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Review

Hepatitis B: diagnosis and management

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Abstract: Globally, hepatitis B virus infection is one of the major causes of chronic liver diseases, apart from hepatitis C virus infection and alcohol abuse. The structure and genetic organization of HBV as well as the natural course and global burden of HBV infection are known in great detail. These advances have been successfully translated into important clinical applications, such as the sensitive and specific diagnosis, therapy and prevention of the hepatitis B virus-associated liver diseases, including liver cirrhosis and hepatocellular carcinoma. While it is possible to successfully prevent hepatitis B by vaccination, treatment of chronic HBV infection is more difficult than hepatitis C virus infection because it rarely eliminates the virus and makes an indefinite therapy necessary in most cases. Therefore, the World Health Organization goal of hepatitis B virus elimination by 2030 poses a major challenge to the medical community as well as to the health care authorities and requires their commitment to coordinated global interventions.

Keywords: hepatitis delta virus; liver cirrhosis; hepatocellular carcinoma; antiviral therapy; preventive measures; vaccination

1. Introduction

Based on the specific and sensitive detection of chronic hepatitis B virus (HBV) infection, its epidemiology and natural course as well as its global burden have been studied in great detail. At the same time highly effective preventive strategies have been developed. By comparison, therapeutic measures against chronic hepatitis B available to date are mostly suppressive and to not definitively eliminate the virus. Therefore, several novel strategies are at the stage of evaluation that should result in a reduced prevalence of HBV infection and its global elimination in the near future [1]. At the same time, the emerging rising prevalence of non-alcoholic fatty liver and its causes (e.g. obesity,

diabetes mellitus) as well as its associated clinical sequelae, i.e., chronic liver disease, liver cirrhosis and HCC, are rising.

2. Epidemiology of HBV infection

HBV infection is a major global public health problem (Figure 1) with about 260 million chronically infected people [2]. It accounts for 500,000–1.2 million deaths per year and is the 10th leading cause of death worldwide. The prevalence of HBV infection varies markedly in different geographic and in different population subgroups (Figure 1). The area with the highest hepatitis B surface antigen (HBsAg) prevalence of >8% is Western sub-Saharan Africa, followed by Eastern sub-Saharan Africa, Central Asia, Southeast Asia, China and Oceania with a high intermediate prevalence of 5–7%, Latin America, Eastern Europe, North Africa, the Middle East, Turkey, Afghanistan, Pakistan, India and Australia with a low intermediate prevalence of 2–4% and the US and Canada, Central America, Brazil and Western Europe with a low prevalence of <2% [3]. From 1990 to 2005 the prevalence of chronic HBV infection decreased in most regions. This was most evident for Central sub-Saharan Africa, Tropical and Central Latin America, Southeast Asia and Central Europe. A significant decline of the prevalence of HBV infection was documented for example in South East Asian children, reflecting the impact of HBV vaccination [3–5]. In the US, acute HBV infection has significantly declined from 8.5 cases per 100,000 population in 1990 to 1.5 cases per 100,000 population in 2007, especially in children and adolescents [6,7]. Today, sexual exposure and injection drug are considered the major risk factors.

Hepatitis delta virus (HDV) is a defective RNA virus that occurs only in association with HBV Data regarding its epidemiology, natural course and global burden indicate that it is also an important cause of chronic liver disease [8]. There are 8 HDV genotypes. Their geographic distribution and the prevalence of HDV infection are well established [9], indicating that it is endemic in central Africa, the Amazon Basin, Eastern and Mediterranean Europe, the Middle East and parts of Asia.in the context of an HBV/HDV coinfection or an HDV superinfection of a HBV infected patient.

3. Natural course of HBV infection

The incubation period of HBV infection is 45–150 days. In immunocompetent/healthy adults >95% will have a spontaneous resolution of the infection with seroconversion from HBsAg to antibodies to HBsAg (anti-HBs). The likelihood of acute liver failure is <1%. By contrast, in newborns and children HBsAg will persist in about 90–95% and will be associated in the vast majority with an asymptomatic clinical course and a so-called “healthy carrier state” [10–12].

Chronic HBV infection is the cause of significant morbidity and mortality, depending on the global, regional and national prevalences and the incidence of their associated liver diseases. In a major concerted effort, the global burden of disease (GBD) was studied in a systematic analysis of global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010 [13] as well as of disability-adjusted life years (DALYs) in patients with 291 diseases and injuries in 21 geographic regions in 1990, 2005 and 2010 [14]. In these studies deaths from hepatitis B and the associated liver cirrhosis and hepatocellular carcinoma (HCC) were considered. More recently, the GBD Study 2013 presented its findings on individuals with disability from 301 acute and chronic

diseases and injuries in 188 countries between 1990 and 2013, including hepatitis B as well as the associated liver cirrhosis and HCC [15] (Table 1).

Chronic HBV infection and its associated liver diseases, i.e., liver cirrhosis and HCCs [16], are responsible for the tremendous DALY rate worldwide, especially in Asia and to lesser degree in Europe (Figure 2a and b) and for more than 1 million deaths worldwide each year (Figure 3) [17]. In fact, by 2040, the deaths from chronic hepatitis B and C are expected to exceed the combined mortality associated with HIV infection, tuberculosis and malaria [18]. Chronic HBV infection is estimated to cause 30% of cases of liver cirrhosis and 45% of HCCs worldwide [19].

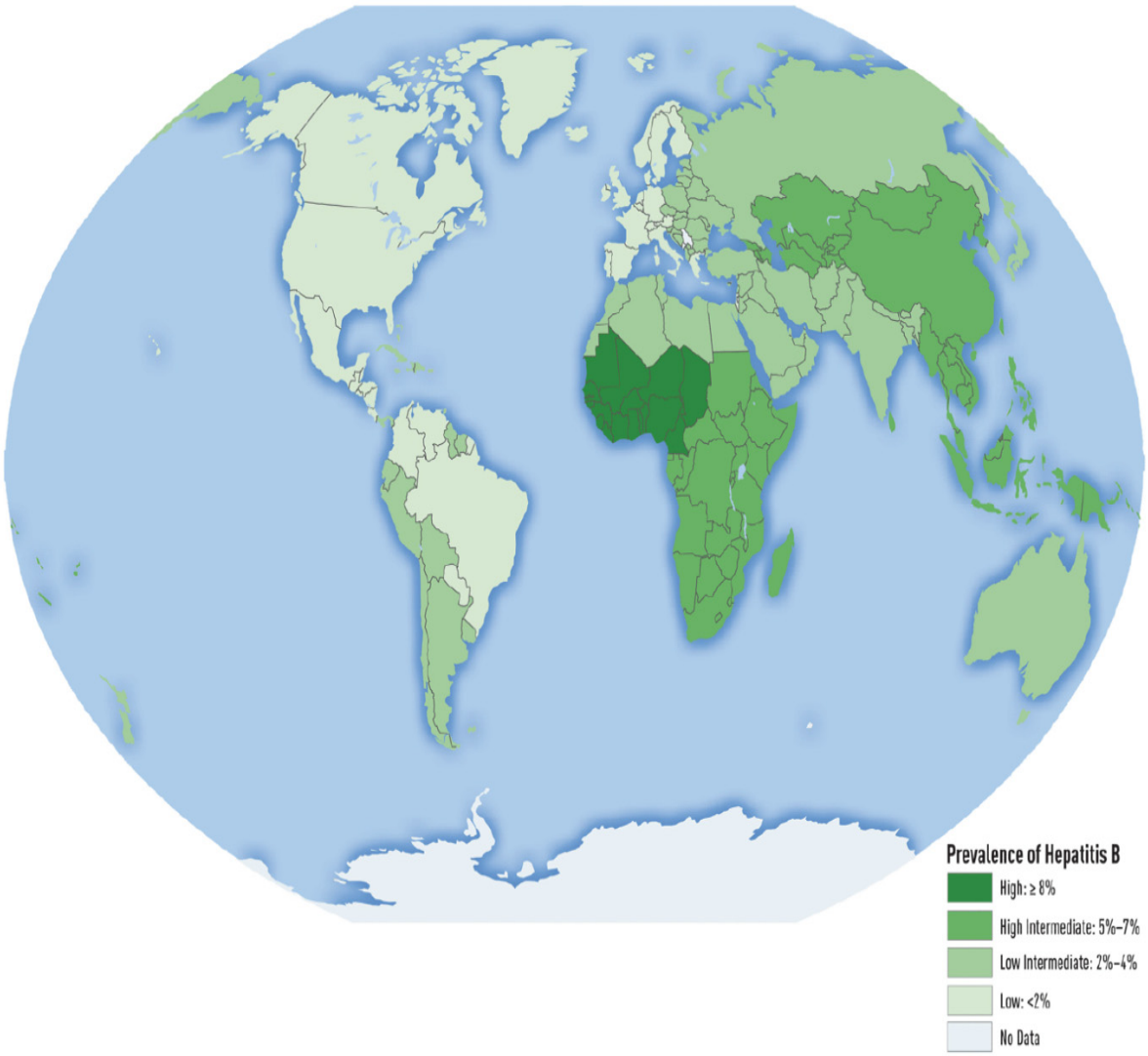

Figure 1. Worldwide prevalence of HBV infection in adults in 2005 [3].

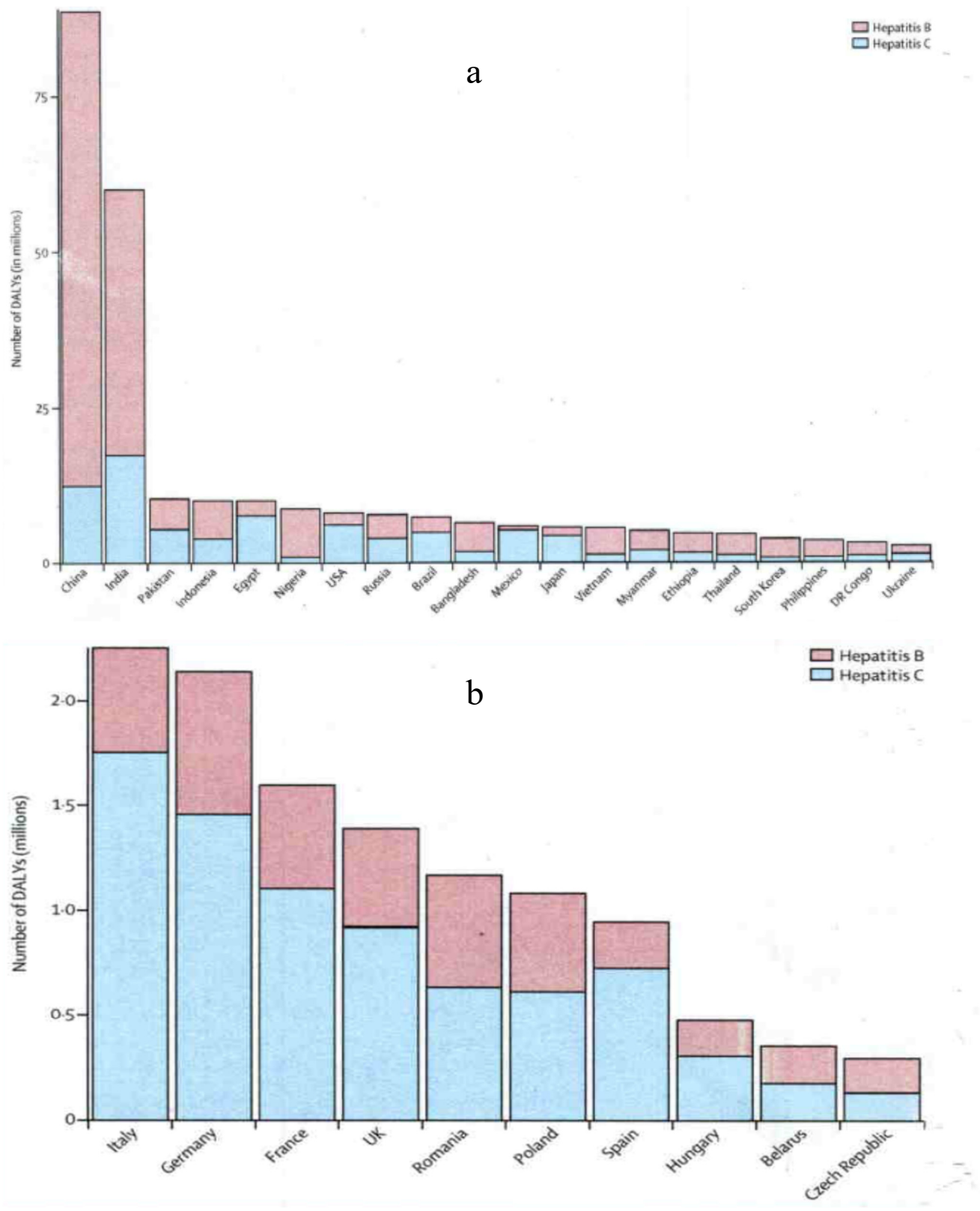

Figure 2. Disability-adjusted life-years (per 100,000 per year) caused by hepatitis B and C worldwide (a) and in Europe (b) [20].

Table 1. Global burden of selected liver diseases: prevalence between 1990 and 2013 adapted from [15].

	Prevalent Cases (×1,000)	
Liver Diseases	2013	Change 1990–2013 (%)
Hepatitis B	331,037	−6
Hepatitis C	147,826	+1
HBV liver cirrhosis	869	+22
HCV liver cirrhosis	885	+61
Alcohol liver cirrhosis	802	+10
HBV HCC	451	+91
HCV HCC	512	+368
Alcohol HCC	197	+10

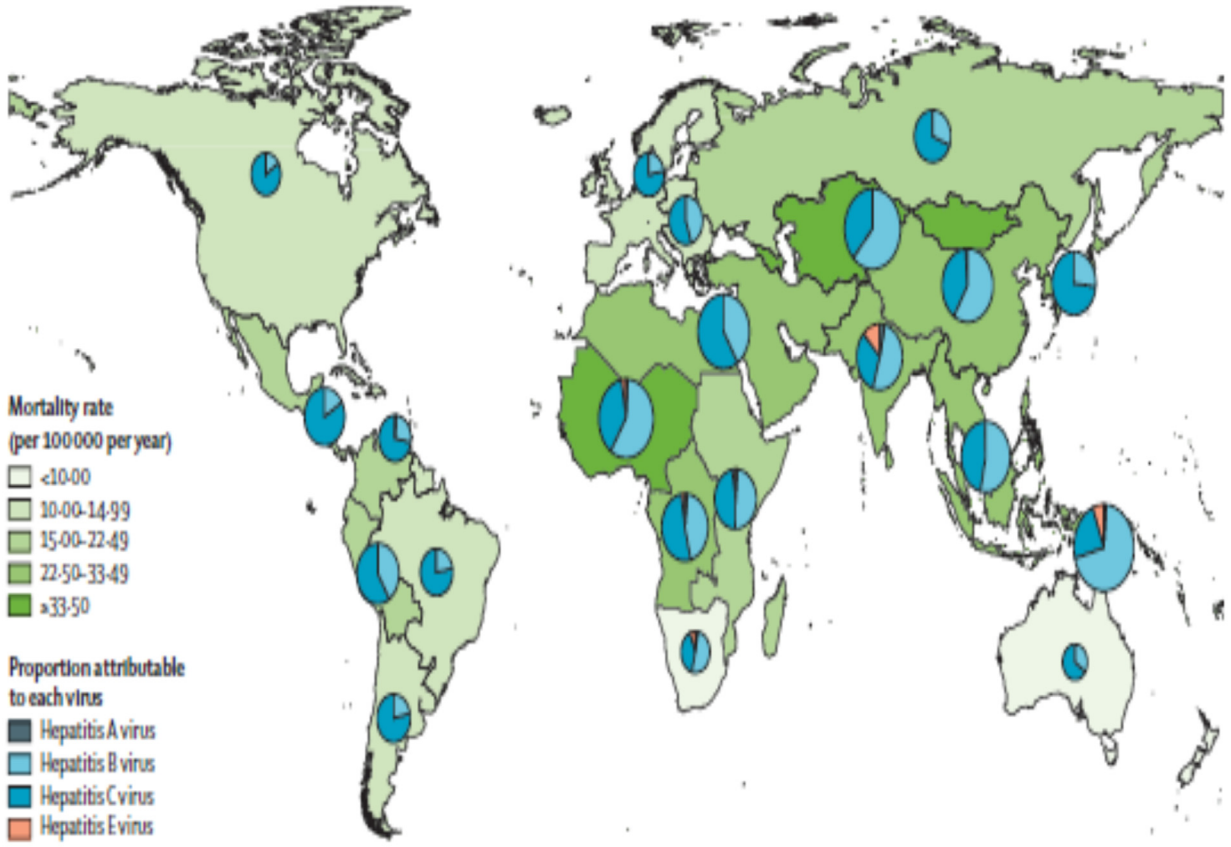

Figure 3. Global viral hepatitis-related mortality rates [17].

4. Diagnosis of HBV infection

The diagnosis of acute HBV infection is based upon elevated AST/ALT levels and the detection of HBsAg and IgM antibodies against hepatitis B core antigen (anti-HBc IgM). Complementary HBV markers are hepatitis B e antigen (HBeAg) and HBV DNA (Table 2). In

healthy/immunocompetent patients infected with HBV in adulthood 90–95% will spontaneously eliminate the virus with normalization of AST/ALT, loss of HBsAg and seroconversion to HBsAg, resulting in immunity against HBV reinfection. By contrast, HBV infection in newborns or adolescents frequently results in a lifelong HBsAg persistence without seroconversion to anti-HBs.

The diagnosis of chronic HBV infection is based on the persistence of HBsAg in serum for more than 6 months [10–12]. Additional HBV markers in serum are HBeAg, antibodies to HBeAg (anti-HBe) and HBV DNA. Their diagnostic relevance is detailed in Table 2. The natural course of chronic HBV infection is predominantly determined by the interplay between viral replication and the host immune response. Many patients who clear HBsAg will remain HBV DNA positive by PCR in serum and/or liver for prolonged periods of time. The sequelae of chronic HBV infection may vary from an inactive carrier state to the development of liver cirrhosis, hepatic decompensation and HCC. Factors predicting disease progression are HBeAg positivity and high HBV DNA levels.

The diagnosis of hepatitis D virus (HDV) co- or superinfection is based on the detection of hepatitis delta antigen (HDAg) and HDV RNA in serum in the context of HBV positivity [9].

5. Therapy of chronic HBV and HDV infection

The primary goal of treatment of patients with chronic HBV infection is the sustained loss of HBsAg with seroconversion to anti-HBs, following elimination of HBV DNA and seroconversion of HBeAg to anti-HBe and a normalization of ALT in parallel with a resolution of necroinflammatory activity as well as of liver fibrosis and a seroconversion. This can be achieved in eligible patients by therapy with pegylated interferon (PegIFN) alfa-2a or 2b for 6–12 months. This treatment results in a successful HBV elimination in <25% only. Predictors of a successful HBV elimination by PegIFN are the infection with HBV genotype A as well as high ALT and low HBV DNA levels.

In the majority of patients one can achieve a suppression of viral replication only by the long-term treatment with a nucleos(t)ide analogue without an elimination of HBV infection and loss of HBsAg and seroconversion to anti-HBs. In clinical practice there are several nucleos(t)ide analogues available: adefovir, entecavir (off-patent since 2018 except for Russia and China), lamivudine, telbivudine, tenofovir disoproxil fumarate (off-patent since 2018 except for Russia and China) and tenofovir alafenamide. The choice of the treatment modality of the individual patients is detailed in updated guidelines [10–12].

The definitive elimination of chronic HBV infection remains a major challenge. This is due to covalently closed circular (ccc) HBV DNA in the nuclei of the infected hepatocytes that can be translated into pregenomic RNA, followed by transcription into HBV DNA. Therefore, despite the effective suppression of HBV replication and normalization of ALT levels by nucleos(t)ide analogues, after termination of antiviral therapy there is a high risk of recurrence of HBV replication. An up to 10-year treatment of HBeAg-negative patients with a nucleos(t)ide analogue results in only about 1% in the loss of HBsAg. In HBeAg-positive patients nucleos(t)ide treatment results in a HBeAg to anti-HBe seroconversion in about 40% and in about 10% in a loss of HBsAg [11,19,21]. The optimal time and constellation of clinical and virological parameters need to be further analyzed in clinical studies before a recommendation for termination of nucleos(t)ide therapy can be made.

In view of the limitations of the available therapeutic strategies to eliminate chronic HBV infection numerous novel strategies are evaluated in clinical studies: inhibitors of HBV entry, of HBV DNA translation, of viral capsid assembly, of HBsAg secretion and others.

Table 2. Diagnostic markers of HBV infection.

Item	HBsAg	HBeAg	anti-HBc IgM	anti-HBc total	antiHBs	anti-HBe	HBV DNA	ALT	Interpretation
Acute HBV Infection									
	+	+	+	+	−	−	+++	+++	Early Phase
	+	+/−	+/−	+	−	+/−	+	+	Window Phase
	−	−	−	+	+	+	−	n	Recovery Phase
Chronic HBV Infection (HBsAg positivity >6 months)									
	+	+	−	+	−	−	++	++	HBeAg pos. hep. B
	+	−	−	+	−	−	+	+	HBeAg neg. hep. B
	+	−	−	+	−	+	+/−	n/(+)	Inactive hep. B
	−	−	−	+	+/−	+/−	+/−	n	Occult hep. B

HDV co-infection with HBV is the most severe and most fatal form of chronic viral hepatitis. The elimination chronic HDV infection remains one of the major challenges in the field of viral hepatitides [9] with only about 10–40% of patients responding to IFN-based strategies, depending among others on the HDV genotype and the duration of antiviral therapy. Similarly, targeting HBV infection by a long-term nucleos(t)ide treatment rarely results in clearance of HBV/HDV infection. Novel experimental strategies, therefore, based on the specific inhibition of HDV prenylation (lonafarnib, lonafarnib plus ritonavir or PegIFN), of HDV entry (myrcludex B/bulevirtide, myrcludex B plus tenofovir) and of virion secretion (REP 2139, a nucleic acid polymer) are presently evaluated in clinical studies.

6. Global elimination of HBV infection

While it is now possible to prevent hepatitis B by vaccination the WHO goals for HBV infection are a decrease from 4.7 million new cases and 884,000 deaths in 2015 to 470,000 new cases and 309,000 deaths in 2030 (Global Hepatitis Report. Geneva: World Health Organization, 2017) [1]. Viral elimination is defined as a 90% reduction of new infections and a 65% reduction of infection-associated deaths related to a 2015 baseline. Modelling studies for HBV infection suggest that these goals can indeed be achieved by 2030 [22,23]. Globally there are 20 heavily burdened countries that account for more than 75% of patients with viral hepatitis B and C, respectively. Key issues are affordable high-quality diagnostics and measures to improve access to vaccination and antiviral treatment as well as efforts to tackle stigma and discrimination. Indeed, progress has been made already in many countries throughout the world, demonstrating that sustained and coordinated efforts can be successful in achieving the WHO elimination goals by 2030 [1,20].

Apart from testing and treatment of HBV-infected individuals, key to achieve these goals is universal HBV vaccination of newborns. In addition, the safety of blood and blood products as well as the implementation of infection control programs are of paramount importance [20,24]. Another important aspect is a better access to diagnostics, including non-hospital settings, vaccination and antiviral therapies.

In view of the limited efficacy of therapeutic strategies, the key concept of the global HBV (and HDV) elimination is the universal vaccination of all individuals at risk for HBV Infection. Universal vaccination against HBV infection was shown to be cost-saving in countries with high and intermediate endemicity. Apart from exposure prophylaxis through personal protection measures, HBV vaccination should be administered to all unvaccinated individuals traveling to areas with high or intermediate HBsAg prevalence [20,24]. Indeed, vaccination against HBV has been a major public health success and has prevented an estimated 310 million cases of hepatitis B between 1990 and 2019 [20]. An excellent example is Taiwan where universal HBV vaccination was implemented in 1984 and has reduced chronic liver disease and HCC-associated mortality by 90% among children and young adults as compared to non-vaccinated individuals [5]. Central to all HBV elimination programs remains a high perinatal/childhood vaccination coverage rate. As of 2015, universal childhood vaccination has been achieved in 185 countries and 84% of children born in 2015 were vaccinated with 3 doses (http://apps.who.int/immunization monitoring/globalsummary/timeseries/tswucoveragehepb3.html).

7. Summary and perspectives

Globally, HBV infection is one of the major causes of chronic liver diseases. The structure and genetic organization of HBV as well as the natural course and global burden of HBV infection are known in great detail. These advances have been successfully translated into important clinical applications, such as the sensitive and specific diagnosis, therapy and most importantly the prevention of the HBV-associated liver diseases, including liver cirrhosis and HCC by HBV vaccination. While it is now possible to prevent hepatitis B and hepatitis D by vaccination against HBV- and to cure hepatitis C by novel therapies with direct acting antiviral agents-, the World Health Organization (WHO) goals of elimination of these infections by 2030 still poses a major challenge to the medical community as well as to the health care authorities and requires their commitment to coordinated global interventions.

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Conflict of interest

The author declares no conflict of interest.

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