

## Prevention of vertical transmission of hepatitis B virus infection

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### Abstract

Hepatitis B virus (HBV) is the leading cause of chronic viral hepatitis. Annually, almost two million children younger than 5 years acquire the infection, mostly through vertical or horizontal transmission in early life. Vertical transmission of HBV is a high efficacy phenomenon ranging, in the absence of any preventive interventions, from 70% to 90% for hepatitis e antigen positive mothers and from 10% to 40% for hepatitis e antigen-negative mothers. Maternal viraemia is a preeminent risk factor for vertical transmission of HBV. Maternal screening is the first step to prevent vertical transmission of HBV. Hepatitis B passive and active immunoprophylaxis at birth together with antiviral treatment of highly viraemic mothers are the key strategies for global elimination of HBV infection. Strategies are needed to promote implementation of birth-dose vaccination and hepatitis B immunoglobulins in low- and middle-income countries where the prevalence of the infection is at the highest.

**Key Words:** Hepatitis B; Vertical transmission; Hepatitis B vaccine; Hepatitis B immune globulin; Neonatal immunoprophylaxis; Tenofovir alafenamide fumarate

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**Core Tip:** Hepatitis B is one of the main causes of morbidity and mortality worldwide. Vertical transmission is the main transmission route, especially in areas with high prevalence of the infection. Maternal viraemia is a preeminent risk factor for vertical transmission of hepatitis B virus (HBV). Breastfeeding is recommended, although all the conditions leading to maternal-foetal microtransfusions with HBV-infected

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maternal blood increase the risk of vertical transmission. Neonatal immunoprophylaxis at birth represent the most important approach to prevent HBV infection. The aim of the present narrative review is to summarise the knowledge on prevention of vertical transmission of HBV infection.

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## INTRODUCTION

Hepatitis B virus (HBV) is the leading cause of chronic viral hepatitis and a major cause of acute and chronic liver disease and associated morbidity and mortality worldwide[1]. According to the latest estimation, in 2016 there were 291 million people chronically infected with HBV in the world corresponding to a global prevalence of 3.9%. Annually, almost two million children younger than 5 years acquire the infection. The highest prevalence has been reported in Africa and in the Western Pacific area. In these regions the coverage with the birth vaccination dose is at the lowest, mostly through vertical transmission in early life[1]. Vertical transmission or infections acquired during early infancy are still responsible for most chronic HBV infections in adults, especially in the areas with high prevalence of the infection[2,3]. Hepatitis B passive and active immunoprophylaxis at birth together with antiviral treatment of highly viraemic mothers are the key strategies for global of HBV infection [4]. According to latest World Health Organization (WHO) estimates, the relative amount of children under 5 years of age chronically infected with HBV dropped to under 1% in 2019, down from around 5% in the pre-vaccine era[5]. In 2019, coverage of three doses of the vaccine reached 85% worldwide compared to around 30% in 2000. However, coverage of the hepatitis B vaccine birth dose remains uneven. Global coverage of the HBV birth dose is 43%, while coverage in the WHO African Region is only 6%[5].

Breast-feeding does not entail any additional risk of transmission in infants who receive a correct immunoprophylaxis[6]. The aim of the present narrative review is to summarise the knowledge on prevention of vertical transmission of HBV infection.

## VERTICAL TRANSMISSION OF HBV: DEFINITION, TIMING AND TRANSMISSION RATE

Vertical transmission of HBV is defined as transmission occurring during pregnancy and in the perinatal period from the HBV-infected mother to the foetus or to the child, resulting in positivity at 6-12 mo of life of the hepatitis B surface antigen (HBsAg) or HBV DNA in infants[7]. Overall, vertical transmission of HBV is a high efficacy phenomenon ranging, in the absence of any preventive interventions, from 70% to 90% for hepatitis e antigen (HBeAg) positive mothers and from 10% to 40% for HBeAg-negative mothers. The high success rate of immunoprophylaxis provided to newborns in reducing the incidence of HBV transmission suggests that most vertical transmissions occur at or near the time of birth. Intrauterine infections take place in < 15% of pregnancies.

## RISK FACTORS FOR VERTICAL TRANSMISSION OF HBV

Maternal viraemia, identified through the detection of HBV DNA or through the positivity of its surrogate markers HBsAg and HBeAg, is a preeminent risk factor for vertical transmission of HBV. HBeAg-positive mothers and mothers with high circulating concentrations of HBV DNA (> 10<sup>6</sup> IU/mL) have the highest risk of transmission[8,9]. All the conditions leading to maternal-foetal microtransfusions with HBV-infected maternal blood increase the risk of vertical transmission. Microtrans-

fusions could occur intrauterine, during labour, or at delivery. Placental leakages due to threatened preterm delivery or abortion, amniocentesis or chorionic villus sampling, and prolonged uterine contractions could be associated with maternal microtransfusions. The exposure of the neonate to the maternal HBV-infected cervical secretions and blood is possible during labour and delivery.

### **Mode of delivery**

The mode of delivery has been examined as a potential risk factor for vertical transmission of HBV, but the resulting evidence is conflicting. In a large study from China, the effect of Caesarean section delivery on vertical transmission of HBV was evaluated in 1409 infants born to 1401 HBsAg-positive mothers of whom 61.5% (863 of 1401) had detectable levels of HBV DNA. All the children enrolled completed appropriate immunization against HBV. A lower vertical transmission rate was observed among infants in the group delivered by elective Caesarean section (1.4%) compared with that of those in the vaginal delivery group (3.4%). In the multivariate analysis, elective Caesarean section was beneficial for vertical transmission prevention only in mothers with maternal HBV DNA levels  $> 200000$  IU/mL. In line with this study, two recent systematic reviews with meta-analysis showed that Caesarean section reduced the risk of vertical transmission in infants of HBeAg-positive mothers who did not receive antiviral therapy during pregnancy[10]. Other previous studies had contradictory results regarding the benefit of elective Caesarean section. Overall, there is no robust evidence to support Caesarean section as the mode of choice for the prevention of HBV transmission. The possible beneficial effect of Caesarean section should be weighed against the efficacy of the other well recognised practices for prevention of transmission, (*i.e.* antiviral therapy during pregnancy and passive and active immunoprophylaxis at birth). Thus far, regardless of viraemia, the mode of delivery of mothers with chronic HBV infection should follow the usual obstetric indications and is not influenced by the presence of the infection.

### **Amniocentesis and other obstetric procedures**

Invasive diagnostic procedures during pregnancy, such as amniocentesis, occur before the timing for immunoprophylaxis and may favour the mixing of maternal and foetal blood. Different studies[11-15] conducted before the routine use of HBV viral load testing did not demonstrate an augmented risk for *in utero* infection after amniocentesis in women with chronic infection. In a recent study enrolling 642 consecutive Chinese infants born to HBsAg positive mothers without antiviral exposure and who completed appropriate immunization, 63 infants with amniocentesis were compared with 198 matched infants selected from the remaining 579 infants without amniocentesis. There was a significantly higher vertical transmission rate in infants with amniocentesis than in those without amniocentesis if the maternal HBV DNA levels were  $\geq 2 \times 10^6$  IU/mL (50% *vs* 4.5%, respectively,  $P = 0.006$ ). On the basis of this result, adequate counselling is advised for HBV-infected women who may necessitate invasive testing (*e.g.*, amniocentesis or chorionic villus sampling) including the possible increased risk for maternal-foetal transmission with HBV viral load  $\geq 2 \times 10^6$  IU/mL[16].

All the procedures that break the skin and mucosal barrier including foetal scalp electrodes and blood sampling and vigorous suctioning of the newborn's airway at birth should be avoided. The risk of traumatizing the foetal skin is lower with vacuum extraction and forceps, and its use should follow obstetric indications.

### **Breastfeeding**

We identified three major questions concerning breastfeeding and vertical transmission of HBV: (1) Does breastfeeding increase the risk of vertical transmission of HBV? (2) Does breastfeeding interfere with the immune response to vaccine? and (3) Is breastfeeding from HBV-infected mothers on antiviral treatment contraindicated? The role of breastfeeding in the transmission of hepatitis B has been discussed for many years. Examination of relevant studies indicates that there is no evidence that breastfeeding poses any additional risk to infants of HBV carrier mothers[17-19]. The risk of vertical transmission of HBV through breastfeeding is negligible if infants born to HBV-positive mothers who receive the hepatitis B immunoglobulins (HBIG)/ hepatitis B vaccine at birth, and the benefits of breastfeeding outweigh any potential risk of infection. HBV infection should not be considered a contraindication to breastfeeding of infants who receive the HBIG and HBV vaccine[20]. Data are insufficient to say whether it is safe or not for the HBV-positive mother to breastfeed if her nipples are cracked and bleeding. Breastfeeding should be temporarily stopped to avoid any

potential exposure to blood, and once nipples are no longer cracked or bleeding, the HBV-positive mother may fully resume breastfeeding.

Wang *et al*[21] have showed that breastfeeding does not interfere with the immune response to the HBV vaccine. A total of 230 babies with HBV immunoprophylaxis at birth were followed up for 1 year in order to measure rates of anti-HBs antibodies at different ages. There were no significant differences in the incidence of immunoprophylaxis failure between breast-fed and formula-fed babies[21]. For mothers who received antivirals during pregnancy, the safety of continuing these drugs after delivery during breastfeeding has been and is a matter of concern and discussion. Although the risk of *in utero* exposure to drugs is likely higher than for infants through breast milk, antivirals are recommended for use during pregnancy but many experts remain concerned about long-term consequences of prolonged antiviral agent exposure in the neonate and of its possible impact on growth and development. However, breastfeeding is advantageous on many issues, especially in low-income countries where formula feeding is not widely available. Furthermore, in human-immunodeficiency setting, antiretroviral treatment could continue during the breastfeeding period in infected women. Only a small quantity of oral nucleoside analogues is secreted in breast milk[22], and the effect on bone growth of exposed children is not significantly different after a follow-up period[23]. In women treated with tenofovir, presence of the drug in breast milk has been reported, but its oral bioavailability is limited, and thus infants are exposed to only small concentrations. Current recommendations by the European Association for the Study of Liver Disease stated that breastfeeding is not contraindicated in HBV-positive mothers on tenofovir-based treatment or prophylaxis.

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## PREVENTION OF VERTICAL TRANSMISSION OF HBV: MANAGEMENT STRATEGIES DURING PREGNANCY

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### **Maternal screening**

The first step to prevent vertical transmission of HBV is to test all pregnant women in the first trimester in order to identify the best management strategy for mothers and the correct immunoprophylaxis schedule for future newborns[24]. In case of positive HBsAg, it is necessary to perform further investigations (hepatitis B core antibody, HBeAg, hepatitis B e antibody, serum aminotransferase levels, quantification of serum HBV DNA, liver imaging) to determine the woman's hepatitis B phase and therefore the possible requirement for treatment during or after pregnancy[25]. In HBsAg negative women with an increased risk of infection (infected partners, infected family members, at risk habits) the evaluation of maternal serological status should also be repeated when entering the hospital at the time of delivery.

In recent years there is a growing interest in new biomarkers of HBV infection, such as covalently-closed circular DNA (cccDNA), hepatitis B core-related antigen, and circulating HBV RNA. cccDNA is a key factor for the persistence of infection and represents a specific marker of replication[26] and was shown to persist in the liver, serum, and peripheral mononuclear cells[27].

### **Hepatitis B vaccination during pregnancy**

Vaccination against HBV during pregnancy is safe and effective[28,29]. There is agreement that pregnant women who are not immune or infected with HBV, whether or not at high risk for HBV infection (as defined by having > one sex partner during the previous 6 mo, a current diagnosis of a sexually transmitted disease, having had an HBsAg-positive sex partner or a recent or current injection drug use), should be vaccinated[16,25]. Following the vaccination, maternal antibodies are passively transferred across the placenta to newborns, although without the active vaccination at birth, its titres rapidly wane over time[28]. Pregnant women can be considered HBV-immune when anti-HBs levels are higher than 10 mIU/mL. Sheffield *et al*[30] have shown that an accelerated vaccination schedule at 0, 1, and 4 mo in high-risk pregnant women is effective and well tolerated.

### **Hepatitis B immunoglobulin during pregnancy**

The rationale behind the possible use of HBIG and/or of antiviral treatment during pregnancy is that up to 10% of infants born to HBV-infected mothers still have HBV infection despite receiving HBIG and HBV vaccine at birth. This suggests that additional interventions during the pre-birth phase could be favourable to decrease

the transmission rate.

HBIG is a purified solution of human immunoglobulin that could be administered to the mother, newborn, or both. When HBIG is administered to pregnant women, the antibodies passively diffuse across the placenta to the foetus. The maternal-foetal diffusion is maximal during the third trimester of pregnancy. Several studies have explored the efficacy of the administration of HBIG to HBV-infected pregnant women [31-34]. Unfortunately, the studies are quite heterogeneous in terms of HBIG doses and routes of administration and of definitions of maternal and neonatal infection. A recent Cochrane review found varying effects of maternal antenatal HBIG in preventing vertical transmission of HBV. This review selected 36 trials originated from China including 6044 pregnant women who were HBsAg, HBeAg, or HBV DNA positive. Most of the trials (30/36; 83%) assessed HBIG 200 IU at 28, 32, and 36 wk of pregnancy. Serological signs of hepatitis B infection of the newborns were reported as HBsAg, HBeAg, and HBV DNA positive results at end of follow-up. Although, overall HBIG seemed to impact the HBsAg and HBV DNA status of the newborn, due to low quality evidence found in the review, the authors concluded for the uncertainty of the effect of benefit of antenatal HBIG administration to the HBV-infected mothers on newborn outcomes as compared with no intervention[35].

### **Antiviral treatment during pregnancy**

The use of nucleoside or nucleotide analogues (lamivudine, telbivudine, or tenofovir [36-38]) during the last trimester of pregnancy in highly viraemic, HBeAg positive mothers, in combination with standard infant immune-prophylaxis, has been shown to be effective in further reducing the vertical transmission of HBV[36,37].

Antiviral treatment should be considered based on HBV DNA quantification, and it has been generally suggested in pregnant women with HBV DNA levels of more than  $2 \times 10^5$  IU/mL. The appropriate time to start and stop antiretroviral drug in pregnant women is still debated. The aim of therapy is to reduce HBV DNA levels below the threshold of transmission or immunoprophylaxis failure at the time of delivery, and for this reason treatment is mainly started around 28 wk to 32 wk of gestation. Earlier may be beneficial and has been suggested for prevention of early placental infection and intrauterine transmission[39]. When the treatment is started only to prevent vertical transmission, it could be discontinued as early as at delivery or, as suggested by the major international societies, prolonged until 12 wk after delivery. While small amounts of drugs are usually present in breast milk, there is a potential risk of maternal hepatitis flare following the end of treatment, most of which are asymptomatic. However, there is no additional benefit in the aspect of hepatitis flare prevention in women who carry on treatment to 4 wk postpartum[40]. Close check of transaminase levels is needed after the end of treatment. Lamivudine[41], telbivudine [42], and tenofovir disoproxil fumarate[43] are the antiretroviral drugs that are considered safe to use during pregnancy. Telbivudine and lamivudine could significantly reduce transmission in infants compared with cases with no treatment, but both drugs have a low genetic barrier to resistance barrier. Therefore, tenofovir disoproxil fumarate is the treatment of choice for HBV-positive mothers because of its potent antiviral activity and high genetic barrier to resistance. Tenofovir alafenamide fumarate is a prodrug of tenofovir that can be administered at a lower dose compared with tenofovir disoproxil fumarate, as its active metabolite could be delivered to the target organs with lower circulating drug levels. The efficacy and safety of tenofovir alafenamide fumarate in HBV-infected pregnant women need to be evaluated before recommending it for use.

Treatment guidelines differ mainly with regard to the type of treatment, the threshold viraemia level, and timing for starting antiviral treatment. Consistency across the different guidelines seems a desirable and achievable target in order to standardise the global approach to mothers with HBV infection and antenatal prevention of vertical transmission.

Indications for treatment including which drug, the threshold of HBV DNA level, when to start, and when to stop treatment, as recommended by the main international scientific societies are summarised in Table 1[44]. Despite the different indications provided by the current guidelines, all societies agree to start antiviral treatment when HBV DNA levels are higher than  $2 \times 10^5$  IU/mL, regardless of maternal serological status (HBeAg positive or negative).

In 2018, a large, double-blinded randomised placebo-controlled trial of tenofovir disoproxil fumarate given from 28 wk of gestational age to 8 wk postpartum to HBeAg-positive pregnant women with a mean HBV DNA of  $10^8$  IU/mL in Thailand, plus birth-dose vaccination and HBIG, did not find a significantly lower vertical transmission rate beyond the low rate already achieved in the comparison group that



**Table 1 Recommendations for antiviral treatment in pregnant women with chronic hepatitis B virus infection**

Societies	Antivirals	HBV-DNA level	When to start treatment	When to stop treatment
American Association for the Study of Liver Diseases[25]	Tenofovir disoproxil fumarate	$> 2 \times 10^5$ IU/mL	28-32 wk	At birth to 3 mo
European Association for the Study of the Liver[24]	Tenofovir disoproxil fumarate	$> 2 \times 10^5$ IU/mL	24-28 wk	Up to 12 wk after delivery
Asian Pacific Association for the Study of the Liver[70]	Tenofovir disoproxil fumarate, telbivudine	$> 10^{6-7}$ IU/mL	28-32 wk	At delivery
Chinese Medical Association[71]	Tenofovir disoproxil fumarate, telbivudine, lamivudine	$> 2 \times 10^6$ IU/mL	24-28 wk	At delivery
National Institute for Health and Care Excellence[72]	Tenofovir disoproxil fumarate	$> 10^7$ IU/mL	3 <sup>rd</sup> trimester	4-12 wk after birth

HBV: Hepatitis B virus.

was given infant HBIG and HBV vaccination initiated at birth[45]. The study confirmed a significant drop at delivery of HBV DNA for the pregnant women treated with tenofovir. However, all infants received HBV vaccine and immunoglobulin at a mean time of 1.2 and 1.3 h after delivery, and the vertical transmission rate with the administration of HBIG and vaccine in the placebo group was low (2% instead of the expected 12%). Furthermore, mothers with signs of HBV-related liver disease (alanine aminotransferase  $> 30$  IU/L) were excluded and both the tenofovir and the placebo groups consisted of mothers with low viral loads at baseline, possibly impacting the results of the study.

## PREVENTION OF VERTICAL TRANSMISSION OF HBV: MANAGEMENT STRATEGIES AT BIRTH

### *Neonatal immunoprophylaxis: The birth vaccine dose*

Post-exposure combined immunoprophylaxis through early administration of the first dose of vaccine and of HBIG is the most effective weapon to prevent vertical transmission of HBV. Without any preventative measures, the risk of vertical transmission for HBeAg-positive and HBeAg negative mothers ranges from 70% to 90% and from 10% to 40%, respectively[46]. The administration of HBV vaccine within 12 h of birth, followed by at least two more doses of vaccine within 6-12 mo[47], is 90%-95% effective in preventing vertical transmission[48,49]. If the administration of HBV vaccine is delayed until 48 h after birth, it would cause significant reduction in neonatal immunoprophylaxis efficacy. The recommendation by the WHO is to provide the first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 h[50], even in areas where HBV is of low endemicity. The combined approach with hepatitis B vaccine and HBIG at birth is not affordable in most of the endemic low and middle income countries. In these countries, considering the limited resources and the lack of access of HBIG, the WHO identifies HBV vaccination within 24 h of birth as the minimum intervention level and the main strategy to prevent infection[51]. In 2016 the coverage for the three-dose series of hepatitis B vaccine in infancy was estimated to be 84% (compared with 1% in 1990), and birth-dose coverage was estimated to be 39%.

### *Neonatal immunoprophylaxis: The combined vaccine and hepatitis B immunoglobulin approach*

In addition to the HBV vaccination, providing a dose of HBIG at birth to the vaccinated infants can further reduce the risk of transmission, especially in highly viraemic mothers, to less than 5%[52-54]. This was first demonstrated by Wong and collaborators[55] in 1984 in a prospective study enrolling 189 infants who were randomly assigned to receive (1) vaccine at birth and at 1, 2, and 6 mo with seven monthly HBIG injections (100 IU); (2) the same vaccine schedule but only one HBIG injection at birth; (3) only the vaccine, at months 0, 1, 2, and 6; and (4) placebos for both vaccine and HBIG. In all three treatment groups, development of the persistent carrier state was significantly less frequent than in the placebo group (2.9%, 6.8%, 21%, and

73.2%, respectively). Vaccination alone was associated with a remarkable protection toward vertical transmission but was significantly less protective than vaccination plus multiple HBIG injections.

HBIG are obtained from plasma donors with high levels of anti-HBs antibodies. Standard immunoglobulins are not indicated for prevention of vertical transmission of HBV because they contain too low antibody titres against HBV. Timely administration of HBIG and hepatitis B vaccine is critical for interrupting vertical transmission[47]. The Centers for Disease Control and Prevention recommends that the birth dose of HBIG and hepatitis B vaccine be given within 12 h after birth through intra-muscular injection but in an anatomic site different from that of the vaccine[47,56,57]. The earlier the administration of HBIG, the higher is the efficacy of the intervention that is unlikely to exceed the 7<sup>th</sup> day of birth. After administration of HBV vaccination combined with HBIG, infection can still occur in 2%-10% of HBeAg-positive or highly viraemic mothers[8,45,58]. Failure of the vaccine and immune-prophylaxis regimen or transplacental or intrauterine infection could account for this[8,9,59]. HBeAg-positive mothers and mothers with high circulating levels of HBV DNA ( $> 10^6$  IU/mL) have the highest risk of transmission[8,9]. The dose of HBIG generally used in infants is between 100 and 200 IU, corresponding to 30-40 IU/kg. It is important to note that the availability of HBIG in many countries, especially in those with low and middle income, that also have the higher endemicity is still low. The need for refrigerated storage, short shelf life, and low cost of the product should be addressed in order to make the use of HBIG feasible in all the different settings[60].

### ***Specific indications for immunoprophylaxis according to the HBsAg status of the mother and the weight of the child***

According to the Advisory Committee on Immunization Practice of the Center for Disease Control (ACIP-CDC) and the Committee on Infection Diseases of the American Academy of Pediatrics, the choice of the post-exposure immunoprophylaxis schedule is based on the mother's antigenic status (HBsAg) and the birth weight of the child (higher or lower than 2000 g)[47,61,62].

#### ***Infants born to HBsAg positive mothers***

All newborns born to a mother with HBsAg must receive the birth dose of vaccine and HBIG within 12 h of birth regardless of the birth weight. The completion of HBV vaccine is different according to the birth weight. According to the ACIP-CDC, newborns of mothers with HBsAg test not available during pregnancy but with highly suggestive evidence of HBV infection (presence of HBV DNA, HBeAg-positive, or mother known to be chronically infected with HBV) must be considered as born to HBsAg positive mothers[47].

#### ***Infants born to women with unknown HBsAg status***

Women with unknown HBsAg status at the time of delivery must be tested as soon as possible. In the meantime, newborns must receive the birth dose of the hepatitis B vaccine within 12 h of birth, regardless of birth weight. If the mother is positive, HBIG should be administered as soon as possible within 7 d of birth. If the mother is negative, the vaccination scheme should be completed as scheduled. In children weighing less than 2000 g, considering the potential reduced immunogenicity of the HBV vaccine in these children, it is recommended to administer HBIG within 12 h of birth even if the maternal status is still unknown. The vaccination schedule should be completed as indicated for HBsAg positive mothers[47].

#### ***Infants born to HBsAg negative mothers***

The WHO Strategic Advisory Groups of Experts recommends that infants receive the HBV vaccine at birth, preferably within 24 h, but administration up to 7 d after birth followed by two or three additional doses can still be effective[63]. In the case of newborns weighing less than 2000 g, the first dose should be administered after 1 mo of life or at the discharge if this occurs earlier.

#### ***Completion of HBV vaccine series after the birth dose***

The birth HBV vaccine dose should be followed by completion of a vaccine series. A study from the United States enrolling 17951 mother-infant pairs showed that the number of HBV vaccine doses was associated with risk of infant infection[64]. Overall, vertical HBV infection occurred among 1% of infants who received HBV vaccine and HBIG. Infection was detected in 6.7% (3 of 45 infants) of infants who received < three vaccine doses, compared with 1.1% (97 of 9207 infants) of infants who received  $\geq$  three

doses. The ACIP recommends immunoprophylaxis consisting of hepatitis B vaccine and HBIG within 12 h of birth, followed by completion of an HBV vaccine series.

According to the indications from WHO, if the birth weight is more than 2000 g, the vaccination schedule must be completed with two or three more doses[60], starting within the 2<sup>nd</sup> month of life and administering the final dose after the 24<sup>th</sup> week of life (164 d). In case of birth weight less than 2000 g, the birth dose should not be considered as part of the vaccination schedule but three additional doses of vaccine will be required for a total of four, starting when the child has reached 1 mo of age[65, 66]. This recommendation is provided because some studies showed that seroconversion rates may decrease among infants with a birth weight < 2000 g after administration of hepatitis B vaccine at birth. However, within the 1<sup>st</sup> month of age, all medically stable preterm newborns, regardless of their initial birth weight or gestational age, are as likely to respond to HBV immunization as term and larger infants.

### Testing infants for anti-HBs and HBsAg

Newborns to HBsAg positive mother should be tested after 1-2 mo from the final vaccine dose and normally at the age of 9-12 mo, through the evaluation of HBsAg and anti-HBs[67,68]. Test should not be executed before 9 mo of age to avoid detection of passive anti-HBs from HBIG administered at birth and to maximise the probability of detecting late HBV infection. Detection of anti-core antibodies is not recommended in infants born to HBsAg positive mothers because can be passively acquired and detected up to the age of 24 mo[47]. HBsAg negative and vaccinated children with anti-HBs titre greater than or equal to 10 mIU/mL have an adequate protection. If anti-HBs titres < 10 mIU/mL, a fourth additional dose should be administered and the test must be repeated after 1-2 mo. In case of persistence of anti-HBs < 10 mIU/mL after four vaccine doses, two additional doses for a total of six may be administered. The test should be repeated 1-2 mo after the sixth dose. In case of non-response, no further doses are expected[69].

## CONCLUSION

Vertical transmission of HBV is the leading mode of acquisition of the infection worldwide. Prevention of vertical transmission is possible in the majority of cases through the correct administration of the birth dose of HBV vaccine and HBIG to the neonate. Strategies are needed to promote implementation of birth-dose vaccination and HBIG in low- and middle-income countries where the prevalence of the infection is at the highest. Breastfeeding should be encouraged as long as the infant receives immunoprophylaxis at birth. Further studies on the use of antivirals (tenofovir alafenamide and tenofovir disoproxil fumarate) during pregnancy are required to increase prevention of HBV infection and their effectiveness in preventing vertical HBV infection when used together with to early active and passive immunoprophylaxis.

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