Prevention of vertical transmission of hepatitis B virus infection

Piero Veronese, Icilio Dodi, Susanna Esposito, Giuseppe Indolfi

ORCID number: Piero Veronese 0000-0002-4416-2269; Icilio Dodi 0000-0002-6772-4180; Susanna Esposito 0000-0003-4103-2837; Giuseppe Indolfi 0000-0003-3830-9823.

Author contributions: Veronese P and Indolfi G wrote the paper; Dodi I and Esposito S revised it critically for significant intellectual content.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/License s/by-nc/4.0/

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Italy

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 hepatitis B virus (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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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
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 (> 10^6 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 > 20000 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 ≥ 2 × 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 ≥ 2 × 10^6 IU/mL[15].

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.

PREVENTION OF VERTICAL TRANSMISSION OF HBV: MANAGEMENT STRATEGIES DURING PREGNANCY

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, HBcAg, 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 term 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 × 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. Telsbivudine 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 × 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 10^5 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
was given infant HBIG and HBV vaccination initiated at birth\cite{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\cite{46}. The administration of HBV vaccine within 12 h of birth, followed by at least two more doses of vaccine within 6-12 mo\cite{47}, is 90%-95% effective in preventing vertical transmission\cite{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\cite{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\cite{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 vireamic mothers, to less than 5%\cite{52-54}. This was first demonstrated by Wong and collaborators\cite{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

---

**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\cite{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\cite{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\cite{70} | Tenofovir disoproxil fumarate, telbivudine       | $> 10^5$ IU/mL     | 28-32 wk                | At delivery            |
| Chinese Medical Association\cite{71}           | Tenofovir disoproxil fumarate, telbivudine, lamivudine | $> 2 \times 10^6$ IU/mL | 24-28 wk                | At delivery            |
| National Institute for Health and Care Excellence\cite{72} | Tenofovir disoproxil fumarate                   | $> 10^7$ IU/mL     | 3rd trimester           | 4-12 wk after birth    |

HBV: Hepatitis B virus.
Vertical transmission of HBV vaccine doses, compared with 1.1% (97 of 9207 infants) of infants who received ≥ three HBIG. Infection was detected in 6.7% (3 of 45 infants) of infants who received < three HBV vaccine doses was associated with risk of infant infection. Study from the United States enrolling 17951 mother-infant pairs showed that the birth dose of HBIG and hepatitis B vaccine be given within 12 h after birth through intra-muscular injection but in an anatomical 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 7th 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 unknow 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 ≥ 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 2nd month of life and administering the final dose after the 24th 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 1st 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[67]. 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.

REFERENCES
1 Zhou YH. Global prevalence of hepatitis B virus infection and prevention of mother-to-child transmission. Lancet Gastroenterol Hepatol 2018; 3: 598 [PMID: 30102180 DOI: 10.1016/S2468-1253(18)30176-6]
2 Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015; 386: 1546-1555 [PMID: 26231459 DOI: 10.1016/S0140-6736(15)61412-X]
3 Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012; 30: 2212-2219 [PMID: 22273662 DOI: 10.1016/j.vaccine.2011.12.116]
4 World Health Organization. Global hepatitis report, 2017. Global Hepatitis Programme, 2017
5 World Health Organization. Hepatitis B. [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
6 Tran TT. Breastfeeding by mothers infected with hepatitis B carries no increased risk of transmission to infants who receive proper immunoprophylaxis: a meta-analysis. Evid Based Med 2012; 17: 125-126 [PMID: 22187494 DOI: 10.1136/ebmed.2011.100378]
7 Borgia G, Carleo MA, Gaeta GB, Gentile I. Hepatitis B in pregnancy. World J Gastroenterol 2012; 18: 4677-4683 [PMID: 23002336 DOI: 10.3748/wjg.v18.i34.4677]
Liu CJ, Jeng YM, Chen CL, Cheng HR, Chen PJ, Chen TC, Liu CH, Lai MY, Chen DS, Kao JH.

Citations:

8. Lin X, Guo Y, Zhou A, Zhang Y, Cao J, Yang M, Xiao F, Zhang B, Du Y. Immunophrophylaxis Failure Against Vertical Transmission of Hepatitis B Virus in the Chinese Population: A Hospital-based Study and a Meta-analysis. *Pediatric Infect Dis J* 2014; 33: 897-903 [DOI: 10.1097/INF.0000000000000153]

9. Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, Chen PJ, Chen DS, Chen HL. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. *J Hepatology* 2013; 59: 24-30 [PMID: 23485519 DOI: 10.1016/j.jhep.2013.02.015]

10. Pan YC, Jia ZF, Wang YQ, Yang N, Liu JX, Zhai XJ, Song Y, Wang C, Li J, Jiang J. The role of caesarean section and nonbreastfeeding in preventing mother-to-child transmission of hepatitis B virus in HBsAg-and HBeAg-positive mothers: results from a prospective cohort study and a meta-analysis. *J Viral Hepat* 2020; 27: 1032-1043 [PMID: 32362050 DOI: 10.1111/jvhe.13314]

11. Ko TM, Tseng LH, Chang MH, Chen DS, Hsieh FJ, Chuang SM, Lee TY. Amniocentesis in mothers who are hepatitis B virus carriers does not expose the infant to an increased risk of hepatitis B virus infection. *Arch Gynecol Obstet* 1994; 255: 25-30 [PMID: 8042875 DOI: 10.1007/BF02390671]

12. Chen LZ, Zhou WQ, Zhao SS, Liu ZY, Wen SW. A nested case-control study of maternal-neonatal transmission of hepatitis B virus in a Chinese population. *World J Gastroenterol* 2011; 17: 3640-3644 [PMID: 21987612 DOI: 10.3748/wjg.v17.i31.3640]

13. Song YM, Sang J, Yang S, Choe YH, Chang YS, Park WS. Factors associated with immunophrophylaxis failure against vertical transmission of hepatitis B virus. *Eur J Pediatr* 2007; 166: 813-818 [PMID: 17120036 DOI: 10.1007/s00431-006-0327-5]

14. Towers CV, Asrat T, Runney P. The presence of hepatitis B surface antigen and deoxyribonucleic acid in amniotic fluid and cord blood. *Am J Obstet Gynecol* 2001; 184: 1514-1518; discussion 1518 [PMID: 11408875 DOI: 10.1067/mob.2001.114866]

15. Gagnon A, Davies G, Wilson RD. GENETICS COMMITTEE. Prenatal invasive procedures in women with hepatitis B, hepatitis C, and/or human immunodeficiency virus infections. *J Gastroenterol Hepatol* 2014; 36: 648-653 [PMID: 25184985 DOI: 10.1111/jgh.12304-6]

16. Society for Maternal-Fetal Medicine (SMFM). Dionne-Odom J, Tita AT, Silverman NS. #38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. *Am J Obstet Gynecol* 2016; 214: 6-14 [PMID: 26454123 DOI: 10.1016/j.ajog.2015.09.090]

17. Hill JB, Sheffield JS, Kim MJ, Alexander JM, Sercey B, Wendel GD. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. *Obstet Gynecol* 2002; 99: 1049-1052 [PMID: 1205298].DOI: 10.1023/a:102000-8

18. Beasley RP, Stevens CE, Shiao IS, Meng HC. Evidence against breast-feeding as a mechanism for vertical transmission of hepatitis B. *Lancet* 1975; 2: 740-741 [PMID: 52772 DOI: 10.1016/s0140-6736(75)90724-2]

19. de Martino M, Appadino C, Resti M, Rossi ME, Muccioli AT, Vierrucci A. Should hepatitis B surface antigen positive mothers breast feed? *Arch Dis Child* 1985; 60: 972-974 [PMID: 4062350 DOI: 10.1136/adc.60.6.972]

20. World Health Organization. Hepatitis B and Breastfeeding. [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/maternal_child_adolescent/documents/pdfs/hepatitis_b_and_breastfeeding.pdf

21. Wang JS, Zhu QR, Wang XL. Breastfeeding does not pose any additional risk of immunophrophylaxis failure on infants of HBV carrier mothers. *Int J Clin Pract* 2003; 57: 100-102 [PMID: 12661791]

22. Benahoud S, Provest A, Coffie PA, Ekouévi DK, Urien S, Arrivé E, Blanche S, Théodoro F, Avit D, Borkowsky W, Van Dyke RB, Miller TL; Pediatric HIV/AIDS Cohort Study. Growth at 2 Years of Age in HIV-exposed Uninfected Children in the United States by Trimester of Maternal Antiretroviral Initiation. *Pediatr Infect Dis J* 2017; 36: 189-197 [PMID: 27798548 DOI: 10.1097/INF.0000000000013877]

23. European Association for the Study of the Liver. ; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatology* 2017; 67: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

24. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; 67: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

25. Singh M, Dicaire A, Waki AE, Luscombe C, Sacks SL. Quantitation of hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) in the liver of HBV-infected patients by LightCycler real-time PCR. *J Virol Methods* 2004; 118: 159-167 [PMID: 15081611 DOI: 10.1016/j.jviromet.2004.02.006]

26. Shi X, Wang X, Xu X, Feng Y, Li S, Feng S, Wang B, Wang S. Impact of HBV replication in peripheral blood mononuclear cell on HBV intrauterine transmission. *Front Med* 2017; 11: 548-553 [PMID: 29170913 DOI: 10.1007/s11684-017-0597-5]

27. Gupta I, Ratho RK. Immunogenicity and safety of two schedules of Hepatitis B vaccination during pregnancy. *J Obstet Gynaecol Res* 2003; 29: 84-86 [PMID: 12755527 DOI: 10.1046/j.1341-8076.2002.00076.x]

28. Liu CJ, Jeng YM, Chen CL, Cheng HR, Chen PJ, Chen TC, Liu CH, Lai MY, Chen DS, Kao JH.
Hepatitis B virus basal core promoter mutation and DNA load correlate with expression of hepatitis B core antigen in patients with chronic hepatitis B. *J Infect Dis* 2009; 199: 742-749 [PMID: 19199543 DOI: 10.1086/596655]

Sheffield JS, Hickman A, Tang J, Moss K, Kourosh A, Crawford NM, Wendel GD Jr. Efficacy of an accelerated hepatitis B vaccination program during pregnancy. *Obstet Gynecol* 2011; 117: 1130-1135 [PMID: 21508752 DOI: 10.1097/AOG.0b013e3182148e6c]

Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, Teng BQ. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. *World J Gastroenterol* 2004; 10: 3215-3217 [PMID: 15457579 DOI: 10.3748/wjg.v10.i21.3215]

Xiao XM, Li AZ, Chen X, Zhu YK, Miao J. Prevention of vertical hepatitis B transmission by hepatitis B immunoglobulin in the third trimester of pregnancy. *Int J Gynaecol Obstet* 2007; 96: 167-170 [PMID: 17296201 DOI: 10.1016/j.ijgo.2006.11.011]

Yuan J, Lin J, Xu A, Li H, Hu B, Chen J, Yao J, Dong H, Jiang M. Antepartum immunoprophylaxis of three doses of hepatitis B immunoglobulin is not effective: a single-centre randomized study. *J Viral Hepat* 2006; 13: 597-604 [PMID: 16907846 DOI: 10.1111/j.1365-2893.2006.00738.x]

Xu Q, Xiao L, Lu XB, Zhang YX, Cai X. A randomized controlled clinical trial: interruption of intrauterine transmission of hepatitis B virus infection with HBIG. *World J Gastroenterol* 2006; 12: 3434-3437 [PMID: 16733865 DOI: 10.3748/wjg.v12.i21.3434]

Eke AC, Eleje GU, Eke UA, Xia Y, Liu J. Hepatitis B immunoglobulin during pregnancy for prevention of mother-to-child transmission of hepatitis B virus. *Cochrane Database Syst Rev* 2017; 2: CD008854 [PMID: 28188612 DOI: 10.1002/14651858.CD008854.pub2]

Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, Zhang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother-To-Child Transmission of Hepatitis B. Tenfovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *N Engl J Med* 2016; 374: 2324-2334 [PMID: 27305192 DOI: 10.1056/NEJMoa1506600]

Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology* 2014; 60: 468-476 [PMID: 25187919 DOI: 10.1002/hep.27034]

Brown RS Jr, McMahon BJ, Lok AS, Wong JB, Ahmed AT, Mouchli MA, Wang Z, Prokop LJ, Murad MH, Mohammed K. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology* 2016; 63: 319-333 [PMID: 26565396 DOI: 10.1002/hep.28302]

Sirilert S, Hongsong T. Hepatitis B Virus Infection in Pregnancy: An Update on Evidence-Based Management. *Obstet Gynecol Surv* 2020; 75: 557-565 [PMID: 32997148 DOI: 10.1097/OGX.0000000000000831]

Nguyen V, Tan PK, Greenup AJ, Glass A, Davison S, Samarasinghe D, Holdaway S, Strasser SI, Chatterjee U, Jackson K, Locarnini SA, Levy MT. Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare. *Aliment Pharmacol Ther* 2014; 39: 1225-1234 [PMID: 24666381 DOI: 10.1111/apt.12726]

Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkins M. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus. *Cochrane Database Syst Rev* 2014: 9 DOI: 10.1002/14651858.CD008854.pub2

Han LF, Zheng JM, Zheng LQ, Gao HB, Chen LX, Xu QL, Chai YH, Zhang X, Pan C, Yao LF. Telbivudine can safely reduce mother-to-child transmission in chronic hepatitis B women after 12 wk of gestation. *BMC Infect Dis* 2019; 19: 614 [PMID: 31299917 DOI: 10.1186/s12879-019-4250-6]

Hyun MH, Lee YS, Kim JH, Je JH, Yoo YJ, Yeon JE, Byun KS. Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. *Aliment Pharmacol Ther* 2017; 45: 1493-1505 [PMID: 28436552 DOI: 10.1111/apt.14068]

Hou J, Cui F, Ding Y, Dou X, Duan Z, Han G, Jia J, Mao Q, Li J, Li Z, Liu X, Wei L, Xie Q, Yang X, Zhang H, Zhuang H. Management Algorithm for Interrupting Mother-To-Child Transmission of Hepatitis B Virus. *Clin Gastroenterol Hepatol* 2019; 17: 1929-1936. e1 [PMID: 30312789 DOI: 10.1016/j.cgh.2018.10.007]

Jourdain G, Ngo-Giang-Huong N, Harrison L, de Vincenzi I, Velland MJ, Reingold A, Harris al, Haber P, Ward JW, Nelson NP. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018; 67: 1-31 [PMID: 29939980 DOI: 10.15585/mmwr.r6701a1]

Thio CL, Guo N, Xie C, Nelson KE, Ehrhardt S. Global elimination of mother-to-child transmission of hepatitis B: revisiting the current strategy. *Lancet Infect Dis* 2015; 15: 981-985 [PMID: 26145195 DOI: 10.1016/S1473-3099(15)00158-9]

Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, Nelson NP. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2018; 67: 1-31 [PMID: 29939980 DOI: 10.15585/mmwr.r6701a1]

Zhang L, Xu A, Yan B, Song L, Li M, Xiao Z, Xu Q, Li L. A significant reduction in hepatitis B
Veronese P et al. Vertical transmission of HBV

virus infection among the children of Shandong Province, China: the effect of 15 years of universal infant hepatitis B vaccination. Int J Infect Dis 2010; 14: e483-e488 [PMID: 19939719 DOI: 10.1016/j.ijid.2009.08.005]

49 Ni YH, Huang LM, Chang MH, Yen CJ, Lu CY, You SL, Kao JH, Lin YC, Chen HL, Hsu HY, Chen DS. Two decades of universal hepatitis B vaccination in taiwan: impact and implication for future strategies. Gastroenterology 2007; 132: 1287-1293 [PMID: 17433222 DOI: 10.1053/j.gastro.2007.02.055]

50 Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018; 3: 383-403 [PMID: 29599078 DOI: 10.1016/S2468-1253(18)30056-6]

51 World Health Organization. Hepatitis B Control Through Immunization: A Reference Guide. [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/immunization/sage/meetings/2015/october/8_WPRO_Hepatitis_B_Prevention_Through_Immunization_Regional_R

52 European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]

53 Lo KJ, Tsai YT, Lee SD, Yeh CL, Wang JY, Chiang BN, Wu TC, Yeh PS, Goudeau A, Coursaget P. Combined passive and active immunization for interruption of perinatal transmission of hepatitis B virus in Taiwan. Hepatogastroenterology 1995; 32: 65-68 [PMID: 315639]

54 Lee C, Gong Y, Brok J, Boxall EH, Gloud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ 2006; 332: 328-336 [PMID: 16483611 DOI: 10.1136/bmj.38719.435833.7C]

55 Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, Ma HK. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet 1984; 1: 921-926 [PMID: 6143868 DOI: 10.1016/S0140-6736(84)92388-2]

56 Weinbaum CM, Mast EE, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. Hepatology 2009; 49: S35-S44 [PMID: 19399812 DOI: 10.1002/hep.22882]

57 Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM Jr, Janssen RS, Ward JW; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep 2006; 55: 1-33; quiz CE1 [PMID: 17159323]

58 Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009; 27: 6550-6557 [PMID: 19729084 DOI: 10.1016/j.vaccine.2009.08.048]

59 Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, Huang FC, Wu SF, Chen SC, Wen WH, Chu CH, Ni YH, Hsu HY, Tsai PL, Chiang CL, Shyu MK, Lee PI, Chang FY, Chang MH. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology 2012; 142: 773-781. e2 [PMID: 22198276 DOI: 10.1053/j.gastro.2011.12.035]

60 World Health Organization. Guideline for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization, 2015: 124

61 World Health Organization. Preventing Perinatal Hepatitis B Virus Transmission: A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination. [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: http://www.who.int/iris/handle/10665/208278

62 Losonsky GA, Wasserman SS, Stephens I, Mahoney F, Armstrong P, Gumpker K, Dukerian S, West DJ, Gewolb IH. Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. Pediatrics 1999; 103: E14 [PMID: 9925860 DOI: 10.1542/peds.103.2.e14]

63 World Health Organization. Hepatitis B vaccines: WHO position paper – July 2017. [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/immunization/policy_position_papers/hepatitis_b/en/

64 Schillie S, Walker T, Vesely S, Crowley S, Dusek C, Lazaroff J, Morris SA, Onye K, Ko S, Fenlon N, Nelson NP, Murphy TV. Outcomes of infants born to women infected with hepatitis B. Pediatrics 2015; 135: e141-e147 [PMID: 25896839 DOI: 10.1542/peds.2014-3213]

65 Saari TN; American Academy of Pediatrics Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics 2003; 112: 193-198 [PMID: 12837889 DOI: 10.1542/peds.112.1.193]

66 World Health Organization. HBV vaccination among low birth weight children (LBW). [cited 5 February 2021]. In: World Health Organization [Internet]. Available from: http://www.who.int/immunization/sage/meetings/2016/october/4_Systematic_review_of_safety_efficacy_hep_b.pdf?ua=1

67 Schillie S, Murphy TV, Fenlon N, Ko S, Ward JW. Update: Shortened Interval for Postvacccination
Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. *MMWR Morb Mortal Wkly Rep* 2015; 64: 1118-1120 [PMID: 26447601 DOI: 10.15585/mmwr.mm6439a6]

68 **Committee on Infectious Diseases**; Committee on Fetus and Newborn. Elimination of Perinatal Hepatitis B: Providing the First Vaccine Dose Within 24 Hours of Birth. *Pediatrics* 2017; 140 [PMID: 28847980 DOI: 10.1542/peds.2017-1870]

69 **Committee on Infectious Disease**. Hepatitis B. In: Kimberlin DW. Red Book. Committee on Infectious Disease, 2018: 401-428

70 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou IL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; 10: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

71 **Hou J**, Wang G, Wang F, Cheng J, Ren H, Zhuang H, Sun J, Li L, Li J, Meng Q, Zhao J, Duan Z, Jia J, Tang H, Sheng J, Peng J, Lu F, Xie Q, Wei L; Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases; Chinese Medical Association. Guideline of Prevention and Treatment for Chronic Hepatitis B (2015 Update). *J Clin Transl Hepatol* 2017; 5: 297-318 [PMID: 29226097 DOI: 10.14218/JCTH.2016.00019]

72 **National Institute for Health and Care Excellence**. Hepatitis B (chronic): diagnosis and management. Clinical guidelines [CG165]. [cited 5 February 2021]. In: National Institute for Health and Care Excellence [Internet]. Available from: https://www.nice.org.uk/guidance/cg165
