

## **Hepatitis B virus infection in children and adolescents**

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## **Abstract**

Hepatitis B virus (HBV) infection is a major cause of acute and chronic liver disease and associated morbidity and mortality worldwide. Vertical and early childhood transmission are the main routes of HBV transmission globally, responsible for most chronic infections – including in adults who bear the greatest burden of morbidity and mortality. Universal infant and birth dose hepatitis B immunization is the key preventative strategy for global elimination of HBV infection, and has been highly effective in reducing new vertical infections. Global progress on HBV testing and treatment, however, has been slow in adults and children. In this review, we summarize current knowledge on epidemiology, natural history, and treatment of chronic HBV infection in adolescents and children, highlighting key differences from the experience with adults, and conclude with key actions to address current policy gaps. The estimated global prevalence in children aged 5 years or less is 1.3%. Most children are in the “high replication, low level of inflammation” infection phase with normal or only minimally raised aminotransferases; cirrhosis and hepatocellular carcinoma are rare. Although entecavir is approved and recommended for children 2 to <18 years, and tenofovir for those 12 to < 18 years, a conservative approach to treatment initiation is currently recommended. Key actions to address current policy gaps include: validation of non-invasive tests for liver disease staging; additional immunopathogenesis studies in HBV infected children, and long-term follow-up of children on nucleoside analogue regimens to inform guidance on when to start treatment; evaluation of different treatment strategies for children with high levels of replication; and establishment of paediatric treatment registries and international consortia to promote collaborative research.

**Key words:** hepatitis B, adolescents, children, elimination, chronic infection, natural history, epidemiology, treatment, hepatocellular carcinoma

## Introduction

Hepatitis B virus (HBV) is a major cause of acute and chronic liver disease and of associated morbidity and mortality worldwide.<sup>1-5</sup> Globally, in 2015, the World Health Organization (WHO) estimated that HBV causes chronic infection in 257 million people<sup>2</sup> and death in 887 000<sup>2</sup>. There are also close to two million new infections annually in children under five years of age, largely through mother-to-child transmission (MTCT) and horizontal transmission in early life.<sup>2,5</sup> Recognising the public health burden of hepatitis and opportunities for action, in 2016 the WHO launched the first Global Health Sector Strategy on Hepatitis 2016–2021. To achieve the goal of elimination of hepatitis B as a public health threat by 2030 – defined as a reduction in incidence of chronic infections by 90% (assessed by reduced prevalence among children aged 5 years) and in liver-related deaths by 65%, the strategy established coverage targets for both preventative interventions (minimum three dose vaccination to 90% of infants, birth-dose vaccination for at least 80% of neonates within 24 hours of birth), diagnosis (achieve diagnosis of 90% of people infected with HBV) and treatment (antiviral treatment of 80% of those diagnosed and eligible for treatment).<sup>6</sup>

The greatest strides towards achieving elimination of HBV have been made with respect to universal infant hepatitis B immunization, which has been highly effective in reducing new infections in children.<sup>7</sup> In contrast, the focus of the global hepatitis response 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<sup>8</sup> or entecavir<sup>9</sup> to suppress viral replication. However, access to affordable HBV testing and treatment remains very limited in low- and middle-income countries (LMICs). Globally in 2015, it was estimated that only 9%, or 22 million persons with chronic hepatitis B infection had been diagnosed, and among those

diagnosed, around 8% or 1.7 million persons were on treatment,<sup>2</sup> although it is recognised that only a proportion of those infected will require treatment.

There has been much less attention paid to testing and treatment strategies for chronic HBV infection among children and adolescents, in part because it is considered that the majority are in the immunotolerant phase of infection and do not require treatment, but also because of significant gaps in evidence from high HBV prevalence, low-income settings to inform paediatric specific management practices. For example, although there have been seven moderately large (>90 enrolled) and long-term (>10 years of follow-up) prospective studies on the natural history of HBV infection in children, these studies are mainly from high-income countries.<sup>10-17</sup> Similarly, only two trials on the safety and efficacy of tenofovir (disoproxil fumarate, TDF)<sup>18</sup> for adolescents (aged 12 years or more) or entecavir<sup>19</sup> (for children older than 2 years of age) have been completed. The objective of this review is to provide a comprehensive synthesis of current knowledge on the epidemiology, natural history, and treatment of chronic HBV infection in children and adolescents and to highlight key differences and similarities from the experience with infection acquired in adulthood. We conclude with key priorities for action, which include strategies to promote scale-up of testing and treatment, and addressing critical evidence gaps to inform future policy development.

## **Methods**

### Search strategy and selection criteria

We undertook a comprehensive narrative literature review using PubMed only 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. Web Annex A provides details on search strategy and inclusion/exclusion criteria. For each of these topics, data was summarised to highlight the main differences (as well as similarities) between infection in adults, and that in children and adolescents. For the purpose of this review, we defined an adult as a person 18 years of age or older; an adolescent as a person from 12 to 17 years; and a child as a person younger than 12 years of age, unless stated otherwise, to conform with the age categories most commonly used in the studies evaluated, although other definitions for adolescents are used by different organisations (e.g. aged 10 to 19 years).

### **Seroprevalence and burden**

A key principle is that while HBsAg prevalence among adults in general reflects historical exposure and prevalence of HBV infection, prevalence among children aged five years and younger largely reflects level of implementation of infant and birth dose HBV vaccination.

The current global estimates of HBV prevalence (as measured by detection of HBsAg), burden, morbidity and mortality are largely based on data from the adult population.<sup>1,2,4,5</sup> Overall, WHO estimates that 257 million persons were estimated to be HBsAg positive in 2015 (3.5% of the general population)<sup>2</sup> which is broadly consistent also with other modelled estimates of 291 million (95% UI 252 000–341 000) and 3.9%<sup>5</sup>. More than half of infected people reside in areas of high and intermediate HBV endemicity<sup>1,2,4</sup> and the highest prevalence (>6%) is in the WHO African and Western Pacific regions, and lowest prevalence in the Americas and Europe.<sup>2</sup> In 2015, WHO estimated the HBsAg prevalence globally in children under five years of age was about 1.3%<sup>2</sup>, which compares with about 4.7% prior to the widespread adoption of universal

infant vaccination (from the 1980s to the early 2000s).<sup>2</sup> Based on a recent report from the Polaris observatory for 2016, this corresponds to approximately 1.8 million (1.6–2.2) new infections in children globally.<sup>5</sup> Sixteen countries accounted for more than 80% of these infections and Nigeria, India, Indonesia, and the Democratic Republic of the Congo alone for almost 57%.<sup>5</sup> The geographical distribution and most affected regions are similar for children and adults, with the highest prevalence in the African region, which also had the lowest timely birth-dose coverage (only 10%) of all regions globally. The lowest prevalence among children aged 5 years (<0.1%) was in the Americas which also had a low prevalence even before widespread vaccination.<sup>5</sup> In Western Europe and North America, HBsAg-positivity in those under 18 years of age is now rare.<sup>1,2</sup> However, these settings have experienced increasing numbers of infected children migrating from higher prevalence countries.<sup>20,21</sup> There are limited data on prevalence in adolescents, and the annual mortality in adolescents and children is unknown.

### **Routes of transmission**

Worldwide, the majority of chronic infections in adults were acquired through perinatal at birth, or during early childhood especially in high-prevalence settings.<sup>1,7,22</sup> The main route of acquisition of new adult infections is through unsafe injections and sexual transmission among men who have sex with men or heterosexual persons with multiple sex partners.<sup>1,23</sup>

MTCT accounts for the majority of transmission in children both in high endemicity countries (seroprevalence >8%) where infant vaccination (and especially birth dose) implementation has been suboptimal, as well as in low endemicity countries. However, intrauterine infections and vaccine or immune-prophylaxis regimen failures may account for rising proportion of failures as infant vaccination coverage improves.<sup>2,24,25</sup> Up to a third of incident HBV infections may be

due to horizontal early childhood transmission through child-to-child, household and intrafamilial transmission, especially in sub-Saharan Africa and among unvaccinated migrant children in Europe,<sup>20,21,26</sup> as well as transmission due to poor infection control and injection safety during medical, surgical and dental procedures<sup>27</sup> and traditional practices (such as scarification or circumcision)<sup>28</sup>.

### **Natural history of hepatitis B infection and development of complications**

HBV causes both acute and chronic infection that can range from asymptomatic infection or mild disease to severe or fulminant hepatitis. Age of acquisition is the key determinant of chronic infection, which occurs in 90% of infected neonates and infants but in <5% when infection is acquired in adulthood.<sup>29-33</sup> Infections are usually asymptomatic and anicteric in vertically infected children,<sup>10,34</sup> but acute infection may be associated with severe symptoms and fulminant hepatitis in both adults,<sup>35</sup> and children.<sup>36</sup> Chronic infection may lead to progressive liver disease and development of complications such as cirrhosis and HCC mainly in adulthood<sup>37</sup> and extrahepatic manifestations that can also present in infancy and early childhood.<sup>38</sup>

The natural history of chronic HBV infection (CHB) is dynamic and complex, progressing non-linearly through several recognizable phases of variable duration,<sup>29,39</sup> and 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 these different phases, but it has been increasingly recognized that these descriptions are not fully 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 Liver (EASL)<sup>40</sup> (Table A, Appendix) (but not yet by the American Association for the Study of Liver Disease



[AASLD])<sup>41</sup> based on the characterisation of infection as either with or without active hepatitis (defined as raised or normal aminotransferase levels, respectively) and on HBeAg status.

Hepatitis B infection acquired in adulthood is more often an acute, symptomatic but self-resolving infection, and uncommonly leads to chronic infection<sup>30,37</sup> and related complications. Based on several large prospective, population-based studies,<sup>42-44</sup> the five-year cumulative incidence of cirrhosis,<sup>29,45,46</sup> hepatic decompensation and HCC in cirrhotic patients is 8 to 20%, 20% and 2 to 5%, respectively.<sup>37,47</sup> CHB has also been associated in adults with the development of HBV-related kidney disease, mainly glomerulonephritis.<sup>48</sup> The natural history and phases of HBV infection in children have been less well delineated. There have been seven large (>90 children enrolled) and long-term (>10 years of follow-up) prospective studies on the natural history of HBV infection in children,<sup>10-17</sup> with some smaller prospective and retrospective studies<sup>49-54</sup> (Table B, Appendix). When hepatitis B infection is acquired perinatally or in early childhood, it is very likely to lead to chronic infection.<sup>10-16,49-54</sup> The main characteristic of vertical perinatally acquired as well as early childhood acquisition of HBV infection is the decades long duration of a high-replication, low-level inflammation phase whereby HBsAg and HBeAg are detectable in serum, serum HBV deoxyribonucleic acid (DNA) concentrations are high, but serum aminotransferases may be normal or only minimally increased. Historically CHB in these patients has been considered as characterized by a state of immunological tolerance. In a 29-year longitudinal study from Italy, 89 of the 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.<sup>10</sup> The immunopathogenesis of chronic infection and the resulting immunotolerance in infants and children is still poorly understood<sup>10,29,30,42,55</sup> and this concept is being challenged.<sup>56</sup> Recent studies have suggested that adolescents may harbour

hepatitis B-functionally active specific T cells and that antigen-specific immune responses exist in “immune-tolerant” persons <sup>113</sup>.

Overall, in longitudinal prospective<sup>10,49</sup> and retrospective studies,<sup>51</sup> cirrhosis has been reported in 1–5% of HBeAg-positive children,<sup>10,49,51</sup> and risk factors were earlier HBeAg seroconversion (before three years of age, consistent with severe necroinflammatory activity), and longer duration of the immune-active phase.<sup>10,11</sup> HBV genotype C infection was associated with delayed spontaneous seroconversion.<sup>57</sup> Although chronic HBV infection accounts for the majority of HCC, the absolute risk of developing HCC in childhood is very low. In a prospective study of 426 children with CHB from Taiwan, two boys developed HCC, with an incidence of 32 per 100 000 person-years,<sup>11</sup> and two of 91 (2.2%) Italian children enrolled in a 29-year longitudinal study developed HCC.<sup>10</sup> However, in some parts of Africa and the Amazon, the incidence of HCC is much higher in infected children and young men.<sup>58,59</sup> Aflatoxin exposure<sup>60</sup> and HBV genotype may contribute to this increased risk.<sup>61,62 10,11,51</sup> The role of viral genotype on the risk of developing HCC in children and adolescents is still to be defined. Genotype B has been associated with an increased risk of HCC.<sup>61</sup> CHB has also been associated with the development of kidney disease in children.<sup>63-65</sup>

### **Prevention of vertical transmission**

In the absence of any intervention, the risk of perinatal vertical transmission ranges from a high of 70-90% with HBeAg-positive mothers to 10-40% with HBeAg-negative mothers in Asia,<sup>66</sup> but in Africa rates are substantially lower.<sup>31</sup> The most important strategy for control of hepatitis B epidemic and prevention of HBV infection in children is administration of hepatitis B vaccine within 24 hours of birth followed by completion of the HBV vaccine series with at least two

more doses within 6–12 months; this regimen is 90–95% effective in preventing infection.<sup>67-69</sup> A dose of hepatitis B immune globulin (HBIG) at birth to infants of highly infectious mothers can further reduce the risk of transmission to less than 5%.<sup>70,71</sup> The global coverage for the three-dose series of hepatitis B vaccine in infancy in 2016 was estimated at 84% (compared to 1% in 1990), and birth dose coverage was 39%.<sup>72</sup> This approach, with some differences in implementation, has substantially reduced HBsAg prevalence by 83 to 95% among children in for example mainland China and Egypt.<sup>68,69,73,74</sup> HBV immunization of infants also greatly reduces the incidence of hepatocellular carcinoma later in life.

Despite the combination of HBV vaccination and HBIG, transmission may occur from 2-10% of HBeAg positive or highly viremic mothers.<sup>71,75</sup> This may be due to transplacental/intrauterine infection or failure of vaccine and immunoprophylaxis regimen.<sup>75,76</sup> HBeAg positive mothers and those with high circulating concentrations of HBV DNA ( $>10^6$  IU/ml) are at highest risk of transmission.<sup>75,77</sup> Several key trials have shown that use of nucleos(t)ide analogues [NAs] such as lamivudine, telbivudine or tenofovir<sup>71,78-80</sup> during the third trimester of pregnancy in highly viraemic, HBeAg positive mothers, in combination with standard infant immunoprophylaxis, was efficacious in further reducing vertical transmission of HBV.<sup>76-80</sup> Although a recent large placebo-controlled trial of maternal tenofovir in HBeAg-positive pregnant women in Thailand did not demonstrate a significantly lower maternal to infant transmission rate beyond the low rate already achieved with infant HBIG and HBV vaccination initiated at birth, the rate in the untreated women was quite low, all infants received immunoprophylaxis in the first hours of life, and no cases at all occurred in the treated group.<sup>71</sup> Tenofovir is the recommended nucleotide analogue for prophylaxis in pregnancy, and can be stopped one to three months post-delivery, if prescribed only to prevent perinatal transmission.<sup>39,81</sup> The WHO regions of Western Pacific<sup>82</sup>

and Pan American Health Organisation,<sup>83</sup> have also established strategies for ‘triple elimination’ of mother-to-child transmission of HIV, hepatitis B (2030 goal of < 0.1% prevalence of HBsAg among children <5 years by 2030) and syphilis, implemented through integration of interventions through maternal, newborn and child health services<sup>82,83</sup>

## **Diagnosis and monitoring**

### Serological diagnosis

The diagnosis of HBV infection in adults, adolescents and children (>12 months of age)<sup>84</sup> is based on detection of HBsAg in serum using a serological assay (in either a rapid diagnostic test [RDT] or laboratory-based immunoassay format) that meets minimum quality, safety and performance standards (with regard to both analytical and clinical sensitivity and specificity).<sup>84</sup> The HBsAg assay may also be repeated at least six months after the first positive test to confirm CHB. Testing of the exposed infant is problematic in the first six months of life, as the presence of both HBsAg and HBV-DNA at birth or in the first few months of life are often transitory events and may not reflect chronic HBV infection.<sup>85</sup> Exposed infants should be tested for HBsAg at 6-12 months of age to limit the possibility of false positive results.<sup>84,86</sup>

### Further assessment and staging of liver disease to guide who to treat

It is estimated that between 5% (in community-based surveys)<sup>87</sup> and up to 40% (in hospital-based studies) of all HBsAg-positive adults will require treatment, depending on stage of liver disease and fibrosis, levels of HBV DNA replication, and alanine aminotransferase (ALT) levels to indicate the extent of liver inflammation. An assessment of these factors is needed to guide further management and need for treatment.<sup>39</sup> Non-invasive tests (NITs) such as transient

elastography (TE), ultrasound shear wave elastography or serum biomarker-based tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), fibrosis-4 (FIB-4) and FibroTest have been validated for staging of liver fibrosis and diagnosis of cirrhosis in adults<sup>88-90</sup> and replaced invasive liver biopsy.<sup>22,39-41</sup>

In contrast to adults, liver biopsy is still considered the standard in children to assess the degree of liver inflammation and stage of fibrosis and indication for treatment<sup>86,91</sup>. The procedure, although invasive, is associated with a low rate of complications when performed by trained operators.<sup>91</sup> The diagnostic and prognostic value of TE in adolescents and children with CHB has not yet been well established,<sup>42,86</sup> but has been evaluated in 140 children with chronic viral hepatitis across five studies.<sup>92-96</sup> However, a formal comparison with liver biopsy results was only available in a subset of 58 children, which demonstrated that TE was reliable in distinguishing different stages of liver fibrosis in paediatric patients with HBV and hepatitis C virus infection. Liver biopsy is of limited applicability resource-limited, non-specialist settings.

### Follow up and Monitoring

Monitoring those not yet on antiviral therapy as well as during and after discontinuation is needed in both adults and children with CHB. The frequency of monitoring will depend on the stage of liver fibrosis, the patient's serological profile (HBeAg positive or negative), and ALT and HBV DNA levels, although the evidence base is limited and the optimal timing is not well established. General recommendations on monitoring of HBV infection in adults and children according to different guidelines are summarized in Table 1.

Only one guideline by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) provides specific guidance for monitoring of children with CHB.<sup>86</sup> In

general, a more conservative approach is proposed, with monitoring of ALT and HBV DNA levels every three to four months for at least one year in HBeAg positive children with increased ALT levels to evaluate the indication for treatment, and in HBeAg-negative children, to rule in HBeAg-negative active disease.<sup>86</sup> Monitoring every six months has been recommended in HBeAg positive children with normal ALT levels. For children receiving treatment, there are no specific recommendations, and frequency of monitoring for safety, adherence and efficacy should be determined on an individual basis.<sup>86</sup>

### **Treatment for CHB**

*Goals of treatment:* The common goals of antiviral treatment for both adults, adolescents and children with CHB are to decrease the risk of disease progression to cirrhosis and HCC through effective and sustained suppression of HBV replication.<sup>22,39,41,86</sup> Attainment of HBsAg loss and seroconversion to anti-HBs is achieved in less than 1% of adults and in 1-6% of children<sup>97</sup> using currently available NA therapy, although the longer the treatment the higher the rate of HBsAg seroconversion.<sup>97</sup> There is now a vibrant research pipeline of new HBV curative combination treatment strategies aimed at eliminating- all replicative intermediates, including covalently closed circular DNA (cccDNA) in the nucleus<sup>98,99</sup> with the potential to transform future indications for treatment. A combination of antiviral and immune modulatory therapies will likely be needed to achieve functional HBV “cure” characterized by sustained loss of HBs antigen with or without HBs antibody seroconversion.<sup>100,101</sup>

*Treatment guidelines and indication to treat:* Treatment guidelines for management of CHB in adults are available from three professional society organisations (EASL, AASLD, and Asian Pacific Association for the Study of Liver [APASL]) and WHO<sup>22,39-41</sup> and in children from the

ESPGHAN and AASLD.<sup>41,86</sup> Across all guidelines, the decision to start treatment is based on a combined assessment of stage of liver disease, HBV DNA concentrations and ALT levels, HBeAg status, as well as other considerations such as family history of HCC and/or co-existence of HIV infection and other liver disease.<sup>22,39-41,86</sup> The possible benefits of treatment need to be evaluated against the need for long-term maintenance antiviral therapy, and the likely natural history of progression in the absence of treatment.<sup>86</sup>

Table 2 summarises the main similarities and differences in recommendations between adults and children across different professional societies<sup>22,40,41,86</sup> and WHO guidelines.<sup>39</sup> In contrast to adults, there are very limited data to guide recommendations on the optimal timing and indications for treatment in adolescents and children. Regardless of age, treatment is recommended for all persons with cirrhosis, across all guidelines, as well as in those with active hepatitis, i.e. HBeAg positive or negative with elevated aminotransferases and HBV DNA levels and histological evidence of necroinflammation and fibrosis.<sup>22,39-41</sup> The AASLD guidelines recommend treatment in HBeAg positive adolescents and children with both elevated ALT and measurable HBV DNA levels,<sup>41</sup> without specifying the duration of ALT elevation (though most studies were based on those with an ALT elevation [ $>1.3$  times upper limit of normal, ULN] for at least six months). In contrast, the European paediatric guidelines require persistent ALT elevation for at least six months in HBeAg positive adolescents and children and 12 months for HBeAg negative adolescents and children, together with a liver biopsy demonstrating the presence of moderate to severe inflammation and fibrosis.<sup>86</sup> The APASL guidelines recommend treatment in HBeAg positive adolescents and children if HBV DNA is  $> 20,000$  IU/mL and ALT is  $> 2$  times ULN for more than 12 months and in those with HBeAg negative hepatitis (ALT  $> 2$  times ULN) when HBV DNA is  $> 2000$  IU/mL.<sup>22</sup> A family history of HCC was an additional

factor to support treatment initiation in both the ESPGHAN and APASL guidelines.<sup>22,86</sup> The AASLD guidelines also recommended deferral of therapy when the HBV DNA level is  $<10^4$  IU/mL, until spontaneous HBeAg seroconversion is excluded.<sup>41</sup> There may be a lower probability of conversion to HBeAg negative chronic hepatitis if HBeAg seroconversion occurs before the age of 18 years.<sup>17</sup> Of note, relatively few children compared to adults, meet the criteria of raised ALT (Table A, Appendix). In particular, most Asian children are HBeAg positive with normal or near normal ALT, and minimal necroinflammation and fibrosis.<sup>49,50</sup> Therefore, for both HBeAg positive children and young adults with normal ALT, a conservative approach to initiation of treatment is generally recommended, as they are less likely to respond to interferon alpha, or will require decades of nucleoside analogue treatment. However, it is recognised that the disease process is already underway in adolescents, and so these recommendations remain under review.<sup>22,39-41,86,102</sup> For both adults and children, treatment is recommended for fulminant or severe acute hepatitis B infection, HBsAg positive persons undergoing immunosuppression or chemotherapy, prior to undergoing liver transplantation or in recipients of grafts from anti-HBc positive donors.<sup>22,39-41,86</sup>

## **Antiviral Treatment**

Over the past three decades, treatment outcomes for CHB have improved, as available medicines have evolved from interferon (IFN)  $\alpha$  to pegylated (PEG) IFN  $\alpha$ , NAs with low (lamivudine, adefovir, telbivudine) and now high (tenofovir and entecavir) genetic barrier to resistance<sup>103 104</sup> (Table 3). These potent HBV inhibitors used as long-term oral treatment to suppress viral replication or for treatment of finite duration (with or without IFN) to obtain sustained off-treatment virological response.<sup>22,39-41,86</sup> In adults, treatment duration with NAs, once commenced, is generally lifelong, as HBeAg seroconversion, or HBsAg loss is relatively



uncommon, and virological relapse is frequent upon treatment withdrawal,<sup>22,39,40,86</sup> but treatment trials of a finite duration have also been conducted.<sup>105</sup>

IFN and PEG IFN act as immune-modulators and can be administered for a predefined duration with the aim of inducing an immune-mediated control of HBV infection and achieving long-lasting suppression of viral replication off-treatment.<sup>22,40,41,86</sup> IFN therapy has been associated with possibly higher rates of HBsAg loss when compared to NAs<sup>97</sup> but cannot be used in infants or pregnant women and is contraindicated in persons with autoimmune conditions, decompensated cirrhosis, uncontrolled psychiatric disease, severe cytopenias, severe cardiac disease, uncontrolled seizures or decompensated cirrhosis.

### Recommended drugs

EASL, AASLD and WHO recommend tenofovir (disoproxil fumarate, TDF or alafenamide, TAF) or entecavir as preferred initial therapy for adults, considering the high genetic barrier and lack of resistance associated with use of these drugs.<sup>39-41</sup> The APASL, EASL and AASLD also recommend consideration of IFN as a therapeutic option.<sup>22,40</sup> IFN was not included in the WHO guidelines<sup>39</sup> as its use in resource limited settings is less feasible because of its high cost, requirement for injection, and significant rate of adverse effects requiring careful monitoring.

IFN, entecavir and TDF are all recommended for treatment of CHB in children by ESPGHAN, AASLD and APASL.<sup>22,41,86</sup> Entecavir is recommended for children 2 to 12 years in WHO guidelines.<sup>39</sup> TDF and adefovir are currently approved<sup>39</sup> by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for children 12 and older and entecavir and lamivudine from age two and three years, respectively. EMA also recently approved the use of tenofovir alafenamide (TAF) for children aged 12 years and older and weighing >35 kg. IFN  $\alpha$

is approved for use in children aged one year and older while, only recently, in September 2017, PEG IFN  $\alpha$ -2b was approved by EMA for use in children older than 2 years. The advantages of IFN and PEG IFN for use in children are the absence of viral resistance and the predictable finite duration of treatment.<sup>41,86</sup> However, use of IFN and PEG IFN is difficult for children as it requires subcutaneous injections three times and once per week, respectively, and is associated with a high risk of adverse events.<sup>40,41,86</sup> The AASLD guideline suggests that providers consider use of PEG IFN  $\alpha$ -2a as it has the advantage of once weekly administration for children older than 5 years with chronic HBV.<sup>41,106</sup>

Overall, IFN  $\alpha$ -2b, PEG IFN  $\alpha$ -2a, lamivudine, adefovir, TDF and entecavir for children and adolescents with CHB were approved based on the results of five randomized placebo-controlled trials and for TAF on the basis of HIV studies (Table 3).<sup>18,19,107-109</sup> A good treatment response (defined by the reduction of serum HBV DNA to undetectable levels, by the loss of serum HBeAg and/or by the normalization of aminotransferases) was associated with higher baseline histology activity index score and aminotransferase levels, and lower baseline HBV DNA levels.

### **Knowledge gaps, research agenda and future strategies**

If adolescents and children are to benefit equally from the global attention and momentum around scale-up of testing and treatment of HBV infection, there is a need to address the remaining critical evidence gaps in prevention, treatment and management to inform policy and management guidelines and improve outcomes. The following key evidence gaps and research needs were identified: **Seroprevalence and burden:** age stratified sero-surveys of prevalence of HBsAg (as well as HIV-HBsAg coinfection), in different populations of adolescents and children (high risk and general population), and with estimates of burden, morbidity, mortality

and treatment need by region. However, as sero-surveys are costly, modelled data may provide an important guide for policy in high prevalence regions.<sup>110</sup> There is a need for inclusion of children and adolescents into routine national data collection and global reporting tool on viral hepatitis cascade. **Diagnosis:** Evaluation of diagnostic performance of serological HBsAg assays (rapid diagnostic tests (RDTs) and immunoassays) in children, and validation of use of NITs (e.g. both blood-based assays and TE) for staging of liver disease for CHB in children and adolescents. Studies are also needed to identify other biomarkers of progression of hepatitis B, rather than just reliance on transition to a low replicative state. **Treatment:** Establish a consensus on when to start treatment in HBV infected children and adolescents, and establishment of long-term follow-up studies that include evaluation of safety of long-term use of NAs regimens in different paediatric populations. Immunopathogenesis studies of immune dysfunction underlying chronic hepatitis B in children are needed, to understand the requirement and efficacy of potential immunotherapies and new curative therapies in development. Different strategies may be required for children with high levels of HBV replication. **Prevention:** Further studies of the efficacy and safety of NAs, especially TDF and TAF, in pregnancy and of effectiveness in prevention of perinatal hepatitis B versus early birth dose vaccination (either with or without HBIG) and vaccination, especially in Asian as well as in African women; and strategies to promote implementation of birth dose vaccination within 24 hours of birth. In particular, there is a clear need for a strong prevention research agenda in African women and children. **Access to care:** Inclusion of recommendations for testing and treatment for children in national policies; evaluation of optimal service delivery models and additional support for children and adolescents living with chronic hepatitis B, and the contribution of stigma and discrimination on access to care, education and work opportunities among older adolescents.

Common challenges to treatment scale-up in children, adolescents and adults include the limited access to diagnosis and clinical assessment, affordable HBV DNA testing in LMICs, and for access to antiviral monotherapy outside HIV/antiretroviral (ART) programmes and appropriate paediatric formulations. To date, insufficient paediatric studies based on large cohorts have been published from LMICs. The HBV paediatric research agenda would benefit from the establishment of new international collaborations, consortia and cohorts of children to inform best practices for the management, care and treatment of children living with HBV infection in high burden settings.

### **Author's contribution**

**PE, MP, CG and GI conceived** the project. GI and PE wrote the first draft of the article and critically revised it. All the authors revised the paper critically for important intellectual content, approved the final version to be published and agreed 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 Review before submission.

### **Declaration of interests**

GD reports grants and personal fees from Gilead Sciences, personal fees from Janssen, grants and personal fees from Abbott laboratories, other from Arbutus, during the conduct of the study; .MJ reports grants from Gilead Sciences, grants from AbbVie, grants from Merck (MSD), during the conduct of the study; grants from Bristol Myers Squibb, grants from Roche/Genentech, other from Gilead Sciences, non-financial support from Echosens, outside the submitted work. CT

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**Table 1.** Comparison of recommendations for monitoring of hepatitis B virus infection in adults and children from five international organisation or professional society guidelines

Scientific Association	Condition	Suggested monitoring
WHO <sup>39</sup>	<ul style="list-style-type: none"> <li>• Untreated adults with CHB</li> <li>• adults receiving NAs once good treatment adherence has been established</li> </ul>	<ul style="list-style-type: none"> <li>• at least annual monitoring of HBeAg and serum ALT, HBV DNA levels and NITs</li> </ul>
	<ul style="list-style-type: none"> <li>• adults with compensated or decompensated cirrhosis receiving treatment</li> <li>• adults with fluctuating elevated ALT or HBV DNA levels (between 2 000 IU/mL and 20 000 IU/mL)</li> <li>• adults during the first year of treatment to assess response and adherence to therapy</li> </ul>	<ul style="list-style-type: none"> <li>• more frequent monitoring</li> </ul>
	<ul style="list-style-type: none"> <li>• adults after discontinuing treatment</li> </ul>	<ul style="list-style-type: none"> <li>• monthly ALT and HBV DNA for the first three months, and then every three months during the first year</li> </ul>
AASLD <sup>41</sup>	<ul style="list-style-type: none"> <li>• all adults with CHB</li> <li>• adults receiving treatment</li> </ul>	<ul style="list-style-type: none"> <li>• serial and regular monitoring of HBV DNA and ALT levels</li> <li>• HBV DNA levels every three months until HBV DNA is undetectable and then every three to six months</li> </ul>
	<ul style="list-style-type: none"> <li>• adults after discontinuation of therapy</li> </ul>	<ul style="list-style-type: none"> <li>• at least every three months for at least one year</li> </ul>
APASL <sup>22</sup>	<ul style="list-style-type: none"> <li>• all adults with CHB</li> </ul>	<ul style="list-style-type: none"> <li>• lifelong monitoring</li> </ul>
	<ul style="list-style-type: none"> <li>• HBeAg negative adults with HBV DNA &lt;2 000 IU/ml and normal ALT</li> </ul>	<ul style="list-style-type: none"> <li>• ALT every three to six months and HBV DNA every six to 12 months</li> </ul>
	<ul style="list-style-type: none"> <li>• adults with elevated ALT levels</li> <li>• adults receiving treatment</li> </ul>	<ul style="list-style-type: none"> <li>• every three months</li> <li>• HBV DNA level at month three and six of therapy and then every three to six months if agents with low genetic barrier are used or every six months in adults treated with entecavir or tenofovir</li> </ul>
	<ul style="list-style-type: none"> <li>• adults receiving PEG IFN</li> </ul>	<ul style="list-style-type: none"> <li>• monthly blood tests</li> </ul>
EASL <sup>40</sup>	<ul style="list-style-type: none"> <li>• untreated adults, younger than 30 years with HBeAg-positive chronic HBV infection</li> </ul>	<ul style="list-style-type: none"> <li>• at least every three to six months</li> </ul>
	<ul style="list-style-type: none"> <li>• adults with HBeAg-negative chronic HBV infection and serum HBV DNA &lt; or &gt; 2 000 IU/ml</li> </ul>	<ul style="list-style-type: none"> <li>• every six to 12 months or every three months for the first year and every six months</li> </ul>
	<ul style="list-style-type: none"> <li>• adults after discontinuation of treatment with NAs</li> </ul>	<ul style="list-style-type: none"> <li>• a closer schedule when treatment is discontinued</li> </ul>
	<ul style="list-style-type: none"> <li>• adults treated with PEG IFN</li> </ul>	<ul style="list-style-type: none"> <li>• periodical monitoring</li> </ul>
ESPGHAN <sup>86</sup>	<ul style="list-style-type: none"> <li>• children with increased ALT levels and HBeAg positive</li> <li>• HBeAg-negative children.</li> </ul>	<ul style="list-style-type: none"> <li>• monitoring of ALT and HBV DNA levels every three to four months for at least one year</li> </ul>
	<ul style="list-style-type: none"> <li>• HBeAg positive children with normal ALT level</li> </ul>	<ul style="list-style-type: none"> <li>• every six months</li> </ul>
	<ul style="list-style-type: none"> <li>• children receiving treatment</li> </ul>	<ul style="list-style-type: none"> <li>• no specific recommendations and frequency of monitoring for safety, adherence and efficacy should be determined on an individual basis</li> </ul>

**Legend:** AASLD, American Association for the Study of Liver Disease; CHB, chronic hepatitis B virus infection; NA, nucleos(t)ide analogues; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; HBV DNA, hepatitis B virus deoxyribonucleic acid; NITs, non-invasive tests; EASL, European Association for the Study of Liver; WHO, World Health Organization; APASL, Asian Pacific Association for the Study of Liver; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition.



**Table 2.** Comparison of the recommendations for treatment of chronic hepatitis B virus infection in adults and children from five international or professional society guidelines

Guideline	Recommendations for Adults	Recommendations for Children
AASLD <sup>41</sup>	<ol style="list-style-type: none"> <li>1. elevation of ALT &gt;2 ULN (30 U/L for males and 19 U/L for females) <b>or</b> evidence of significant histological disease <b>plus</b> HBV DNA above 2,000 IU/mL (HBeAg negative) or above 20,000 IU/mL (HBeAg positive);</li> <li>2. adults &gt;40 years of age with normal ALT <b>and</b> elevated HBV DNA (&gt;1,000,000 IU/mL) <b>and</b> liver biopsy showing significant necroinflammation or fibrosis;</li> <li>3. adults with compensated cirrhosis and low levels of viremia (&lt;2,000 IU/mL);</li> <li>4. HBsAg-positive adults with decompensated cirrhosis be treated with antiviral therapy indefinitely <b>regardless of</b> HBV DNA level, HBeAg status, or ALT level;</li> <li>5. HBsAg-positive pregnant women with an HBV DNA level &gt;200,000 IU/mL.</li> </ol>	<ol style="list-style-type: none"> <li>1. HBeAg positive children (ages 2 to &lt;18 years) with both elevated ALT and measurable HBV DNA levels</li> </ol>
EASL <sup>40</sup>	<ol style="list-style-type: none"> <li>1. HBV DNA levels &gt; 2000 IU/ml <b>and</b> ALT &gt; ULN <b>and/or</b> at least moderate liver necroinflammation or fibrosis;</li> <li>2. patients with compensated or decompensated cirrhosis <b>and</b> detectable HBV DNA independently of ALT levels;</li> <li>3. HBV DNA &gt; 20 000 IU/ml and ALT &gt; 2xULN regardless of the degree of fibrosis;</li> <li>4. patients older than 30 years with HBeAg-positive chronic HBV infection (normal ALT and high HBV DNA levels) regardless of the severity of liver histological lesions</li> <li>5. patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations</li> </ol>	<ol style="list-style-type: none"> <li>1. A conservative approach is warranted</li> </ol>
WHO <sup>39</sup>	<ol style="list-style-type: none"> <li>1. all adults with clinical evidence of compensated or decompensated cirrhosis (or cirrhosis based on APRI score &gt;2 in adults) should be treated <b>regardless</b> of ALT levels, HBeAg status or HBV DNA levels;</li> <li>2. adults without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults) but aged more than 30 years <b>and</b> persistently abnormal ALT levels <b>and</b> (if available) evidence of high-level HBV replication (HBV DNA &gt;20,000 IU/mL), <b>regardless</b> of HBeAg status.</li> </ol>	<ol style="list-style-type: none"> <li>1. All adolescents and children with clinical evidence of compensated or decompensated cirrhosis should be treated <b>regardless</b> of ALT levels, HBeAg status or HBV DNA levels</li> </ol>
APASL <sup>22</sup>	<ol style="list-style-type: none"> <li>1. decompensated cirrhosis and detectable HBV DNA or severe reactivation (decompensation) of chronic infection;</li> <li>2. compensated cirrhosis and HBV DNA &gt; 2,000 IU/ml;</li> <li>3. adults with persistently elevated (at least 1 month between observations) ALT levels &gt;2 times the upper limit of normal <b>and</b> HBV DNA &gt;20,000 IU/ml if HBeAg positive or &gt; 2,000 IU/ml if HBeAg negative (liver biopsy or noninvasive method for the estimation of the extent of fibrosis may provide additional useful information);</li> </ol>	<ol style="list-style-type: none"> <li>1. children with cirrhosis (compensated or decompensated) and children with severe reactivation of chronic HBV (detectable HBV DNA and elevated ALT)</li> <li>2. children with noncirrhotic HBeAg-positive CHB: <ul style="list-style-type: none"> <li>- HBV DNA &gt; 20 000 IU/mL and ALT &gt; 2 ULN for more than 12 months</li> </ul> </li> </ol>

	4. adults with normal or minimally elevated ALT levels or HBV DNA <20,000 IU/ml if HBeAg positive or < 2,000 IU/ml if HBeAg negative <b>with</b> significant fibrosis.	- HBV DNA > 20 000 IU/mL and ALT < 2 ULN for more than 12 months or family history of HCC or cirrhosis and moderate to severe inflammation or significant fibrosis - HBV DNA < 20 000 and moderate to severe inflammation or significant fibrosis 3. Noncirrhotic HBeAg-negative CHB: - HBV DNA > 2000 IU/mL and ALT > 2 ULN - any value of HBV DNA and moderate to severe inflammation or significant fibrosis	
<b>ESPGHAN children<sup>86</sup></b>		1. children with elevated serum ALT levels for at least 6 months (12 months if HBeAg-negative) <b>and</b> HBV DNA >2,000 IU/ml <b>and</b> moderate necroinflammation or moderate fibrosis <b>or</b> mild inflammation or fibrosis with family history of hepatocellular carcinoma.	

**Legend:** AASLD, American Association for the Study of Liver Disease; ALT, alanine aminotransferase; ULN, upper limit of normal; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; EASL, European Association for the Study of Liver; WHO, World Health Organization; APASL, Asian Pacific Association for the Study of Liver; ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition.

**Table 3.** Antiviral drugs approved for adults, adolescents and children with chronic hepatitis B virus infection

<b>Drug</b>	<b>Use in children</b>	<b>Dose</b>	<b>Formulation</b>	<b>No of randomized controlled trials evaluating the effects of treatment</b>
interferon- $\alpha$ -2b	$\geq 1$ year	6 million IU/m <sup>2</sup> 3 times a week	subcutaneous injections	8
pegylated-interferon- $\alpha$ -2a	$\geq 3$ years	180 $\mu$ g/1.73 m <sup>2</sup> once a week	subcutaneous injections	1
pegylated-interferon- $\alpha$ -2b	not approved			0
lamivudine	$\geq 3$ years	3 mg/kg daily (max 100 mg)	oral solution (5 mg/mL) tablets (100 mg)	1
entecavir	$\geq 2$ years	10-30 kg: 0.015 mg/kg daily (max 0.5 mg)	oral solution (0.05 mg/mL) tablets (0.5 mg and 1 mg)	1
adefovir	$\geq 12$ years	10 mg daily	tablets (10 mg)	1
tenofovir disoproxil fumarate	$\geq 12$ years	300 mg daily	oral powder (40 mg per 1 g) tablets (150, 200, 250 and 300 mg)	1; paediatric (>2 years) trial ongoing (NCT 01651403)
tenofovir alafenamide	$\geq 12$ years	25 mg daily	tablets (25 mg)	0*; paediatric (>2 years) trial ongoing (NCT 02932150)
telbivudine	not approved			0; paediatric trial ongoing (NCT 02058108)

\*data available for children with human immunodeficiency virus infection

