children. Consequently, they also managed to reduce the incidenceof fulminant hepatitis in infants and HCC in the population[81].Similarly, the success of HBV vaccination program in China is attributed to thegovernment commitment for reducing MTCT rate. Early in the program, the parentshave to cover the cost of the infants' HBV vaccination, which affected the rateof vaccine coverage in the country. However, in 2002, the Chinese governmentsuccessfully built a collaborative project with Global Alliance for Vaccinesand Immunization (GAVI) to ensure all children can receive HBV vaccination,even in the poorer western provinces. This collaboration has increased thevaccination coverage rate in infants from 30% in 1992 to 93.4% in 2005, withreduction of HBsAg prevalence from 2.1% to 1%[107]. Indeed, GAVI provided support onvaccine-related financial and logistical cost since 2001, including vaccinecost reduction to below USD 1 per dose and availability of pentavalent vaccines(DPT-HepB-Hib), has greatly increased the vaccine coverage rate in GAVI-supportedcountries [108].

Availability of HBIG supply is a costly investment, andas such HBIG is often not readily available in low-income countries. To try to overcomethis shortcoming, a clinical trial is performed in Cambodia to assess thefeasibility of the immunoglobulin-free strategy for MTCT in a limited-resourceregion. More than 1,000 HBsAg-positive pregnant women were recruited in theTA-PROHM study from 2017-2020, and 28% (338/1194) of these women received TDFtreatment. In infants not receiving HBIG

injection, the MTCT rate was zero(n = 227) in those born from women who received TDF for more than four weeksbefore delivery. However, in those born from women who received TDF for lessthan four weeks, the MTCT rate was 8% (3/36). These results showed that evenwithout neonatal HBIG administration, TDF treatment was sufficient to reduce theMTCT rate[109]. They also added that determination of the mothers'eligibility for TDF treatment can be done using the HBeAg rapid detection testand alanine aminotransferase (ALT)-based algorithm[109,110], which would be more feasible to practice in alimited-resource setting with high HBV prevalence.

Cases of immunoprophylaxis failure ininfants

Despite the protective effect ofadministration of immunoprophylaxis for infants of HBsAg-positive mothers,cases of immunoprophylaxis failure have been reported. A 2021 Chinese studyreported nine cases of immunoprophylaxis failure (n = 982) in newborns receivingboth HBIG and HepB-BD within an hour after delivery, who were born from womenwith high HBV DNA VL (> 6.4 Log_{10} IU/mL)[82]. In infants bornfrom HBeAg-positive mothers, the frequency of immunoprophylaxis failure washigher at 5.2% (16/306) compared to those born from HBeAg-negative mothers.This immunoprophylaxis failure was associated with very high HBV DNA levels (≥ 8 Log_{10} IU/mL, OR 4.53, 95%CI1.19-17.34), inadequate initial injections (OR 7.69, 95%CI 1.71-34.59), anddelayed vaccination time (OR 4.14, 95%CI 1.00-17.18)[96].

A 2021 birth cohort study in CentralVietnam discovered that in children born to HBsAg seropositive mothers, 13.1%(16/122) who received complete HepB doses had HBV infection at the 2-yearfollow-up period, and 20.5% (9/44) who received incomplete HepB doses were alsoinfected. In addition, in children born to HBeAg-positive mothers, 28.3%(15/53) who received complete HepB doses got HBV infection, while 53.3% (8/15)who received incomplete HepB doses also got infected[111]. This studyshowed the importance of post-vaccination serological testing for vaccinatedinfants born from HBsAg seropositive mothers, to determine the seroprotectivelevel of anti-HBs in these children. In addition, other vaccination strategymay be needed to reduce the rates of

immunoprophylaxis failure in high HBVprevalent region, by changing the dose of the HepB vaccine and/or HBIG forat-risk infants.

A multicenter study in China enrolled 955pairs of infants and their HBsAg-positive mothers. The infants all receivedHBIG injection (at 0 and 1 month) and either 10 μg or 20 μg HepB vaccine (at 0,1, and 6 months). Their result showed that the immunoprophylaxis failure ratein the 20 μg HepB vaccine group was not significantly different compared to the10 μg group, regardless of the maternal HBV DNA level, with both doses havinggood safety profiles for the infants. However, the higher HepB vaccine dose wasassociated with significant reduction of the low-response rate (anti-HBs titre10–100 IU/L) and middle-response rate(anti-HBs titre 100–1000 IU/L), andincreased the high-response rate (anti-HBs titre ≥ 1000 IU/L) in infants bornto mothers with low HBV DNA level (< 5 Log_{10} IU/mL)[112].

In regard to HBIG doses, there arecurrently two recommended HBIG doses used in several countries for newborninjection, 100 IU and 200 IU. Wei *et al*. had shown that for infants bornto HBsAg-positive mothers, the infection rate of infants injected with either100 or 200 IU HBIG did not significantly differ, with respective prevalence of1.5% (8/545) and 1.9% (12/632). The respective anti-HBs positive rates in thetwo groups were 98.5% (529/537) and 98.2% (609/620), with comparable anti-HBslevels of 707.95 mIU/mL and 602.56 mIU/mL at the 7-month follow-up period. Inthe 200 IU HBIG group, however, one non-responder infants became HBsAgseropositive at the 12-month follow-up period[113]. A RCT study in331 pairs of infants and HBsAg- and HBeAg-positive mothers in China confirmedthe previous finding. They found that in vaccinated infants born to HBsAg- andHBeAg-positive mothers, higher dosage of HBIG (200 IU) did not provide addedprotective effect against MTCT compared to the lower HBIG dose (100 IU). However,in relation to the cost of infants' vaccination,their analysis concluded that the use of three-dose HepB vaccination and asingle dose of 100 IU HBIG as the more cost-effective approach in preventing HBVMTCT in the country[114].

Availability of HBVDNA testing

Tosuccessfully implement prenatal intervention on HBsAg seropositive pregnantwomen, access to laboratory testing for HBV screening is crucial. Poor accessto laboratory-based screening of HBV seromarkers (HBsAg and/or HBeAg) and HBVDNA VL quantification are often reported in resource-limited countries.Further, in area where the appropriate laboratory facilities are alreadyavailable, the high cost of the tests might also be an issue[46,47].

HBV DNA VL quantification is considered as thebest method to determine whether a CHB pregnant mother is eligible for TDFtreatment, as most of the antiviral prophylaxis guidelines used the maternalHBV DNA level of $^{3}5.3$ Log_{10} IU/mL as the cut-off for antiviral treatment initiation.However, not all countries have the resources and facilities to perform routineHBV DNA quantification test. As such a reliable surrogate marker for HBV DNAlevel is needed, especially in a limited-resource setting. HBeAg detection andquantitative HBsAg level test have been identified as possible alternativecost-effective test for HBV DNA level quantification[7,45].

A 2020 Cambodian study in 515HBsAg-positive women had demonstrated the potential use of a combined algorithmof HBeAg rapid diagnostic test and ALT levels for identifying women eligiblefor TDF treatment. They found that positive HBeAg rapid test and ALT thresholdlevel of 40 IU/L have sensitivity and specificity of 79% and 93% for HBV DNAlevel > 5.3 Log_{10} IU/mL, and 88% and 93% for HBV DNA level > 7.3 Log_{10} IU/mL[110].HBsAg levels had also been shown to positively correlate with HBV DNA levels inHBeAg seropositive pregnant women, with correlation of low HBsAg levels of < 3 Log_{10} IU/mL with HBV DNA levels < 6 Log_{10} IU/mL.Thus, HBsAg quantitative level may serve as a good viral load predictor inHBeAg-positive pregnant women[115].Additionally, the detection of Hepatitis B core-related antigen (HBcrAg) hasalso shown good correlation with HBV DNA level, where a value of 5.3 Log U/mLis equal to HBV DNA level of $^{3}5.3$ Log_{10} IU/mL. Thus, HBcrAg may also be used as an alternateserological marker to identify high viremia in the treatment-naïve CHB patients[65,116].

Development of a rapid, affordable,and point of care test (POCT) or near-POCT for HBV DNA may also reducedependency for HBeAg testing[46,47]. Further, availability of inexpensive POCT for HBV DNA maysimplify the need for two separate tests for HBsAg and HBV DNA viral load into asingle HBV test for diagnostic and risk stratification purposes for pregnant women[46,47]. Widely available HBV DNA test would also allow for moreidentification of OBI cases in at-risk cases, although OBI is not considered asa significant risk factor for MTCT as OBI cases typically have low HBV DNAlevel [46,47]. In China, they introduced a multilevel step HBV MTCTprevention program to solve the issue of lack of trained healthcareworkers and limitation of infrastructure. The multilevel approaches on theirSHIELD program allows for proper training for the healthcare workers andgradual improvement of the healthcare infrastructure to ensure a goodcompliance rate (83.2%) in the antiviral-treated pregnant women[46].

Other available approach to improveaccessibility to HBV testing is by combining resources with the HIV infectionelimination program. Established infrastructure for HIV MTCT prevention can beshared for the HBV MTCT prevention program due to their similar approaches,especially in resource-poor settings in Africa[117].The use of dried blood spots for hepatitis B testing may also be considered,especially in the low-resource settings with limited access to well-equippedhealthcare facilities[100].

Lack of awareness forHBV screening

There are several identified barriers that may impedea successful HBV prevention MTCT program, which include lack of awareness forHBV screening and the benefit of HBV vaccination for at-risk infants and thecaregivers. WHO have identified that HBV immunoprophylaxis program expansion isgreatly impacted by the local and diverse characteristics of the targetpopulation and the cultural beliefs and political acceptance in the country[46,47,108]. As such,enhancing health education and awareness on risk factors of HBV infection,chronic liver disease progression, and effective screening and treatmentregimens are crucial, along with advocacy and adequate representation

forspecific at-risk population including rural communities, migrant population,and marginalised groups[46,47].

In Africa, where some countries still have nodedicated HBV programs, expanding the existing HIV MTCT prevention program willenable for HBV screening test for the pregnant women, resulting in improve identificationand access to care for the HBV monoinfected pregnant women [100]. Meanwhile, in the high-income countries, the HBVundiagnosed individuals usually come from vulnerable populations, includingintravenous drug users, homeless persons, and illegal immigrants[108].These peoples are often difficult to reach, therefore community-based HBVscreening and outreach program may be beneficial in identifying these at-riskindividuals[46,47].

Increasing awareness for HBV screening in pregnantwomen may also be beneficial for MTCT prevention program. In Nigeria, motherswith good knowledge of HBV (with receiving tertiary education as an indicator)were more likely to vaccinate their newborns[105]. Similarly, in China, mothers with high educationallevels were the most likely to perform PVST follow-up after their infants'vaccination[88]. Overall, it is crucial to combine effective treatment andcomprehensive policies in the infection prevention, political commitment,financial structure, stakeholder engagement, and healthcare system integration[108].

CONCLUSION

Vast and significant efforts in reducing the risk and prevalence of MTCT of HBV had been noticeable in many countries, including in HBV endemic regions in Asia Pacific region. Still, additional approaches are needed to achieve zero MTCT rate, including HBV screening for pregnant women, interventions of HBV transmission during delivery, and infants' immunoprophylaxis. These should be also accompanied by the availability and the affordability of the cost of HBV tests, HBIG, and antiviral therapies.

ACKNOWLEDGEMENTS

Supported by an internal grant Rumah Program 2024 of Research Organization for Health, National Research and Innovation Agency (BRIN) of Indonesia. DPW and SJ are funded by Manajemen Talenta, BRIN. CS is awarded 2024 grant of the Fondazione Veronesi, Milan, Italy.

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