Viral hepatitis in children and adolescents 1

Hepatitis B virus infection in children and adolescents

Giuseppe Indolfi, Philippa Easterbrook*, Geoffrey Dusheiko, George Siberry, Mei-Hwei Chang, Claire Thorne, Marc Bulterys, Po-Lin Chan, Manal H El-Sayed, Carlo Giaquinto, Maureen M Jonas, Tammy Meyers, Nick Walsh, Stefan Wirth, Martina Penazzato*

Hepatitis B virus (HBV) infection is a major cause of acute and chronic liver disease and associated morbidity and mortality worldwide. Vertical (mother-to-child) and horizontal early childhood transmission are the main routes of HBV transmission and are responsible for most chronic infections, including among adults who bear the greatest burden of morbidity and mortality. Universal hepatitis B immunisation at birth and in infancy is the key strategy for global elimination of HBV infection, and has been highly effective in reducing new vertical infections. However, global progress in scale-up of HBV testing and treatment has been slow in adults and children. In this Series paper, we summarise knowledge on the epidemiology, natural history, and treatment of chronic HBV infection in adolescents and children, and we highlight key differences from HBV infection in adults. The estimated global prevalence of HBV infection in children aged 5 years or younger is 1·3%. Most children are in the high-replication, low-inflammation phase of infection, with normal or only slightly raised aminotransferases; cirrhosis and hepatocellular carcinoma are rare. Although entecavir is approved and recommended for children aged 2–17 years, and tenofovir for those aged 12–18 years, a conservative approach to treatment initiation in children is recommended. Key actions to address current policy gaps include: validation of non-invasive tests for liver disease staging; additional immunopathogenesis studies in children with HBV infection; long-term follow-up of children on nucleoside or nucleotide analogue regimens to inform guidance on when to start treatment; evaluation of different treatment strategies for children with high rates of HBV replication; and establishment of paediatric treatment registries and international consortia to promote collaborative research.

Introduction

Hepatitis B virus (HBV) is a major cause of acute and chronic liver disease and associated morbidity and mortality worldwide.[1–5] Globally, WHO estimates that HBV caused chronic infection in 257 million people and 887 000 deaths in 2015.[2] Annually, there are almost 2 million new infections in children younger than 5 years, mostly through mother-to-child transmission, and horizontal transmission in early life.[2,5] In 2016, recognising the public health burden of hepatitis and opportunities for action, WHO launched the Global Health Sector Strategy on Hepatitis 2016–21. The strategy aims to eliminate hepatitis B as a public health threat by 2030, which is defined as a 90% reduction in the incidence of chronic infections (assessed by reduced prevalence among children aged 5 years) and a 65% reduction in liver-related deaths. The strategy established coverage targets for preventive interventions (three or more doses of vaccination for 90% of infants, and birth-dose vaccination for at least 90% of neonates within 24 h of birth), diagnosis (diagnosis of 90% of people infected with HBV), and treatment (antiviral treatment of 80% of people who are diagnosed and eligible for treatment).[6]

Considerable progress has been made towards achieving elimination of HBV through universal infant hepatitis B immunisation, which has been highly effective in reducing new infections in children.[7] By contrast, the focus of global efforts to combat hepatitis in adults has been on reducing morbidity and mortality due to chronic liver disease, through scale-up of testing, case finding and long-term antiviral treatment with tenofovir[8] or entecavir[9] to suppress viral replication. However, access to affordable HBV testing and treatment remains poor in low-income and middle-income countries. In 2015, only 9% of people with chronic hepatitis B infection, or 22 million people, were estimated to have been diagnosed globally, and of those, around 8% (ie, 1·7 million people) were receiving treatment,[2] although it is recognised that only a proportion of those infected will require treatment.

Compared with adults, little attention has been given to testing and treatment strategies for chronic HBV infection among children and adolescents, partly because most patients are in the immunotolerant phase of infection and do not require treatment, but also because of the absence of evidence from low-income settings with high HBV prevalence to inform paediatric-specific management practices. For example, although there have been seven moderately large (>90 patients enrolled) and long-term (>10 years of follow-up) prospective studies on the natural history of HBV infection in children, these studies have mainly been from high-income countries.[10–17] Similarly, only one trial on the safety and efficacy of tenofovir disoproxil fumarate for adolescents (aged ≥12 years),[18] and one trial on entecavir for children (>2 years), have been completed.[19] The aim of this Series paper is to provide an overview of the epidemiology, natural history, and treatment of chronic HBV infection in children and adolescents, and to highlight key differences and similarities when compared with infection acquired in adulthood. We conclude with key

Lancet Gastroenterol Hepatol 2019

Published Online
April 11 , 2019
http://dx.doi.org/10.1016/S2468-1253(19)30042-1

This is the first in a Series of two papers about viral hepatitis in children and adolescents

*Contributed equally

Paediatric and Liver Unit, Meyer Children's University Hospital of Florence, Florence, Italy (G Indolfi MD); **Global Hepatitis Programme and HIV Department, World Health Organization, Geneva, Switzerland** (Prof P Easterbrook MD, M Bulterys MD, M Penazzato MD); **King's College Hospital, London, UK** (Prof G Dusheiko MD); **University College London Medical School, London, UK** (Prof G Dusheiko); **Office of the US Global AIDS Coordinator, US Department of State, Washington, DC, USA** (G Siberry MD); **Department of Paediatrics, National Taiwan University Hospital, Taipei, Taiwan** (Prof M-H Chang MD); **UCL Great Ormond Street Institute of Child Health, University College London, London, UK** (C Thorne PhD); **World Health Organization Regional Office for the Western Pacific, Manila, Philippines** (P-L Chan MD); **Department of Paediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt** (Prof M H El-Sayed MD); **Department of Women and Child Health, University of Padova, Padova, Italy** (Prof C Giaquinto MD); **Division of Gastroenterology, Hepatology, and Nutrition, Boston Children's Hospital, Boston, MA, USA** (Prof M M Jonas MD); **Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, South Africa** (Prof T Meyers MD); **Pan American Health Organization,**

World Health Organization Regional Office for the Americas, Washington, DC, USA (N Walsh PhD)**; and Department of Paediatrics, Helios Medical Centre Wuppertal, Witten-Herdecke University, Witten, Germany** (Prof S Wirth MD)

Correspondence to: Prof Philippa Easterbrook, Global Hepatitis Programme and HIV Department, World Health Organization, Geneva 1211, Switzerland
easterbrookp@who.int

priorities for action, which include promoting the scale-up of testing and treatment, and addressing important evidence gaps to inform future policy development.

Seroprevalence and burden

Whereas HBsAg prevalence among adults generally reflects historical exposure and prevalence of HBV infection, HBsAg prevalence among children aged 5 years and younger largely reflects the extent of infant and birth-dose HBV vaccination. Global estimates of HBV prevalence (as measured by detection of HBsAg), burden, morbidity, and mortality are largely based on data from the adult population.[1,2,4,5] Overall, WHO estimates that 257 million people were HBsAg-positive in 2015 (3·5% of the global population),[2] which is broadly consistent with the Polaris Observatory collaborators' modelled estimate of 291 million (95% uncertainty interval 252–341 million), corresponding to a global prevalence of 3·9%.[5] More than half of people who are infected with HBV reside in areas of high and intermediate HBV endemicity.[1,2,4] The countries with the highest prevalence (>6%) are in the WHO African and Western Pacific Regions, and the countries with the lowest prevalence are in the Region of the Americas and the European Region.[2] In 2015, WHO estimated that the global HBsAg prevalence in children younger than 5 years was approximately 1·3%,[2] compared with a prevalence of approximately 4·7% before the widespread adoption of universal infant vaccination (from the 1980s to the early 2000s).[2] According to a report from the Polaris Observatory,[5] there were approximately 1·8 million (95% uncertainty interval 1·6–2·2 million) new infections in children globally in 2016. 16 countries account for more than 80% of new infections, and Nigeria, India, Indonesia, and the Democratic Republic of the Congo account for almost 57% of new infections.[5] The geographical distribution of HBV infection, and the most affected regions, are similar for children and adults. The highest prevalence in children and adults is in the WHO African Region, which also had the lowest coverage of timely birth-dose vaccination within 24 h of birth (10%) of all regions globally. The lowest prevalence among children aged 5 years or younger (<0·1%) was in the Americas, which also had a low prevalence even before widespread vaccination was implemented.[5] In western Europe and North America, it is rare for people younger than 18 years to be HBsAg-positive.[1,2] However, an increasing number of children with HBV infection are migrating to Europe and North America from countries with higher prevalence.[20,21] Data for the prevalence of HBV in adolescents are scarce, and the annual mortality in adolescents and children is unknown.

See Online for appendix

Routes of transmission

Most chronic HBV infections in adults have been acquired through mother-to-child transmission at birth or during early childhood, especially in high-prevalence settings.[1,7,22] The main routes of acquisition of new adult infections are through unsafe injections, sexual transmission among men who have sex with men, or sex with multiple sexual partners.[1,23]

Mother-to-child transmission accounts for most HBV infections in children, both in high-endemicity countries (HBsAg seroprevalence >8%) where the implementation of infant vaccination (especially birth-dose vaccination) has been suboptimal, as well as in low-endemicity countries. However, intrauterine infections and vaccine or immune-prophylaxis regimen failures could also account for some new infections as infant vaccination coverage improves.[2,24,25] Up to a third of incident HBV infections could be due to horizontal transmission in early childhood, in the form of child-to-child, household, or intrafamilial transmission, especially in sub-Saharan Africa and among unvaccinated children who migrate to Europe.[20,21,26] Transmission can also result from poor infection control and injection safety during medical, surgical, and dental procedures,[27] and traditional practices (such as scarification or circumcision).[28]

Natural history of HBV infection

HBV causes both acute and chronic infection that can range from asymptomatic infection or mild disease to severe or fulminant hepatitis. The key determinant of chronic infection is the age of infection. Chronic infection occurs in 90% of infected neonates and infants but in less than 5% of patients who acquire infection in adulthood.[29–33] Infections are usually asymptomatic and anicteric in children who are infected vertically,[10,34] but acute infection is sometimes associated with severe symptoms and fulminant hepatitis in both adults[35] and children.[36] Chronic infection can lead to progressive liver disease and development of complications, such as cirrhosis and hepatocellular carcinoma (mainly in adulthood),[37] and extrahepatic manifestations (that can also present in infancy and early childhood).[38]

The natural history of chronic HBV infection is dynamic and complex, progressing non-linearly through several recognisable phases of variable duration.[29,39] Disease progression depends on a complex interplay between the virus and the immune system. The terms immune-tolerant, immune-active, immune-control, and immune-escape have been used to describe the different phases of infection, but it has been increasingly recognised that these descriptions are not supported by immunological data and do not always relate directly to indications for antiviral therapy. New nomenclature has been adopted by the European Association for the Study of the Liver (EASL; appendix p 1),[40] based on the characterisation of infection as either with or without active hepatitis (defined as raised or normal alanine aminotransferase concentrations, respectively) and on HBeAg status. However, this new nomenclature has not yet been adopted by other professional societies,

including the American Association for the Study of Liver Disease (AASLD).[41]

Hepatitis B infection acquired in adulthood is usually an acute and symptomatic infection that is self-resolving, and rarely leads to chronic infection[30,37] or related complications. Based on several large, prospective, population-based studies,[42–44] the 5-year cumulative incidence of cirrhosis in adults with chronic infection is 8–20%,[29,45,46] and of hepatic decompensation and hepatocellular carcinoma among patients with cirrhosis is 20%[37] and 2–5%,[47] respectively. In adults, chronic HBV infection is also associated with the development of HBV-related kidney disease, mainly glomerulonephritis.[48]

The natural history and phases of HBV infection in children have been less well delineated. Seven large (>90 children enrolled) and long-term (>10 years of follow-up) prospective studies have been done on the natural history of HBV infection in children,[10–17] as well as some smaller prospective and retrospective studies (appendix pp 3–5).[49–54] When HBV infection is acquired perinatally or in early childhood, it is likely to lead to chronic infection.[10–16,49–54] The main characteristic of HBV infection that is acquired perinatally or during early childhood is a high-replication, low-inflammation phase that can last several decades, in which HBsAg and HBeAg are detectable in the serum, serum HBV DNA concentrations are high, and serum aminotransferase concentrations are normal or only slightly increased. Previously, chronic HBV infection in patients who acquired HBV infection perinatally or during early childhood was thought to be characterised by a state of immunological tolerance. In a 29-year longitudinal study from Italy, 89 of 91 HBeAg-positive children underwent HBeAg seroconversion to anti-HBe, and the median age of onset of the HBeAg-positive, immune-active phase after perinatal infection was 30 years.[10] The immunopathogenesis of chronic infection and the resulting immunotolerance in infants and children is still poorly understood,[10,29,30,42,55] and the concept of immunotolerance is being challenged.[56] Recent studies have suggested that adolescents might harbour functionally active HBV-specific T cells and that antigen-specific immune responses exist in so-called immune-tolerant people.[57]

In longitudinal prospective[10,49] and retrospective[51] studies, cirrhosis has been reported in 1–5% of HBeAg-positive children.[10,49,51] Risk factors for cirrhosis are earlier HBeAg seroconversion (ie, at <3 years of age, consistent with severe necroinflammatory activity), and longer duration of the immune-active phase.[10,11] HBV genotype C infection is associated with delayed spontaneous seroconversion.[58] Although chronic HBV infection accounts for most cases of hepatocellular carcinoma, the absolute risk of developing hepatocellular carcinoma in childhood is very low. In a prospective study of 426 children with chronic HBV infection from Taiwan, only two boys (<1%) developed hepatocellular carcinoma in childhood, or an incidence of 32 per 100 000 person-years,[11] and two (2%) of 91 Italian children enrolled in a 29-year longitudinal study developed hepatocellular carcinoma during childhood.[10] By contrast, in some parts of Africa and the Amazon Basin, the incidence of hepatocellular carcinoma in infected children and young men is much higher.[59,60] Aflatoxin exposure[61] and HBV genotype might contribute to this increased risk.[10,11,51,62,63] The effect of viral genotype on the risk of developing hepatocellular carcinoma in children and adolescents is still to be defined, although genotype B is associated with an increased risk of hepatocellular carcinoma.[62] Chronic HBV infection is also associated with the development of kidney disease in children.[64–66]

Prevention of vertical transmission

In the absence of any preventative interventions, the risk of perinatal vertical transmission was found to range from 70% to 90% for HBeAg-positive mothers and from 10% to 40% for HBeAg-negative mothers in Asia,[67] whereas the risk was found to be substantially lower in Africa.[31] The most important strategy for control of the HBV epidemic and prevention of HBV infection in children is the administration of HBV vaccine within 24 h of birth, followed by at least two more doses of vaccine within 6–12 months. This regimen is 90–95% effective in preventing infection.[68–70] A dose of hepatitis B immunoglobulin (HBIG) given at birth to infants of mothers who are highly infectious can further reduce the risk of transmission to less than 5%.[71,72] The global coverage for the three-dose series of HBV vaccine in infancy in 2016 was estimated to be 84% (compared with 1% in 1990), and birth-dose coverage was estimated to be 39%.[73] This strategy, with some variation in implementation, has reduced HBsAg prevalence by 83–95% among children in China and Egypt.[69,70,74,75] HBV immunisation of infants also greatly reduces the incidence of hepatocellular carcinoma later in life.

After treatment with a combination of HBV vaccination and HBIG, vertical transmission can still occur in 2–10% of HBeAg-positive or highly viraemic mothers.[72,76] This could be due to transplacental or intrauterine infection or failure of the vaccine and immune-prophylaxis regimen.[76,77] HBeAg-positive mothers and mothers with high circulating concentrations of HBV DNA (>10^6 IU/mL) have the highest risk of transmission.[76,78] Several trials have shown that the use of nucleoside or nucleotide analogues, such as lamivudine, telbivudine, or tenofovir,[72,79–81] during the third trimester of pregnancy in highly viraemic, HBeAg-positive mothers, in combination with standard infant immune-prophylaxis, is effective in further reducing the vertical transmission of HBV.[77–81] In 2018, a large, placebo-controlled trial of maternal tenofovir given to HBeAg-positive pregnant women in the last trimester in Thailand, plus birth-dose vaccination and HBIG, did not find a significantly lower mother-to-child

	Adults	Children
American Association for the Study of Liver Diseases[41]	Elevation of ALT more than two times ULN (30 U/L for men and 19 U/L for women) or evidence of substantial histological disease, plus HBV DNA >2000 IU/mL (HBeAg-negative) or >20 000 IU/mL (HBeAg-positive) Adults >40 years old with normal ALT, elevated HBV DNA (>1 000 000 IU/mL), and liver biopsy showing substantial necroinflammation or fibrosis Adults with compensated cirrhosis and low viraemia (<2000 IU/mL) HBsAg-positive adults with decompensated cirrhosis regardless of HBV DNA concentration, HBeAg status, or ALT concentration (these patients should be treated with antiviral therapy indefinitely) HBsAg-positive pregnant women with HBV DNA >200 000 IU/mL	HBeAg-positive children (aged 2–17 years) with elevated ALT and measurable HBV DNA concentrations
European Association for the Study of the Liver[40]	HBV DNA concentration >2000 IU/mL and one or both of: ALT higher than ULN, and at least moderate liver necroinflammation or fibrosis Patients with compensated or decompensated cirrhosis and detectable HBV DNA, independent of ALT concentration; HBV DNA >20 000 IU/mL and ALT more than two times ULN, regardless of the degree of fibrosis Patients >30 years of age with HBeAg-positive chronic HBV infection (normal ALT and high HBV DNA), regardless of the severity of liver histology Patients with HBeAg-positive or HBeAg-negative chronic HBV infection, a family history of hepatocellular carcinoma or cirrhosis, and extrahepatic manifestations	A conservative approach is warranted
WHO[39]	All adults with clinical evidence of compensated or decompensated cirrhosis (or APRI score >2 in adults), regardless of ALT concentration, HBeAg status, or HBV DNA concentration Adults >30 years old without clinical evidence of cirrhosis (or APRI score ≤2 in adults) but with persistently abnormal ALT concentration and (if available) evidence of high HBV replication (HBV DNA >20 000 IU/mL), regardless of HBeAg status	All adolescents and children with clinical evidence of compensated or decompensated cirrhosis, regardless of ALT concentration, HBeAg status, or HBV DNA concentration
Asian Pacific Association for the Study of the Liver[22]	Decompensated cirrhosis, and detectable HBV DNA or severe reactivation (decompensation) of chronic infection; compensated cirrhosis and HBV DNA >2000 IU/mL Persistently elevated (≥1 month between observations) ALT concentration more than two times ULN and HBV DNA >20 000 IU/mL if HBeAg-positive or >2000 IU/mL if HBeAg-negative (liver biopsy or a non-invasive method to estimate the extent of fibrosis might provide further useful information); pronounced fibrosis, and normal or slightly elevated ALT concentration or HBV DNA <20 000 IU/mL if HBeAg-positive or <2000 IU/mL if HBeAg-negative	Children with cirrhosis (compensated or decompensated) Children with severe reactivation of chronic HBV (detectable HBV DNA and elevated ALT) Non-cirrhotic, HBeAg-positive chronic HBV infection, HBV DNA >20 000 IU/mL, and ALT more than two times ULN for >12 months Non-cirrhotic, HBeAg-positive chronic HBV infection and either HBV DNA >20 000 IU/mL and ALT more than two times ULN for more than 12 months, or a family history of hepatocellular carcinoma or cirrhosis and moderate-to-severe inflammation or pronounced fibrosis Non-cirrhotic, HBeAg-positive chronic HBV infection, HBV DNA <20 000 IU/mL, and moderate to severe inflammation or pronounced fibrosis Non-cirrhotic, HBeAg-negative chronic HBV infection, HBV DNA >2000 IU/mL, and ALT more than two times ULN Non-cirrhotic, HBeAg-negative chronic HBV infection and moderate to severe inflammation or pronounced fibrosis, regardless of HBV DNA concentration
European Society for Paediatric Gastroenterology, Hepatology and Nutrition[87]	NA	Elevated serum ALT for ≥6 months if HBeAg-positive (or ≥12 months if HBeAg-negative), HBV DNA >2000 IU/mL, and either moderate necroinflammation or fibrosis, or mild inflammation or fibrosis with a family history of hepatocellular carcinoma

Patients who meet the criteria in the table are recommended to receive treatment. ALT=alanine aminotransferase. HBV=hepatitis B virus. ULN=upper limit of normal. APRI=aspartate aminotransferase-to-platelet ratio index. NA=not applicable.

Table 1: **Comparison of recommendations and indications for treatment of chronic HBV infection in adults, adolescents, and children from five professional societies or international organisations**

transmission rate beyond the low rate already achieved in the comparison group that was given infant HBIG and HBV vaccination initiated at birth.[72] Tenofovir is the recommended nucleotide analogue for prophylaxis in pregnancy, and can be stopped 1–3 months post-delivery, if it is prescribed only to prevent perinatal transmission.[39,82] The WHO Regional Office for the Western Pacific[83] and the Pan American Health Organization[84] have established strategies for triple elimination of mother-to-child transmission of HIV, hepatitis B (goal of <0·1% prevalence of HBsAg among children <5 years by 2030), and syphilis, which will be implemented through integration of the interventions provided by maternal, neonatal, and child health services.[83,84]

Diagnosis and monitoring

HBV infection in adults, adolescents, and children (>12 months)[85] is diagnosed by detection of HBsAg in the serum with a serological assay (either a rapid diagnostic test or a laboratory-based immunoassay) that meets minimum quality, safety, and performance standards, in terms of both analytical and clinical sensitivity and specificity.[85] The HBsAg assay might also be repeated at

least 6 months after the first positive test to confirm chronic HBV infection. Testing of exposed infants in the first 6 months of life is problematic, because HBsAg and HBV DNA can be transiently present at birth or in the first few months of life and might not reflect chronic HBV infection.[86] Exposed infants should be tested for HBsAg at 6–12 months of age to reduce the risk of false-positive results.[85,87]

It is estimated that between 5% (from a community-based study in Africa)[88] and 40% (from hospital-based studies) of all HBsAg-positive adults might require treatment for HBV, dependent on stage of liver disease and fibrosis, levels of HBV DNA replication, and alanine aminotranferase concentrations to indicate the extent of liver inflammation. An assessment of these factors is needed to guide further management and to decide whether treatment is required.[39] Non-invasive tests, such as transient elastography, ultrasound shear wave elastography, or serum biomarker-based tests (eg, aspartate aminotransferase-to-platelet ratio index, Fibrosis 4, and FibroTest scores) have been validated for staging of liver fibrosis and diagnosis of cirrhosis in adults,[89–91] and have replaced the use of invasive liver biopsy.[22,39–41]

By contrast with adults, in children, liver biopsy is still considered the standard test to assess the degree of liver inflammation, the stage of fibrosis, and indication for treatment.[87,92] Although the procedure is invasive, it is associated with a low risk of complications when done by trained operators.[92] The diagnostic and prognostic value of transient elastography in adolescents and children with chronic HBV infection is not yet well established.[42,87] Transient elastography has been evaluated in 140 children with chronic viral hepatitis across five studies,[93–97] but a formal comparison with liver biopsy results was only available in a subset of 58 children. In this subset, transient elastography was reliable in distinguishing different stages of liver fibrosis in patients with HBV and hepatitis C virus infection. There is a need to validate other non-invasive diagnostic tests for children and adolescents, because of the major challenges of doing liver biopsies in resource-limited, non-specialist settings.

Before, during, and after antiviral treatment, monitoring is required for both adults and children with chronic HBV infection. The frequency of monitoring will depend on the stage of liver fibrosis, the patient's serological profile (HBeAg-positive or HBeAg-negative), and concentrations of alanine aminotransferase and HBV DNA. However, the evidence base is small and the optimal schedule for monitoring is not well established. Recommendations on the monitoring of HBV infection in adults and children according to guidelines from different organisations are summarised in the appendix (pp 7–9).

Guidelines from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) provide specific guidance for monitoring of children with chronic HBV infection.[87] More frequent monitoring is proposed for children than for adults, with monitoring of alanine aminotransferase and HBV DNA concentrations every 3–4 months for at least 1 year in HBeAg-positive children with an increased alanine aminotransferase concentration, to evaluate the indication for treatment. In HBeAg-negative children, the same monitoring schedule is recommended to rule out HBeAg-negative active disease.[87] For HBeAg-positive children with normal alanine aminotransferase concentrations, monitoring every 6 months is recommended.[87] For children receiving treatment, there are no specific recommendations, and the frequency of monitoring for safety, adherence, and efficacy should be determined on an individual basis.[87]

Treatment for chronic HBV infection

The common goals of antiviral treatment for adults, adolescents, and children with chronic HBV infection are to decrease the risk of disease progression to cirrhosis and hepatocellular carcinoma through effective and sustained suppression of HBV replication.[22,39,41,87] With use of available nucleoside or nucleotide analogue therapies, HBsAg loss and seroconversion to anti-HBs is achieved in less than 1% of adults and in 1–6% of children,[98] although the longer the duration of treatment, the higher the rate of HBsAg seroconversion.[98] New HBV curative combination treatment strategies aimed at eliminating all replicative intermediates, including covalently closed circular DNA in the nucleus, are being researched,[99,100] with the potential to transform future indications for treatment. A combination of antiviral and immune-modulatory therapies will probably be needed to achieve a functional cure for HBV, characterised by sustained loss of HBsAg with or without HBs antibody seroconversion.[101,102]

Treatment guidelines for the management of chronic HBV infection in adults are available from three professional organisations (EASL, AASLD, and the Asian Pacific Association for the Study of the Liver [APASL]) and WHO.[22,39–41] Guidelines for children are available from ESPGHAN and AASLD.[41,87] Across all guidelines, the decision to start treatment is based on a combined assessment of stage of liver disease, HBV DNA and alanine aminotransferase concentrations, and HBeAg status, as well as other considerations, such as a family history of hepatocellular carcinoma and co-incidence of HIV infection or other liver disease.[22,39–41,87] The possible benefits of treatment need to be evaluated against the disadvantages of initiating long-term antiviral therapy in children and the likely natural history of progression in the absence of treatment.[87]

Table 1 summarises the main similarities and differences between recommendations for adults and children from professional societies[22,40,41,87] and WHO.[39] By contrast with adults, little evidence is available to guide recommendations on the optimal timing and indications for treatment in adolescents and children. Regardless of age, all guidelines recommend treatment for patients with cirrhosis, as well as for patients with active hepatitis (ie, HBeAg-positive or HBeAg-negative with elevated

	Ages for which drug is approved	Doses	Formulations	Number of randomised controlled trials on effects of treatment
Interferon alfa-2b	≥1 year	6 million IU/m^2 three times a week	Subcutaneous injection	8
Peginterferon alfa-2a	≥3 years	180 μg/1·73 m^2 once a week	Subcutaneous injection	1
Peginterferon alfa-2b	Not approved	NA	NA	0
Lamivudine	≥3 years	3 mg/kg daily (maximum 100 mg)	Oral solution (5 mg/mL) or tablets (100 mg)	1
Entecavir	≥2 years	10–30 kg: 0·015 mg/kg daily (maximum 0·5 mg); >30 kg: 0·5 mg daily	Oral solution (0·05 mg/mL) or tablets (0·5 mg and 1 mg)	1
Adefovir	≥12 years	10 mg daily	Tablets (10 mg)	1
Tenofovir disoproxil fumarate	≥2 years*	300 mg daily	Oral powder (40 mg per 1 g) Tablets (150 mg, 200 mg, 250 mg, and 300 mg)	1; an additional paediatric trial (2–17 years) is ongoing (NCT01651403)
Tenofovir alafenamide	≥12 years	25 mg daily	Tablets (25 mg)	0†; a paediatric trial (2–17 years) is ongoing (NCT02932150)
Telbivudine	Not approved	NA	NA	0; a paediatric trial is ongoing (NCT02058108)

*Approved for ≥2 years by the European Medicines Agency (January, 2019), and ≥12 years by the US Food and Drug Administration. †Data are available for children with HIV infection. NA=not applicable.

Table 2: **Antiviral drugs that are approved for adults, adolescents, and children with chronic hepatitis B virus infection**

aminotransferases and HBV DNA concentrations, and histological evidence of necroinflammation and fibrosis).[22,39–41] AASLD guidelines recommend treatment for HBeAg-positive adolescents and children with both elevated alanine aminotransferase and measurable HBV DNA concentrations,[41] but do not specify the duration of alanine aminotransferase elevation (although most studies were based on patients with an alanine aminotransferase elevation of more than 1·3 times the upper limit of normal for ≥6 months). By contrast, guidelines from ESPGHAN recommend treatment if the patient has persistent alanine aminotransferase elevation for at least 6 months in HBeAg-positive adolescents and children, or for at least 12 months in HBeAg-negative adolescents and children, together with liver biopsy results showing moderate-to-severe inflammation and fibrosis.[87] APASL guidelines recommend treatment in HBeAg-positive adolescents and children if the HBV DNA concentration is higher than 20 000 IU/mL and alanine aminotransferase is more than twice the upper limit of normal for more than 12 months, and in HBeAg-negative hepatitis (with alanine aminotransferase more than twice the upper limit of normal) when HBV DNA is more than 2000 IU/mL.[22] A family history of hepatocellular carcinoma is an additional factor to support treatment initiation in both the ESPGHAN and APASL guidelines.[22,87] The AASLD guidelines recommend deferral of therapy when the HBV DNA concentration is less than 10^4 IU/mL, until spontaneous HBeAg seroconversion is excluded.[41] There might be a lower probability of conversion to HBeAg-negative chronic HBV infection if HBeAg seroconversion occurs before the age of 18 years.[17] Compared with adults, only a small proportion of children meet the criteria of raised alanine aminotransferase concentration (appendix p 3–5). In particular, most children in China and Japan are HBeAg-positive with normal or only slightly raised alanine aminotransferase concentrations, and minimal necroinflammation and fibrosis.[49,50] Therefore, for both HBeAg-positive children and young adults with normal alanine aminotransferase concentrations, a conservative approach to initiation of treatment is generally recommended, because these patients are unlikely to respond to interferon alfa, or will require decades of nucleoside analogue treatment. However, it is recognised that the disease process is already underway in adolescents infected at birth or in early childhood, therefore these recommendations remain under review.[22,39–41,87,103] For both adults and children, treatment is recommended for patients with fulminant or severe acute hepatitis B infection, HBsAg-positive patients undergoing immunosuppression or chemotherapy, HBsAg-positive patients who are about to have a liver transplant, and patients receiving grafts from anti-HBc-positive donors.[22,39–41,87]

Antiviral treatment

Over the past three decades, treatment outcomes for chronic HBV infection have improved because available medicines have evolved. In addition to interferon alfa and peginterferon alfa, nucleoside or nucleotide analogues with low (lamivudine, adefovir, and telbivudine) and high (tenofovir and entecavir) genetic barriers to resistance have been developed (table 2).[104,105] Nucleoside and nucleotide analogues are potent HBV inhibitors that are used as long-term oral treatments to suppress viral replication, or as treatments of finite

duration (with or without interferon) to obtain a sustained off-treatment virological response.[22,39–41,87] In adults, once treatment with nucleoside or nucleotide analogues has been commenced, it is generally lifelong, because HBeAg seroconversion or HBsAg loss are rare, and virological relapse is common upon withdrawal of treatment.[22,39,40,87] However, trials with a finite duration of treatment are also now being done.[106]

Interferon alfa and peginterferon alfa act as immune modulators and can be administered for a predefined duration, with the aim of inducing immune-mediated control of HBV infection and achieving long-lasting suppression of viral replication off treatment.[22,40,41,87] Interferon therapy might be associated with higher rates of HBsAg loss when compared with nucleoside or nucleotide analogues.[98] However, interferon therapy cannot be given to infants or pregnant women because of its toxicity profile, and it is contraindicated in people with autoimmune conditions, decompensated cirrhosis, uncontrolled psychiatric disease, severe cytopenia, severe cardiac disease, or uncontrolled seizures.

EASL, AASLD, and WHO recommend tenofovir (tenofovir disoproxil fumarate or tenofovir alafenamide) or entecavir as preferred initial therapies for adults, because of the high genetic barrier and therefore very low risk of resistance associated with use of these drugs.[39–41] APASL, EASL, and AASLD also recommend that interferon alfa is considered as a therapeutic option.[22,40] Interferon is not included in WHO guidelines[39] because its use in resource-limited settings is often not feasible as a result of its high cost, requirement for injection, and high rate of adverse effects that require careful monitoring.

Interferon, entecavir, and tenofovir disoproxil fumarate are recommended for treatment of chronic HBV infection in children by ESPGHAN, AASLD, and APASL.[22,41,87] Entecavir is recommended for children aged 2–12 years in WHO guidelines.[39] The US Food and Drug Administration and the European Medicines Agency have approved tenofovir disoproxil fumarate and adefovir for children aged 12 years and older, entecavir for children aged 2 years and older, and lamivudine for children aged 3 years and older. The European Medicines Agency also approved the use of tenofovir alafenamide for children aged 12 years and older and weighing more than 35 kg in 2018, and the use of tenofovir disoproxil fumarate for children aged 2–11 years in January, 2019. Interferon alfa is approved by the US Food and Drug Administration and the European Medicines Agency for use in children aged 1 year and older. In September, 2017, peginterferon alfa-2b was approved by the European Medicines Agency for use in children older than 2 years. The advantages of interferon and peginterferon for use in children, as compared with nucleoside and nucleotide analogues, are the absence of viral resistance and the predictable finite duration of treatment.[41,87] However, the use of interferon and peginterferon is difficult for children because it requires subcutaneous injections (three times a week for interferon or once a week for peginterferon) and is associated with a high risk of adverse events.[40,41,87] AASLD guidelines suggest that the use of peginterferon alfa-2a should be considered for children older than 5 years with chronic HBV, because it has the advantage of once-weekly administration, as compared with three times a week for interferon alfa.[41,107]

Interferon alfa-2b, peginterferon alfa-2a, lamivudine, adefovir, tenofovir disoproxil fumarate, and entecavir were approved for treatment of children and adolescents with chronic HBV infection on the basis of six randomised placebo-controlled trials (appendix p 6),[18,19,107–110] and tenofovir alafenamide was approved on the basis of studies of its use in HIV infection. A good treatment response (defined by the reduction of serum HBV DNA to undetectable concentrations, and by the loss of serum HBeAg, the normalisation of aminotransferases, or both) was associated with higher baseline histology activity index score, increased baseline aminotransferase concentrations, and lower baseline HBV DNA concentrations.[18,19,108–110]

Knowledge gaps, research agendas, and future strategies

If adolescents and children are to benefit equally from the global scale-up of testing and treatment of HBV infection, important gaps in the evidence on prevention, treatment, and management need to be addressed, to inform policy and management guidelines and improve outcomes. Age-stratified serosurveys need to be done to assess the prevalence of HBsAg (and HIV-HBV co-infection), in different populations of adolescents and children (both high-risk populations and the general population), with estimates of burden, morbidity, mortality, and treatment need by region. However, because serosurveys are costly, modelled data could guide policy in high-prevalence regions.[111] Children and adolescents need to be included in routine national data collection and global reporting tools on the viral hepatitis cascade.

The diagnostic performance of serological HBsAg assays (rapid diagnostic tests and immunoassays) in children should be evaluated, and the use of non-invasive tests (eg, blood-based assays and transient elastography) for staging of liver disease in children and adolescents requires validation. Studies are also needed to identify other biomarkers of progression of HBV, rather than relying on transition to a low replicative state.

A consensus is required on when to start treatment in children and adolescents with HBV infection, and long-term follow-up studies should be done to evaluate the safety of long-term use of nucleoside or nucleotide analogue regimens in different paediatric populations. Immunopathogenesis studies of immune dysfunction underlying chronic HBV infection in children are needed to understand the requirement and efficacy of potential immunotherapies and new curative therapies

Search strategy and selection criteria

We did a comprehensive narrative literature review using PubMed to identify key studies on paediatric HBV infection in the following areas: epidemiology (seroprevalence and burden), transmission, natural history, diagnosis with assessment of disease stage, and treatment (including criteria for treatment, treatment options, and outcome). A formal, quantitative systematic review was not considered appropriate for this initial comprehensive review. We searched for English language publications with the use of broad search terms: "hepatitis B virus" AND ("child" OR "adolescent") AND "epidemiology", "transmission", "natural history", "prevention", "diagnosis", or "treatment" from Jan 1, 2010, to Dec 31, 2017. The age limit "birth–18 years" was applied. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports. Animal studies and in-vitro studies were excluded. We also searched reference lists of articles identified through this strategy and included additional relevant studies. The final list of eligible studies was based on an assessment by co-authors of direct relevance to the key topics of this review. For each of the topics, we summarised the findings to highlight the main differences (as well as similarities) between infection in adults compared with children and adolescents. For the purpose of this review, we defined an adult as a person who is 18 years old or older; an adolescent as a person who is 12–17 years old; and a child as a person who is younger than 12 years, unless stated otherwise. These definitions were consistent with the age categories used in most of the evaluated studies.

that are in development. Different therapeutic strategies might be required for children with high rates of HBV replication.

To improve prevention of HBV infection, further studies are required on the use of nucleoside or nucleotide analogues, particularly tenofovir disoproxil fumarate and tenofovir alafenamide, during pregnancy, and their effectiveness in preventing perinatal HBV infection when used in addition to early birth-dose and infant vaccination (with or without HBIG), especially in Asian and African women. Strategies are also needed to promote implementation of birth-dose vaccination within 24 h of birth. In particular, a strong prevention research agenda in African women and children is a priority.

To improve access to care for HBV, recommendations for the testing and treatment of children should be included in national policies together with optimal service delivery models, and additional support is required for children and adolescents living with chronic HBV infection. Among older adolescents, stigma and discrimination can reduce access to care, education, and work opportunities.

Common challenges to treatment scale-up in children, adolescents, and adults include poor access to diagnosis and clinical assessment, the affordability of HBV DNA testing in low-income and middle-income countries, poor access to antiviral monotherapy outside HIV antiretroviral therapy programmes, and poor access to appropriate paediatric formulations. Very few paediatric studies based on large cohorts have been published from low-income and middle-income countries. The HBV paediatric research agenda would benefit from the establishment of new international collaborations, consortia, and cohorts of children with chronic HBV infection to inform best practices for the management, care, and treatment of children with HBV infection in high-burden settings.

Contributors

GI, PE, CG, and MP conceived the project. GI and PE wrote the first draft of the article and made critical revisions. All authors critically revised the paper for important intellectual content and approved the final version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the final version of the paper before submission.

Declaration of interests

GD reports grants and personal fees from Gilead Sciences, personal fees from Janssen, and grants and personal fees from Abbott Laboratories and Arbutus during the conduct of the study. CT reports grants from ViiV Healthcare via PENTA Foundation and personal fees from ViiV Healthcare outside the submitted work. MMJ reports grants from Gilead Sciences, AbbVie, and Merck during the conduct of the study, grants from Bristol-Myers Squibb, Roche/Genentech, and Gilead Sciences, and non-financial support from Echosens outside the submitted work. All other authors declare no competing interests.

References

1 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:** 1546–55.

2 WHO. Global hepatitis report, 2017. Geneva: World Health Organization, 2017.

3 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385:** 117–71.

4 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **386:** 743–800.

5 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.

6 United Nations. Transforming our world: the 2030 agenda for sustainable development. New York: United Nations, 2015.

7 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:** 2212–19.

8 Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011; **140:** 132–43.

9 Seto WK, Lam YF, Fung J, et al. Changes of HBsAg and HBV DNA levels in Chinese chronic hepatitis B patients after 5 years of entecavir treatment. *J Gastroenterol Hepatol* 2014; **29:** 1028–34.

10 Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. *Hepatology* 2006; **43:** 556–62.

11 Wen WH, Chang MH, Hsu HY, Ni YH, Chen HL. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. *J Pediatr* 2004; **144:** 397–99.

12 Marx G, Martin SR, Chicoine JF, Alvarez F. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. *J Infect Dis* 2002; **186:** 295–301.

13 Wu JF, Su YR, Chen CH, et al. Predictive effect of serial serum alanine aminotransferase levels on spontaneous HBeAg seroconversion in chronic genotype B and C HBV-infected children. *J Pediatr Gastroenterol Nutr* 2012; **54:** 97–100.

14 Ni YH, Chang MH, Wang KJ, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. *Gastroenterology* 2004; **127:** 1733–38.

15 Roushan MR, Bijani A, Ramzaninejad S, Roushan MH, Amiri MJ, Baiani M. HBeAg seroconversion in children infected during early childhood with hepatitis B virus. *J Clin Virol* 2012; **55:** 30–33.

16 Tseng YR, Wu JF, Ni YH, et al. Long-term effect of maternal HBeAg on delayed HBeAg seroconversion in offspring with chronic hepatitis B infection. *Liver Int* 2011; **31:** 1373–80.

17 Wu JF, Chiu YC, Chang KC, et al. Predictors of hepatitis B e antigen-negative hepatitis in chronic hepatitis B virus-infected patients from childhood to adulthood. *Hepatology* 2016; **63:** 74–82.

18 Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology* 2012; **56:** 2018–26.

19 Jonas MM, Chang MH, Sokal E, et al. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. *Hepatology* 2016; **63:** 377–87.

20 Liu HF, Sokal E, Goubau P. Wide variety of genotypes and geographic origins of hepatitis B virus in Belgian children. *J Pediatr Gastroenterol Nutr* 2001; **32:** 274–77.

21 Belhassen-García M, Pérez Del Villar L, Pardo-Lledias J, et al. Imported transmissible diseases in minors coming to Spain from low-income areas. *Clin Microbiol Infect* 2015; **21:** 370.e5–8.

22 Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10:** 1–98.

23 Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; **378:** 571–83.

24 Ni YH, Chang MH, Jan CF, et al. Continuing decrease in hepatitis B virus infection 30 years after initiation of infant vaccination program in Taiwan. *Clin Gastroenterol Hepatol* 2016; **14:** 1324–30.

25 Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Progress toward viral hepatitis elimination in the United States, 2017. Atlanta, GA: Centers for Disease Control and Prevention, 2017.

26 Gupta S, Gupta R, Joshi YK, Singh S. Role of horizontal transmission in hepatitis B virus spread among household contacts in north India. *Intervirology* 2008; **51:** 7–13.

27 Gupta E, Bajpai M, Sharma P, Shah A, Sarin S. Unsafe injection practices: a potential weapon for the outbreak of blood borne viruses in the community. *Ann Med Health Sci Res* 2013; **3:** 177–81.

28 Nishioka Sde A, Gyorkos TW, Joseph L, Collet JP, Maclean JD. Tattooing and risk for transfusion-transmitted diseases: the role of the type, number and design of the tattoos, and the conditions in which they were performed. *Epidemiol Infect* 2002; **128:** 63–71.

29 McMahon BJ. The natural history of chronic hepatitis B virus infection. *Semin Liver Dis* 2004; **24** (suppl 1)**:** 17–21.

30 McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985; **151:** 599–603.

31 Shimakawa Y, Toure-Kane C, Mendy M, Thursz M, Lemoine M. Mother-to-child transmission of hepatitis B in sub-Saharan Africa. *Lancet Infect Dis* 2016; **16:** 19–20.

32 Beasley RP. Rocks along the road to the control of HBV and HCC. *Ann Epidemiol* 2009; **19:** 231–34.

33 Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med* 1975; **292:** 771–74.

34 Tseng YR, Wu JF, Kong MS, et al. Infantile hepatitis B in immunized children: risk for fulminant hepatitis and long-term outcomes. *PLoS One* 2014; **9:** e111825.

35 Wai CT, Fontana RJ, Polson J, et al. Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. *J Viral Hepat* 2005; **12:** 192–98.

36 Chang MH, Lee CY, Chen DS, Hsu HC, Lai MY. Fulminant hepatitis in children in Taiwan: the important role of hepatitis B virus. *J Pediatr* 1987; **111:** 34–9.

37 McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology* 2009; **49** (suppl)**:** S45–55.

38 Sun YH, Lei XY, Sai YP, Chen JH, Sun YC, Gao X. Relationship between genotypes and clinical manifestation, pathology, and cccDNA in Chinese children with hepatitis B virus-associated glomerulonephritis. *World J Pediatr* 2016; **12:** 347–52.

39 WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization, 2015.

40 European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67:** 370–98.

41 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67:** 1560–99.

42 McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. *Ann Intern Med* 2001; **135:** 759–68.

43 Hoofnagle JH, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. *Ann Intern Med* 1981; **94:** 744–48.

44 Liaw YF, Chu CM, Su IJ, Huang MJ, Lin DY, Chang-Chien CS. Clinical and histological events preceding hepatitis B e antigen seroconversion in chronic type B hepatitis. *Gastroenterology* 1983; **84:** 216–19.

45 Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; **45:** 1056–75.

46 Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis* 2003; **23:** 47–58.

47 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127** (suppl 1)**:** S35–50.

48 Fabrizi F, Donato FM, Messa P. Association between hepatitis B virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2017; **16:** 21–47.

49 Chang MH, Hsu HY, Hsu HC, Ni YH, Chen JS, Chen DS. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. *Hepatology* 1995; **22:** 1387–92.

50 Fujisawa T, Komatsu H, Inui A, et al. Long-term outcome of chronic hepatitis B in adolescents or young adults in follow-up from childhood. *J Pediatr Gastroenterol Nutr* 2000; **30:** 201–06.

51 Iorio R, Giannattasio A, Cirillo F, D'Alessandro L, Vegnente A. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. *Clin Infect Dis* 2007; **45:** 943–49.

52 Ni YH, Chang MH, Chen PJ, et al. Viremia profiles in children with chronic hepatitis B virus infection and spontaneous e antigen seroconversion. *Gastroenterology* 2007; **132:** 2340–45.

53 Ruiz-Moreno M, Otero M, Millan A, et al. Clinical and histological outcome after hepatitis B e antigen to antibody seroconversion in children with chronic hepatitis B. *Hepatology* 1999; **29:** 572–75.

54 Popalis C, Yeung LT, Ling SC, Ng V, Roberts EA. Chronic hepatitis B virus (HBV) infection in children: 25 years' experience. *J Viral Hepat* 2013; **20:** e20–26.

55 Prendergast AJ, Klenerman P, Goulder PJ. The impact of differential antiviral immunity in children and adults. *Nat Rev Immunol* 2012; **12:** 636–48.

56 Seto WK, Yuen MF. Viral hepatitis: 'Immune tolerance' in HBV infection: danger lurks. *Nat Rev Gastroenterol Hepatol* 2016; **13:** 627–28.

57 Block TM, Locarnini S, McMahon BJ, Rehermann B, Peters MG. Use of current and new endpoints in the evaluation of experimental hepatitis B therapeutics. *Clin Infect Dis* 2017; **64:** 1283–88.

58 Livingston SE, Simonetti JP, Bulkow LR, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. *Gastroenterology* 2007; **133:** 1452–57.

59 Hsu HC, Wu MZ, Chang MH, Su IJ, Chen DS. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. *J Hepatol* 1987; **5:** 260–67.

60 Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997; **336:** 1855–59.

61 Yeh FS, Mo CC, Yen RC. Risk factors for hepatocellular carcinoma in Guangxi, People's Republic of China. *Natl Cancer Inst Monogr* 1985; **69:** 47–48.

62 Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000; **118:** 554–59.

63 Livingston SE, Simonetti JP, McMahon BJ, et al. Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F. *J Infect Dis* 2007; **195:** 5–11.

64 Gooden M, Miller M, Shah D, Soyibo AK, Williams J, Barton EN. Clinicopathological features of atypical nephrotic syndrome in Jamaican children. *West Indian Med J* 2010; **59:** 319–24.

65 Ozdamar SO, Gucer S, Tinaztepe K. Hepatitis-B virus associated nephropathies: a clinicopathological study in 14 children. *Pediatr Nephrol* 2003; **18:** 23–28.

66 Slusarczyk J, Michalak T, Nazarewicz-de Mezer T, Krawczyński K, Nowosławski A. Membranous glomerulopathy associated with hepatitis B core antigen immune complexes in children. *Am J Pathol* 1980; **98:** 29–43.

67 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:** 981–85.

68 WHO. Hepatitis B vaccines: WHO position paper: July 2017. *Wkly Epidemiol Rec* 2017; **92:** 369–92.

69 Zhang L, Xu A, Yan B, et al. A significant reduction in hepatitis B 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:** e483–88.

70 Ni YH, Huang LM, Chang MH, et al. Two decades of universal hepatitis B vaccination in Taiwan: impact and implication for future strategies. *Gastroenterology* 2007; **132:** 1287–93.

71 Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. *Cochrane Database Syst Rev* 2006; **2:** CD004790.

72 Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med* 2018; **378:** 911–23.

73 WHO. Immunization, vaccines and biologicals: hepatitis B. 2017. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/hepatitis/en/ (accessed April 1, 2019).

74 Egypt Ministry of Health and Population, El-Zanaty and Associates, ICF International. Egypt health issues survey 2015. Cairo, Egypt: Ministry of Health and Population, 2015.

75 Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China: declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009; **27:** 6550–57.

76 Lin X, Guo Y, Zhou A, et al. Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. *Pediatr Infect Dis J* 2014; **33:** 897–903.

77 Chen HL, Lin LH, Hu FC, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. *Gastroenterology* 2012; **142:** 773–81.e2.

78 Wen WH, Chang MH, Zhao LL, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. *J Hepatol* 2013; **59:** 24–30.

79 Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med* 2016; **374:** 2324–34.

80 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:** 468–76.

81 Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. *Hepatology* 2016; **63:** 319–33.

82 Dusheiko G. A shift in thinking to reduce mother-to-infant transmission of hepatitis B. *N Engl J Med* 2018; **378:** 952–53.

83 WHO Regional Office for the Western Pacific. Regional framework for the triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis in Asia and the Pacific, 2018–2030. Manila: World Health Organization Regional Office for the Western Pacific, 2018.

84 Pan American Health Organization. Plan of action for the prevention and control of HIV and sexually transmitted infections 2016–2021. Washington, DC: Pan American Health Organization, 2016.

85 WHO. Guidelines on hepatitis B and C testing. Geneva: World Health Organization, 2017.

86 Yin Y, Wu L, Zhang J, Zhou J, Zhang P, Hou H. Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. *J Infect* 2013; **66:** 447–52.

87 Sokal EM, Paganelli M, Wirth S, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *J Hepatol* 2013; **59:** 814–29.

88 Lemoine M, Shimakawa Y, Njie R, et al. Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. *Lancet Glob Health* 2016; **4:** e559–67.

89 Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology* 2012; **142:** 1293–302.e4.

90 Park SH, Kim CH, Kim DJ, et al. Usefulness of multiple biomarkers for the prediction of significant fibrosis in chronic hepatitis B. *J Clin Gastroenterol* 2011; **45:** 361–65.

91 Zhang YG, Wang BE, Wang TL, Ou XJ. Assessment of hepatic fibrosis by transient elastography in patients with chronic hepatitis B. *Pathol Int* 2010; **60:** 284–90.

92 Dezsőfi A, Baumann U, Dhawan A, et al. Liver biopsy in children: position paper of the ESPGHAN Hepatology Committee. *J Pediatr Gastroenterol Nutr* 2015; **60:** 408–20.

93 El-Asrar MA, Elbarbary NS, Ismail EA, Elshenity AM. Serum YKL-40 in young patients with β-thalassemia major: relation to hepatitis C virus infection, liver stiffness by transient elastography and cardiovascular complications. *Cells Mol Dis* 2016; **56**(1): 1–8.

94 Awad ME-D, Shiha GE, Sallam FA, Mohamed A, El Tawab A. Evaluation of liver stiffness measurement by fibroscan as compared to liver biopsy for assessment of hepatic fibrosis in children with chronic hepatitis C. *J Egypt Soc Parasitol* 2013; **43:** 805–19.

95 Garazzino S, Calitri C, Versace A, et al. Natural history of vertically acquired HCV infection and associated autoimmune phenomena. *Eur J Pediatr* 2014; **173:** 1025–31.

96 Fitzpatrick E, Quaglia A, Vimalesvaran S, Basso MS, Dhawan A. Transient elastography is a useful noninvasive tool for the evaluation of fibrosis in paediatric chronic liver disease. *J Pediatr Gastroenterol Nutr* 2013; **56:** 72–76.

97 Lee CK, Perez-Atayde AR, Mitchell PD, Raza R, Afdhal NH, Jonas MM. Serum biomarkers and transient elastography as predictors of advanced liver fibrosis in a United States cohort: the Boston children's hospital experience. *J Pediatr* 2013; **163:** 1058–64.e2.

98 Jonas MM, Lok AS, McMahon BJ, et al. Antiviral therapy in management of chronic hepatitis B viral infection in children: a systematic review and meta-analysis. *Hepatology* 2016; **63:** 307–18.

99 Durantel D, Zoulim F. New antiviral targets for innovative treatment concepts for hepatitis B virus and hepatitis delta virus. *J Hepatol* 2016; **64** (Suppl): S117–31.

100 Xia Y, Liang TJ. Development of direct-acting antiviral and host-targeting agents for treatment of HBV infection. *Gastroenterology* 2019; **156:** 311–24.

101 Block TM, Locarnini S, McMahon BJ, Rehermann B, Peters MG. Use of current and new endpoints in the evaluation of experimental hepatitis B therapeutics. *Clin Infect Dis* 2017; **64:** 1283–88.

102 Lin CL, Kao JH. Review article: novel therapies for hepatitis B virus cure: advances and perspectives. *Aliment Pharmacol Ther* 2016; **44:** 213–22.

103 Mason WS, Gill US, Litwin S, et al. HBV DNA integration and clonal hepatocyte expansion in chronic hepatitis B patients considered immune tolerant. *Gastroenterology* 2016; **151:** 986–98.e4.

104 Dusheiko G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. *Liver Int* 2013; **33** (suppl 1): 137–50.

105 Grossi G, Vigano M, Loglio A, Lampertico P. Hepatitis B virus long-term impact of antiviral therapy nucleot(s)ide analogues (NUCs). *Liver Int* 2017; **37** (suppl 1): 45–51.

106 van Bömmel F, Berg T. Stopping long-term treatment with nucleos(t)ide analogues is a favourable option for selected patients with HBeAg-negative chronic hepatitis B. *Liver Int* 2018; **38** (suppl 1): 90–96.

107 Wirth S, Zhang H, Hardikar W, et al. Efficacy and safety of peginterferon alfa-2a (40KD) in children with chronic hepatitis B: the PEG-B-ACTIVE study. *Hepatology* 2018; **68:** 1681–94.

108 Sokal EM, Conjeevaram HS, Roberts EA, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology* 1998; **114:** 988–95.

109 Jonas MM, Mizerski J, Badia IB, et al. Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346:** 1706–13.

110 Jonas MM, Kelly D, Pollack H, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *Hepatology* 2008; **47:** 1863–71.

111 Dusheiko G, Agarwal K. Delineating the global challenges of hepatitis B virus infection. *Lancet Gastroenterol Hepatol* 2018; **3:** 372–73.