ADC Online First, published on December 16, 2016 as 10.1136/archdischild-2016-312043

Hepatitis B: changing epidemiology and interventions

Pilar Nannini, Etienne M Sokal

Université Catholique de Louvain, Cliniques Universitaires St Luc, Service de Gastroentérologie et Hépatologie Pédiatrique, Brussels, Belgium

Correspondence to
Professor Etienne M Sokal, Université Catholique de Louvain, Cliniques. Universitaires St Luc, Service de Gastroentérologie et Hépatologie Pédiatrique, Avenue Hippocrate 10, Brussels 1200, Belgium; etienne.sokal@uclouvain.be

Received 12 October 2016
Revised 22 November 2016
Accepted 25 November 2016

ABSTRACT

Hepatitis B virus infection is still a major public health problem worldwide, since more than 350 million people have chronic, lifelong infection and nearly 1 million deaths occur each year owing to complications. Most infections are acquired at birth or during early childhood. Nowadays, low- and middle-income countries bear the majority of the burden of hepatitis B-related liver cancer deaths despite the availability of an effective vaccine and antiviral treatments. In this review the epidemiology, strategies of prevention and the recent advances in therapy, genotype diversity and resistance are discussed.

EPIDEMIOLOGY

Hepatitis B virus (HBV) is the prototype member of the Hepadnaviridae family. Its genome is a relaxed partially double-stranded circular DNA with four overlapping open reading frames (ORFs): pre-S/S (surface proteins), pre-C/C (pre-core/core), X (transcriptional co-activator) and P (DNA polymerase). Despite the availability of an effective vaccine and antiviral treatments, chronic HBV infection is still a major public health problem worldwide. According to the Centre for Disease Control (Atlanta, USA) more than 350 million people have this chronic, lifelong infection, and nearly 1 million deaths occur each year owing to complications, including cirrhosis and hepatocellular carcinoma (HCC).[1] Twenty-five per cent of people who acquire HBV in childhood will develop cirrhosis or HCC in adulthood. The risk of developing chronic HBV infection is directly related to the age of infection, ranging from about 90% when infection occurs perinatally up to 6 months of age, to 20–60% when infection occurs between the ages of 6 months and 5 years. Currently, low- and middle-income countries have the greatest burden of hepatitis B-related complications and deaths.[2] The distribution of HBV genotypes and subgenotypes follows a characteristic ethno-geographic pattern: genotypes A (A1–A7) and D (D1–D8) are ubiquitous but most prevalent in Europe and Africa; genotypes B and C are confined to Asia and Oceania. Sub-genotypes D1–D4 are prevalent primarily in Europe, Africa and Asia. Infections with genotypes E, F, G and H are occasionally seen in Asia. The more rare genotype I can be found in Laos, Vietnam, India and China, and genotype J has been observed in Japan and Ryukyu (table 1).[3]

Africa shows a low–intermediate HBV endemicity (6% of hepatitis B surface antigen (HBsAg) chronic carriers in the general population) in sub-Saharan countries, where infections occur mainly before adolescence from mother-to-child transmission or through horizontal transmission between children, while northern African countries show low–intermediate endemicity (2–8% HBsAg prevalence). Zimbabwe and Burkina Faso are the regions with the highest HBsAg prevalence (25% and 14.5%, respectively), as a result of tribal and sexual behaviours. The higher percentage of HBsAg is in men harbouring HBV chronic infection and in rural areas. The Arabian Peninsula, including Saudi Arabia, Yemen, Oman, Bahrain, the United Arab Emirates and Kuwait, has an HBsAg prevalence ranging from 1.5% to >8%. In the Levant Arabian region, comprising Syria, Iraq, Lebanon, Jordan and the Gaza Strip, HBsAg prevalence ranges from 0.6% in the general population in Iraq to 3.8% among blood donors in the Gaza Strip.[4]

Seventy-five per cent of chronically HBV-infected people reside in Asian-Pacific countries, and the major prevalence is among younger patients aged 18–25 years (2.73%), compared with those aged 26–35 years (2.13%), 36–45 years (2.03%) and 46–58 years (1.71%).[5] Most chronic HBV infections are acquired perinatally or during early childhood; thus, the patients usually have a long immune tolerance phase with minimal histological change and disease progression. The most prevalent genotype is type C, which is associated with a more progressive disease course, and also is less responsive to interferon (IFN)-based therapy.[6] Other risk factors of transplacental transmission are high viral load and genotype B2, in addition to maternal hepatitis B e antigen (HBeAg) positivity. A nationwide HBV survey in 2006 in China showed that 7.2% of the population aged 1–59 years were HBsAg carriers. In 1995 the 'Law on Chinese Maternal and Infant Health Care' was enacted, which led to detection of an estimated 270 000–540 000 people with HBV infection. Since 2003, when compliance with this law became voluntary rather than mandatory, a reduced rate of HBV infection has been reported, leading to a diagnosis of between 10 800 and 21 600 new HBV infections a year, among which about 30–50% occur through perinatal and early childhood close contact.[7] The Eastern European countries, Poland and the Russian Federation demonstrate increasing HBsAg prevalence, as do some high-income countries such as Australia and Canada (figure 1).

PREVENTION STRATEGIES IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES

Most middle- and low-income countries have insufficient medical care systems, a lack of awareness among healthcare providers and low awareness of the disease among the general population; adequate antiviral therapy is restricted to those who can afford it, sometimes against the current guidelines for treatment in immunotolerant children. To date, the protective efficacy rate of a three- or four-dose HB vaccine series alone is 70–80%, but the synergistic effect of the HBV vaccine plus hepatitis B

To cite: Nannini P, Sokal EM. *Arch Dis Child* Published Online First: [*please include* Day Month Year] doi:10.1136/archdischild-2016-312043

Table 1 Worldwide distribution of hepatitis B virus (HBV) genotypes and sub-genotypes

Genotypes	Sub-genotypes
A: Eastern Europe (Poland, Czech Republic, Bulgaria, Hungary), Central Europe (Spain, Italy), Central Africa, Morocco, India, Guadalajara, Jalisco, Gambia, Nigeria, Haiti, Congo, Rwanda, Cameroon, Japan, Philippines, USA, Canada, Mexico, Argentina, Brazil	**A1** Southern and Eastern Africa, India, Brazil, Philippines **A2** South Africa, Bulgaria, Brazil, Morocco **A4–7** Gambia, Nigeria, Haiti, Congo, Rwanda, Cameroon
B: China, Indonesia, Latin America (Asian immigrants), Vietnam, Taiwan, Hong Kong, Philippines, Thailand, Canada	**B2** Southern China, Taiwan **B3** Indonesia **B5** Taiwan, Philippines **B7** Indonesia **B2–5** Vietnam
C: China, Indonesia, Vietnam, Latin America (Asian immigrants), South Korea, Hong Kong, Japan, Philippines, India, Thailand, Canada, Australia	**C1** China Indonesia, Japan, Thailand **C2** China, Japan, Thailand **C3** Japan, Thailand **C4** Thailand, Australia **C5** Philippines, Thailand **C5-16** Vietnam
D: Saudi Arabia, Southeastern Europe, India, Russia, Baltic region, Belarus, Romania, Hungary, Serbia, Croatia, Lithuania, Romania, Bulgaria, Central Europe (Italy, Spain), Tunisia, Canada, Central and Southern Africa, Iran, Mongolia, Pakistan, Australia	**D1** Northern Africa, Persian Gulf (Iran, Syria, Turkey), India, Pakistan, Saudi Arabia **D2, D3, D4, D9** India, Turkey **D3** South Africa **D4** Central Africa, Australia **D7** Northern Africa
E: Western Africa, Central Africa, Saudi Arabia	**C1** Southern China, India **C2** Northern China
D: Guadalajara, Jalisco, Mexico, Argentina, Turkey, USA	**D1** Bulgaria **D2** Albania, Russia, Estonia, Siberia, Eastern Russia **D3** Serbia
F: Latin America (Brazil, Argentina), Tunisia, Spain	**F1** Central America, Eastern South America **F2** Venezuela, Brazil (F2a) **F3** Panama, Colombia, Venezuela **F4** Bolivia, Argentina, Brazil
H: Amerindians and Mestizos in Mexico, USA	–
G: USA, Canada	–
I: Vietnam, Canada, Laos, India, China	–
J: Japan, Ryukyu	–
Recombinant A/D and A/E: Africa	–
Recombinant C/D1–CD2: Western China	–

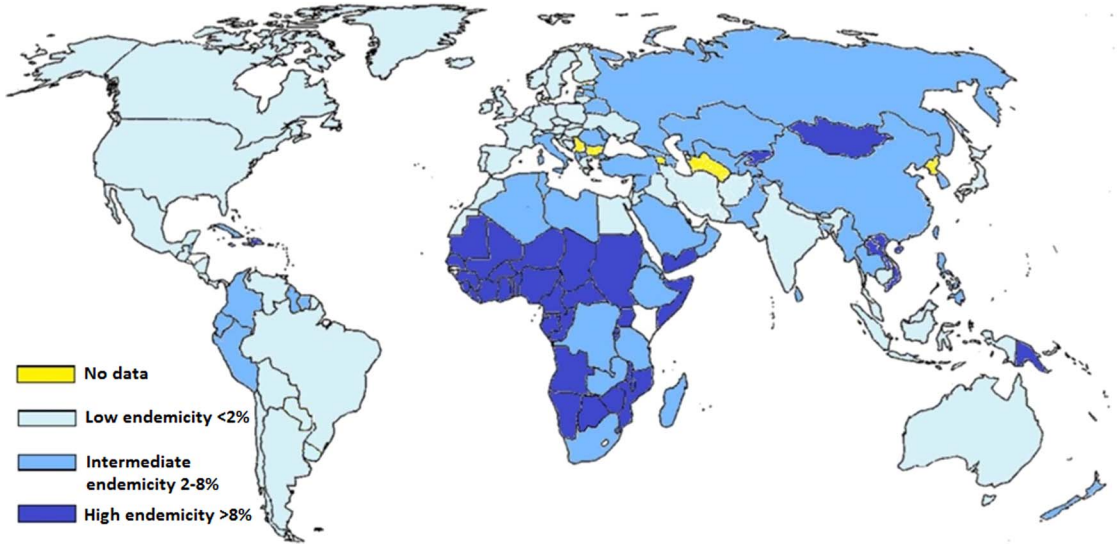

Figure 1 Worldwide distribution of hepatitis B surface antigen endemicity 2011–2016.

immunoglobulin (HBIG) increases the protective efficacy rate to 95% in perinatal transmission. For newborns whose mothers are HBsAg- and HBeAg-positive, HBIG prophylaxis, in conjunction with the HBV vaccination, is shown to be useful in reducing the rate of vertical transmission (HBsAg or HBV-DNA positivity at 6–12 months of life in an infant born to an infected mother). However, in full-term neonates born to mothers who are HBsAg-positive but HBeAg-negative, protection against

perinatally acquired infection achieved by immediate vaccination against HBV (given within 24 hours) may not be significantly improved by the addition of HBIG, although it is shown to decrease the risk of fulminant hepatitis.[8] Screening of pregnant women in low-income countries is not recommended by WHO because of the expense. Accordingly, the current HBV prevention strategies are classified into three groups: universal vaccination without screening of pregnant women, universal vaccination with screening of pregnant women plus HBIG and selective vaccination with screening of pregnant women plus HBIG.[9]

VACCINATION STRATEGIES

A vaccine against HBV has been available since 1982, and since 1991 the WHO has recommended universal vaccination of newborn babies with yeast-derived recombinant S protein. The current rate of infant vaccination is 92–96% in East Asia, North Africa and the Middle East, but it continues to be insufficient in other areas, such as central Africa (56% in 2013). All African governments have incorporated the HBV vaccine into their expanded programmes on immunisation. After vaccination, the overall seroprotection rate among African children is shown to be 57.2%, a significant decrease from 90.2% among children <3 years to 30.5% among children ≥15 years.

Among Arab countries, Saudi Arabia, which was the first Arab country to adopt an HBV vaccination programme, showed a steady decline in the prevalence of HBsAg in children aged 1–12 years, from 7% in 1989 (before the introduction of the vaccination programme) to 0.31% in 1997 and 0% in 2008. The schedule adopted by most of the Arab countries is birth, 2, 4, 6 and 18 months, while a few Arab countries have adopted a 6-, 10- and 14-week schedule.[10]

In Indonesia, the introduction in 1997 of universal vaccination for every newborn during the first 7 days of life led to a decrease in HBsAg prevalence from 6.2% to 1.4% among children aged <5 years in the Lombok region and 0% in Surabaya and North Sulawesi.[11]

In Russia, after the initiation of the HBV vaccination, there was a more than 33-fold reduction in the number of acute hepatitis B infections among the general population, from 43.8 per 100 000 in 1999 to 1.3 per 100 000 in 2014. Immunisation of adolescents at 13 years of age was added to the schedule in 2001, but mass immunisation started in 2004, leading to immunisation of a total of 45 million adults aged 18–59, constituting almost half of the entire adult population of Russia. However, the incidence of chronic hepatitis B (CHB) in Russia is still a source of concern; it decreased by only 3% from 2008 to 2014 (11.3 per 100 000 people in 2014), indicating that CHB infection is still prevalent among the Russian population.[12]

CURRENT THERAPY AND RECENT ADVANCES

The goal of treatment is to reduce the risk of progression of liver disease, cirrhosis and HCC. The time at which treatment should be started is based on alanine aminotransferase (ALT) levels, HBeAg positivity, HBV-DNA levels, liver histology, family history of cirrhosis and HCC or coexisting liver disease. The upper limit of normal for ALT levels in children has not yet been established; however, it is well demonstrated that anti-HBV therapy should be started when ALT levels are >1.5 times the laboratory upper limit of normal or >60 IU/L, since lower ALT levels have been shown to respond poorly to treatment. Moreover, serum ALT levels have to be increased for at least 6 months (or 12 if HBeAg is negative), in order to avoid treating patients who undergo spontaneous HBeAg seroconversion. Children with cirrhosis, HBV-related glomerulonephritis, co-infection with hepatitis D virus, hepatitis C virus, or HIV could benefit from treatment regardless of ALT, HBV-DNA and liver histology, given the risk of rapid disease progression, as could children who are going to receive immunosuppressive or cytotoxic therapy, given the increased risk of HBV reactivation.[13]

Although many effective and safe anti-HBV therapies are available for adults, few drugs are licensed for use in the paediatric group: conventional IFN-α can be used in children aged >1 year, lamivudine (LAM) in children aged >3 years and adefovir dipivoxil in children aged >12 years (table 2). Tenofovir disoproxil fumarate (TDF), currently approved for therapy in HBV-infected adolescents aged ≥12 years, has been shown to be well tolerated and highly effective in viral suppression and in normalisation of ALT values, both in treatment-naïve patients and in those with prior exposure to IFN or LAM therapy.[14] Entecavir, a nucleoside analogue approved for treatment of HBV-infected children aged 2–18 years, has recently shown to be effective in suppressing HBV at <50 IU/mL, HBeAg seroconversion and ALT normalisation.[15]

However, some of these therapies consistently have adverse events; for example, IFN-α therapy is associated with hypersensitivity reactions, fever, fatigue, diarrhoea, alopecia, flu-like symptoms, insomnia, psychiatric complications and transient growth impairment. Long-term treatment with LAM can lead to the development of mutations in the YMDD (tyrosine, methionine, aspartate and aspartate) motif of the reverse-transcriptase domain in the polymerase gene, which is associated with a high rate of drug resistance.[16 17]

New antiviral approaches that target various steps and components of the HBV lifecycle are being investigated, with the hope of achieving a functional cure of infection or, if possible, complete viral eradication. These approaches include HBV entry inhibitors, such as Myrcludex B (Myrc), a lipo-myristolated peptide mimicking the pre-S1 domain that competes with HBV particles to bind to the sodium taurocholate co-transporting polypeptide (NTCP). The susceptibility of the human liver to HBsAg depends on the specific binding of the myristolated domain to NTCP, targeting the NTCP with the synthetic homologous peptide competes to bind with the natural HBsAg, and results in the restriction of virion uptake in the cell. Since the concentration (IC50) of Myrc that blocks HBV and hepatitis D virus entry through NTCP is 100 times lower than that which inhibits bile acid transport, viral block should be achieved without interfering with bile acid transport. Studies on the drug's safety were carried out on healthy adult volunteers, and showed modest and transient elevations of amylase and lipase, without clinical relevance in a low percentage of patients, which resolved spontaneously.[18]

Tenofovir alafenamide fumarate (TAF) was approved by the Food and Drug Administration in 2015 as part of a co-formulation that also includes the integrase inhibitor elvitegravir, the pharmacokinetic enhancer cobicistat and the nucleoside analogue emtricitabine (also called FTC). In this fixed-dose co-formulation, it is intended for use in the HIV treatment of adults and paediatric patients ≥12 years of age who have no HIV resistance to the component drugs. Gilead Sciences has reported results of two phase III studies of TAF in treatment-naïve and treatment-experienced adults with HBeAg-negative or HBeAg-positive HBV infection. For bone mineral density impairment, studies comparing TAF and TDF in initial treatment showed that TAF reduces bone density at the hip and the spine, but less so than TDF. In switch studies of patients on TDF-containing regimens, slight increases in hip and

Table 2 Treatments for hepatitis B in children and adolescents approved by the Food and Drug Administration

Generic names	Manufacturer's Name	Indication	Adverse effects
Entecavir	Bristol-Myers Squibb	Adults and children at least 2 years of age and at least 10 kg in weight, with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease	Most common adverse reactions (≥3%, all severity grades) are headache, fatigue, dizziness and nausea
Lamivudine	GlaxoSmithKline	Chronic hepatitis B associated with hepatitis B viral replication and active liver inflammation	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues and other antiretroviral agents. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors
Adefovir dipivoxil	Gilead Sciences	Chronic hepatitis B in patients aged >12 years	Severe acute exacerbations of hepatitis, nephrotoxicity, HIV resistance, lactic acidosis and severe hepatomegaly with steatosis
Interferon α-2b	Schering	Chronic hepatitis B in patients aged ≥1 year with compensated liver disease	Depression, difficult or laboured breathing, swelling or puffiness of the face, tightness in the chest and weight loss
Telbivudine	Novartis	Chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease	Transient increase of CK, arthralgia, fatigue, pyrexia, headache, elevation in AST and ALT, lactic acidosis, hepatomegaly with steatosis, hypercholesterolaemia, diarrhoea, abdominal pain, nausea, abdominal pain, rash, pruritus, neutropenia and thrombocytopenia
Tenofovir	Gilead Sciences	Chronic hepatitis B in adolescents aged >12 years	Nausea, abdominal pain, diarrhoea, headache, dizziness, fatigue, nasopharyngitis, back pain and skin rash. Renal failure, Fanconi syndrome, proximal renal tubulopathy, increased creatinine, nephrogenic diabetes insipidus and acute tubular necrosis have also been reported during postmarketing experience

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

spine bone mineral density were seen at 48 weeks in those who changed to TAF-containing regimens, while slight decreases in bone mineral density at those sites occurred in patients who continued to receive TDF. Similar differences in the effects on bone mineral density between TAF and TDF have been described in other studies.[19 20]

FTC, a nucleoside analogue HIV-1 reverse-transcriptase inhibitor, is approved in paediatric patients in combination with other antiretroviral agents for the treatment of HIV-1 infection, but is not yet approved for the treatment of chronic HBV infection, and its safety and efficacy have not been established in HBV–HIV co-infected patients. However, generic FTC has been approved for treatment of naive patients with CHB in China. Data are limited for this agent in paediatric patients, and a clinical trial to test the effect of FTC in children with CHB, including naive HBeAg-positive and HBeAg-negative CHB patients, is still ongoing among Chinese children.[21]

GENOTYPES, RESISTANCE AND CLINICAL IMPLICATIONS

The efforts to treat and prevent HBV infection are hindered by the emergence of drug-resistant mutants and vaccine-escape mutants that are found in infants born to HBsAg-positive mothers who underwent passive/active immunoprophylaxis at birth, in HBsAg-positive liver transplant recipients treated with hyperimmune anti-HBs immunoglobulin and in patients who experienced loss of HBsAg after anti-HBV therapy. The most frequently detected vaccine-escape mutant is G145R, which is stable over time and horizontally transmissible. Other less common mutations, such as G145A, F134L, D144E and others, have also been found to cause vaccine escape.[22]

In addition to genomic mutations, the host's immune status might also contribute to the progression of liver disease. A diminished response to HBV vaccination among immunocompromised patients has repeatedly been shown in patients infected by HIV, as well as in HIV–HBV co-infected children and adults.[23 24] The weakening effect of the HIV virus on the immune response is shown to produce lower anti-HBsAg titres after vaccination in these populations than in uninfected patients. Gene variants, including human leucocyte antigen (HLA) classes I and II alleles, as well as non-HLA genes, can influence the natural history of HBV infection in hosts through their ability to attract and bind viral peptides. Genome-wide association studies have shown that single nucleotide polymorphisms near HLA-DP, HLA-DQ and HLA-DR loci are significantly correlated with HBV infection outcomes. HLA class II gene variations are strongly associated with persistent HBV infection, spontaneous HBV clearance and seroconversion, disease progression, cirrhosis and HCC. Such variations also affect IFN and nucleoside analogue treatment efficacy and the response to HBV vaccines among different ethnic subjects.[25]

THE GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS 2016–2021

Viral hepatitis is a leading cause of death and disability worldwide. According to a recent report, the absolute numbers of deaths attributed to viral hepatitis rose substantially from 1990 to 2013.[26] In May 2016, The World Health Assembly adopted the first 'Global Health Sector Strategy on Viral Hepatitis, 2016–2021', which has the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030. The response of the World Health Assembly to viral hepatitis is investment in five core intervention areas: large-scale implementation of HBV vaccination programmes among children, prevention of mother-to-child transmission (by enhancing antenatal testing and the use of antiviral drugs), prevention of horizontal transmission (by ensuring access to sterile injecting equipment), availability of new oral, well-tolerated medicines and new treatment regimens for people with CHB virus infection.

Twitter Follow Etienne Sokal @ESokal

Contributors PN wrote the first draft of the manuscript, EMS supervised and contributed to subsequent drafts.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

1 Hamborsky J, Kroger A, Wolfe S. *Centers for disease control and prevention. Epidemiology and prevention of vaccine-preventable diseases*. Washington DC: Public Health Foundation, 2015:149–74.
2 Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.
3 Zampino R, Boemio A, Sagnelli C, *et al*. Hepatitis B virus burden in developing countries. *World J Gastroenterol* 2015;21:11941–53.
4 Merican I, Guan R, Amarapuka D, *et al*. Chronic hepatitis B virus infection in Asian countries. *J Gastroenterol Hepatol* 2000;15:1356–61.
5 Allain JP, Opare-Sem O. Screening and diagnosis of HBV in low-income and middle-income countries. *Nat Rev Gastroenterol Hepatol* 2016;13:643–53.
6 Wen WH, Chen HL, Ni YH, *et al*. Secular trend of the viral genotype distribution in children with chronic hepatitis B virus infection after universal infant immunization. *Hepatology* 2011;53:429–36.
7 Zhang C, Zhong Y, Guo L. Strategies to prevent hepatitis B virus infection in China: immunization, screening, and standard medical practices. *Biosci Trends* 2013;7:7–12.
8 Komatsu H. Hepatitis B virus: where do we stand and what is the next step for eradication? *World J Gastroenterol* 2014;20:8998–9016.
9 Chen H-L, Lin L-H, 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.
10 WHO Global policy report on the prevention and control of viral hepatitis in WHO Member States, World Health Organization, Geneva (2013) http://www.who.int.pros.lib.unimi.it/hepatitis/publications/global_report/en/
11 Alfaleh F, Alshehri S, Alansari S, *et al*. Long-term protection of hepatitis B vaccine in Saudi Arabia 18 years after vaccination. *J Infect* 2008;57:404–9.
12 Utsumi T, Lusida MI, Yano Y, *et al*. Progress in the control of hepatitis B virus infection among children in Indonesia. *J Vaccines Vaccin* 2014;5:247.
13 Paganelli M, Stephenne X, Sokal EM. Chronic hepatitis B in children and adolescents. *J Hepatol* 2012;57:885–96.
14 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.
15 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.
16 Sokal EM, Kelly DA, Mizerski J, *et al*. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. *Hepatology* 2006;43:225–32.
17 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;59:814e29.
18 Rizzetto M, Niro GA. Myrcludex B, a novel therapy for chronic hepatitis D? *J Hepatol* 2016;65:465–6.
19 Sax PE, Wohl D, Yin MT, *et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;385:2606–15.
20 Gallant JE, Daar ES, Raffi F, *et al*. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV* 2016;3:e158–65.
21 Emtricitabine for Naive Chinese Chronic Hepatitis B Patients. https://clinicaltrials.gov/ct2/show/NCT02327663
22 Coppola N, Onorato L, Minichini C, *et al*. Clinical significance of hepatitis B surface antigen mutants. *World J Hepatol* 2015;7:2729–39.
23 Kim HN, Harrington RD, Crane HM, *et al*. Hepatitis B vaccination in HIV-infected adults: current evidence, recommendations and practical considerations. *Int J STD AIDS* 2009;20:595–600.
24 Beghin JC, Ruelle J, Sokal E, *et al*. Effectiveness of the South African Expanded Program of Immunization Against Hepatitis B in Children Infected With Human Immunodeficiency Virus-1 Living in a Resource-Limited Setting of Kwazulu-Natal. *J Med Virol* 2017;89:182–5.
25 Matsuura K, Isogawa M, Tanaka Y. Host genetic variants influencing the clinical course of Hepatitis B virus infection. *J Med Virol* 2016;88:371–9.
26 Stanaway JD, Flaxman AD, Naghavi M, *et al*. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016;388:1081–8.

Hepatitis B: changing epidemiology and interventions

Pilar Nannini and Etienne M Sokal

Arch Dis Child published online December 16, 2016

Notes