Epidemiology and Natural History of Chronic Hepatitis B Virus Infection

4

Yael Bogler, Robert J. Wong, and Robert G. Gish

Abstract

Hepatitis B virus (HBV) infection is a major public health issue worldwide despite the availability of an effective vaccine and the development of effective antiviral treatments. The World Health Organization estimates that 248 million people worldwide are chronically infected with HBV, with the highest prevalence in East Asia, sub-Saharan Africa, and the Pacific Islands. Complications of chronic HBV infection include hepatocellular carcinoma, end-stage liver disease, liver transplant, and death, with the risk of these complications varying by mode of transmission and disease duration. Annually, an estimated 650,000 people die from complications of chronic HBV, with 40% of these deaths occurring in Global Vaccine Alliance countries. Perinatal transmission is the leading cause of HBV transmission worldwide, accounting for more than 60% of all childhood-acquired HBV. Implementation of national vaccination programs has significantly decreased prevalence in multiple countries in both Asia and Africa. The initiation of antiviral therapy in pregnant mothers with detectable virus can also reduce the risk of perinatal HBV transmission when combined with vaccination and, where available, HBIG. Chronic HBV is defined as hepatic necroinflammation due to the persistent presence of infection (hepatitis B surface

Y. Bogler, M.D.
Department of Medicine, Alameda Health System – Highland Hospital, Oakland, CA, USA

R.J. Wong, M.D., M.S.
Division of Gastroenterology and Hepatology, Alameda Health System – Highland Hospital, Oakland, CA, USA

R.G. Gish, M.D. (✉)
Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, USA

Hepatitis B Foundation, Doylestown, PA, USA
e-mail: rgish@robertgish.com

J.-H. Kao, D.-S. Chen (eds.), *Hepatitis B Virus and Liver Disease*,
https://doi.org/10.1007/978-981-10-4843-2_4

antigen-positive) beyond 6 months and can be divided into at least five major phases of infection. Each phase is associated with characteristic patterns of ALT, HBV DNA levels, hepatitis B e antigen (HBeAg) status, liver histology, and response to antiviral therapy. The age the infection is acquired largely dictates the immune response against acute HBV infection and the subsequent natural history of chronic infection.

Keywords
Hepatitis B virus • Natural History • Phases of Infection • Prevalence • Epidemiology • Interpretation of Serologies • Genotypes

1 Introduction

Hepatitis B virus (HBV) infection is a major public health issue worldwide despite the availability of an effective vaccine and the development of effective antiviral treatments. It is estimated that approximately 248 million people are chronically infected with HBV worldwide, with the highest prevalence seen predominantly in Asia, sub-Saharan Africa, and the Pacific Islands (Schweitzer et al. 2015). Approximately 15–40% of people with chronic HBV (CHB) will develop serious complications during their lifetime (Bosch et al. 2005), with an increased risk for cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) (Beasley 1988). CHB is thought to be the cause of 45% of HCC cases and 30% of cirrhosis cases worldwide (Demma and Dusheiko 2016), with the risk of these complications varying by mode of transmission (Goldstein et al. 2005). Annually, an estimated 650,000 people die from complications of CHB, with 40% of these deaths occurring in persons living in Global Vaccine Alliance countries (Demma and Dusheiko 2016). The WHO has recently adopted the 2030 Agenda for Sustainable Development which outlines strategies to combat and eliminate chronic viral hepatitis (United Nations General Assembly 2016). The strategies include gathering information for focused action, formulating high-impact interventions, achieving equitable coverage, reducing costs for those requiring services, and promoting rapid progress and innovation. The ultimate goal of these strategies is to eliminate viral hepatitis as a major public health threat by the year 2030 by reducing the number of infections to under one million (down from six to ten million infections from all types of viral hepatitis viruses) and reducing the number of deaths to less than 500,000 (from 1.4 million) by 2030 (United Nations General Assembly 2016; World Health Organization 2012).

Several factors contribute to the high prevalence of CHB and its complications in Asian and African populations: the delayed implementation of effective programs for screening and vaccination of newborns (Goldstein et al. 2005), the lack of access to effective antiviral therapies, and the high risk of acute HBV exposure resulting in chronic infection with both mother-to-child (MTC) vertical transmission and early

childhood horizontal transmission (Lavanchy 2004). The risk of developing chronic infection after acute HBV exposure, defined as persistence of hepatitis B surface antigen (HBsAg) for at least 6 months, is correlated with age of initial infection, with earlier age of initial infection associated with higher risk of chronic infection (Goldstein et al. 2005). The importance of understanding the epidemiology and natural history of CHB lies in the opportunity to raise awareness of the need for expansion of screening and vaccination efforts and for early detection and management to prevent HBV-related complications and mortality. In this chapter, we will review the epidemiology and natural history of chronic HBV with a focus on high-prevalence regions.

2 Epidemiology

Up-to-date national level epidemiological information is crucial not only for assessing the burden of disease but also for identifying appropriate prevention and control strategies and determining their impact (Schweitzer et al. 2015). CHB endemicity levels have been defined based on the prevalence of HBsAg. Areas of low endemicity are defined as HBsAg <2%, low-intermediate areas as 2–4.99%, high-intermediate areas as 5–7.99%, and high-endemicity areas as ≥8% (Schweitzer et al. 2015) (see Fig. 4.1 (Schweitzer et al. 2015; Ott et al. 2012; MacLachlan et al. 2013; Robinson et al. 2005; Khan and Attaullah 2011; Mulwa 1994; McMahon et al. 1998; Musa et al. 2015; Paat et al. 2009; Chu et al. 2013; Cui and Jia 2013; Yano et al. 2015; Poorolajal and Majdzadeh 2009; Unnewehr and Stich 2015; Centre for Disease Prevention and Control of Latvia 2015; Rabenau et al. 2010; Mohamed et al. 2012; Chen et al. 2007)). An estimated 45% of the world's population resides in regions of high HBV endemicity. The greatest burden of disease lies in Asia where approximately 75% of infected persons reside (Mohamed et al. 2012). In China, certain islands in the Pacific, and regions of sub-Saharan Africa, up to 60–90% of the population has some serologic marker of HBV infection (Chen et al. 2007). One study estimating the worldwide prevalence of CHB based on data published between 1965 and 2013 estimated the global prevalence of HBsAg to be 3.61%, a total of 248 million people chronically infected, with a wide variation in prevalence between countries (Schweitzer et al. 2015). There is also substantial variation in prevalence between certain population groups within some countries.

2.1 CHB in Africa

The overall CHB prevalence in Africa is high (8.83%), with a total of over 75 million people estimated to be living with CHB (Schweitzer et al. 2015). Between 56 and 98% of the adult population of sub-Saharan Africa has some serologic marker of HBV infection (Kiire 1996). Out of the 54 countries in Africa, only 3 have low prevalence—Egypt (1.71%), Morocco (1.09%), and the Seychelles (0.48%)—and 5 low-intermediate prevalence—Algeria (2.89%), Botswana (3.8%), Eritrea (2.49%),

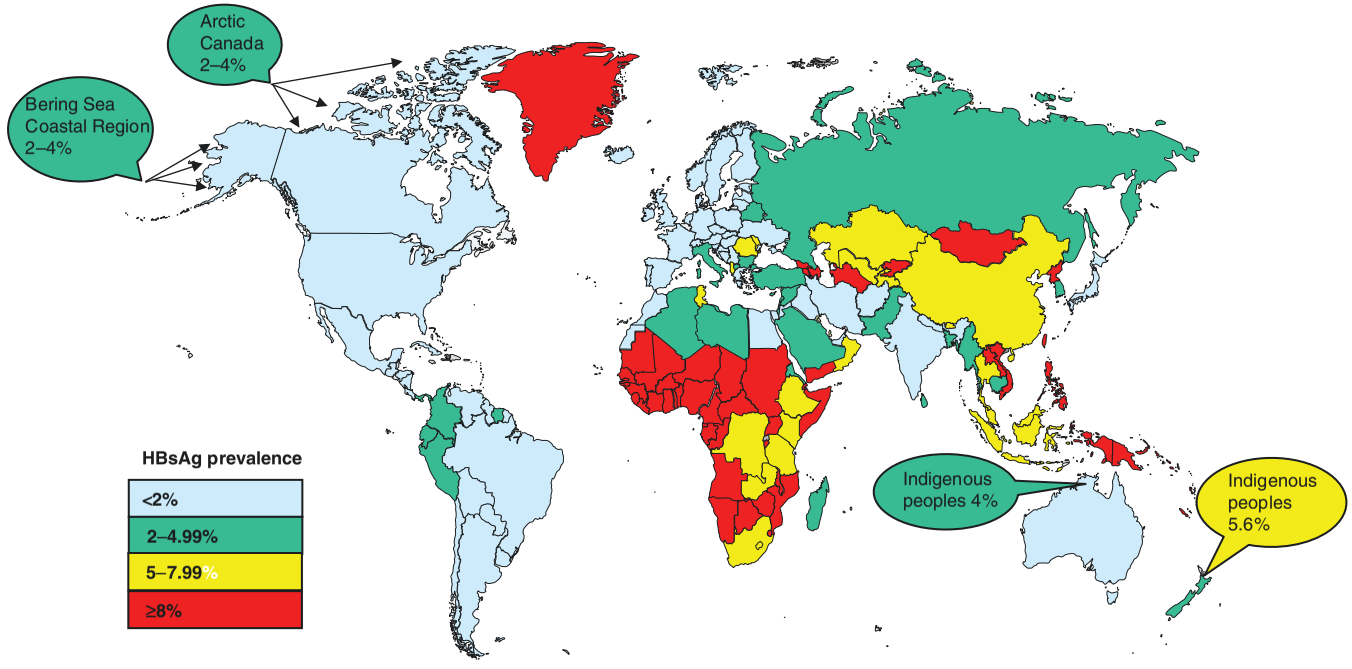

Fig. 4.1 Bering Sea coastal region: HBsAg prevalence is 2–4% in this region where the population is predominantly Alaska natives, compared to <2% in the rest of Alaska. Arctic Canada: HBsAg prevalence is 2–4% here compared to <2% in the rest of Canada. Australia and New Zealand: HBsAg prevalence is higher in indigenous peoples, 4% in Australia (compared to 0.9% in the nonindigenous) and 5.6% in New Zealand, predominantly on the North Island (compared to 4.1% in the nonindigenous). The estimated resident Aboriginal and Torres Strait Islander population of Australia is 669,900 people, 3% of the total Australian population. In New Zealand, 682,200 people identify as Maori, 15.4% of the population. In New Zealand, particularly high HBsAg prevalence has also been shown in other Pacific Islanders, including Tongan (13.1%), Niuean (8.6%), and Cook Islands (6.3%) peoples, as well as in Chinese (8.9%) and SE Asians (8.1%). Prevalence data compiled from multiple sources (Schweitzer et al. 2015; Gust 1996; Lin et al. 2005; Ott et al. 2012; MacLachlan et al. 2013; Robinson et al. 2005; Khan and Attaullah 2011; Mulwa 1994; McMahon et al. 1998; Musa et al. 2015; Paat et al. 2009; Chu et al. 2013; Cui and Jia 2013; Yano et al. 2015; Poorolajal and Majdzadeh 2009; Unnewehr and Stich 2015; Centre for Disease Prevention and Control of Latvia 2015; Rabenau et al. 2010) by Gish RG, Locarnini S, and McMahon, BJ. © 2017

Libya (2.16%), and Madagascar (4.6%) (Schweitzer et al. 2015; Matthews et al. 2015). Countries with high-intermediate prevalence are Cape Verde (7.26%), the Democratic Republic of the Congo (5.99%), Ethiopia (6.03%), Kenya (5.16%), Lesotho (5.5%), Rwanda (6.67%), South Africa (6.7%), Tanzania (7.17%), and Zambia (6.06%) (Schweitzer et al. 2015; Rabenau et al. 2010). All the other countries in Africa have high CHB prevalence (Schweitzer et al. 2015). In some of these, prevalence is extremely high, including Benin (15.57%), Guinea (15.06%), Liberia (17.55%), Mauritania (16.16%), Niger (15.48%), South Sudan (22.38%), and Swaziland (19.00%) (Schweitzer et al. 2015). Although improved screening of blood products and vaccination programs have resulted in an overall prevalence decrease between 1990 and 2005 in Western and Central sub-Saharan Africa, increases were actually seen during those years among children aged 0–14 in Southern sub-Saharan Africa and in children of the youngest ages in Eastern sub-Saharan Africa (Ott et al. 2012).

Throughout Africa, most CHB is the result of early childhood horizontal transmission (Kiire 1996; Hadziyannis 2011; Whittle et al. 1983), with most infections occurring between the ages of 1 and 5 years (Dumpis et al. 2001). In 1996, it was reported that in West Africa infection rates would increase rapidly beginning at 6 months of age, resulting in 40% of children being infected, 15% with CHB, by age 2, and 90% being infected, 20% with CHB, by age 10 (Kiire 1996). In a study of family members in Gambia, phylogenetic tree analysis of sequences from the pre-core and core regions showed a high likelihood of intrafamilial transmission of HBV in at least two-thirds of the families studied (Dumpis et al. 2001). Sibling to sibling transmission is common (Whittle et al. 1983). Several studies have shown that major risk factors for transmission in Africa include shared use of toiletries and sharp objects, tattooing, and tribal scarification, as well as medical procedures and injections (Kiire 1996; Jombo et al. 2005; Otegbayo et al. 2003; McCarthy et al. 1994). It has also been shown that sexual activity is a risk factor for HBV transmission in both urban and rural communities (Jombo et al. 2005; Komas et al. 2013; Sirisena et al. 2002). The need for both improved screening and vaccination and for education of both the general public and health-care practitioners on risk factors for transmission is clear.

Although the national immunization programs of all sub-Saharan countries now include HBV vaccine, most countries schedule the initial dose at 6–8 weeks of age, in part because of the difficulties associated with vaccine delivery at birth in areas where home delivery is common and in part because only the pentavalent vaccine (DTP-HepB-Hib) is provided by the Global Alliance for Vaccines and Immunization (GAVI) and it is not licensed for birth administration (Miyahara et al. 2016). Thus, vaccine delivery program improvements are clearly needed.

Although Bacillus Calmette-Guerin (BCG) and oral polio vaccine are scheduled at birth in 48 and 39 of the 49 countries in sub-Saharan Africa, respectively, only 8 of these countries (Botswana, Cape Verde, Djibouti, the Gambia, Namibia, Nigeria, Mauritania, and Sao Tome and Principe) have introduced HBV vaccine at birth (World Health Organization 2015). In addition, only 77% of infants in the WHO Africa region receive the third dose of HBV vaccine (World Health

Organization-UNICEF 2015). WHO defines universal infant immunization as the most important strategy for reducing CHB prevalence, with the first vaccine dose given within 24 h of birth, followed by two doses, either given along with the first and third doses of DTP vaccine or, if preferred, by three doses coinciding with DTP or other infant vaccinations; the minimum interval between doses is 4 weeks. The first dose being given within 24 h of birth is considered crucial (World Health Organization 2010). This early administration of the vaccine is important to prevent both MTC and early horizontal HBV transmission (Miyahara et al. 2016). Although the former is not as common in Africa as in Asia, timely vaccination could substantially lessen the risk of both MTC transmission and the horizontal transmission at very young ages that is very common throughout Africa.

In a recent study carried out in the Gambia, it was found that although 93.1% of children had received the first dose of HBV vaccine by the age of 6 months, only 1.1% received the dose within 24 h of birth, 5.4% by day 7, and 58.4% by day 28 (Miyahara et al. 2016). Delayed vaccination was found to be associated with birth a long distance from vaccination delivery points, low maternal education, living in urban and peri-urban settings, and Fula ethnicity. Although the association between delayed vaccine delivery and living in an urban area might seem counterintuitive, it is thought to be the result of Gambia's primary health-care system in rural areas that includes village-based traditional birth attendants and health workers who are responsible for informing villagers about the outreach clinics where vaccines are delivered. Unfortunately, birth in a health facility was not associated with timely vaccination, pointing clearly to the need to educate health-care workers in both rural and urban areas on the importance of this and to integrate HBV vaccine delivery into maternal and neonatal services in all areas. In addition, education on the need for a timely birth dose of vaccine should be directed toward the traditional birth attendants who often attend home births and toward the general population and pregnant women so that knowledge about the need for this becomes widespread.

Maintaining constant refrigeration of the hepatitis B vaccine may be problematic in parts of both Africa and Asia and may reduce the likelihood of timely delivery of the birth vaccine, particularly in the case of home births. In general, it is recommended that hepatitis B vaccine be stored at +2 to +8 °C (35.6–46.4 °F), maintaining its potency for up to 4 years, and that freezing must categorically be avoided since it degrades potency. However, WHO reports that some yeast-derived recombinant DNA hepatitis B vaccines are apparently stable at increased temperatures, although data on vaccines from several manufacturers showed large differences in stability; at temperatures of 20–26 °C (68–78.8 °F), vaccine stability ranged from 1 month to 1 year and at 37 °C (98.6 °F), from 1 week to 6 months. The vaccine vial monitor (VVM) provides additional assurance that vaccines can be safely used. According to WHO, at the time of vaccine administration, the VVM indicates if the vaccine has been exposed to a combination of excessive temperature over time and thus is likely to have been damaged, thereby indicating to health-care workers whether a vaccine can be used; if health-care workers have been properly trained to interpret VVM readings correctly and to discard any vial that has reached its discard

point, vaccines with VVMs can be taken out of the cold chain (World Health Organization 2006). Careful use of this information might improve vaccine accessibility in resource-limited settings and thus improve timely vaccine delivery in many parts of Africa and Asia.

2.2 CHB in Asia and the Pacific Islands

Worldwide, more than 75% of people with CHB live in WHO's Western Pacific and Southeast Asia regions (Gust 1996). The home of 95 million people with CHB, the Western Pacific region is comprised of 37 countries and areas, including highly developed countries like Australia where HBsAg prevalence is the lowest in the region (0.37%) and much less developed island nations like Kiribati, the Solomon Islands, Nauru, Vanuatu, Tonga, Papua New Guinea, and Niue where prevalence is very high (22.7%, 18.83%, 17.55%, 17.54%, 14.81%, 14.59%, and 11.86%, respectively) (Schweitzer et al. 2015). In many countries in this region, prevalence varies substantially between population groups. For example, in Australia, HBsAg prevalence is substantially higher in indigenous peoples (4%) compared to the prevalence in the nonindigenous. The same is true in New Zealand where prevalence is 5.6% in indigenous peoples, located predominantly on the North Island, compared to 4.1% in the nonindigenous.

In addition to the small island nations already mentioned, several countries in the Western Pacific region have particularly high prevalence. In the Philippines, national HBsAg seroprevalence is estimated to be 16.7%, corresponding to an estimated 7.3 million adults with CHB in the Philippines (Wong et al. 2013). However, a wide variation has been reported there between ethnic groups, ranging from only 5.2% among Tagalogs in Oriental Mindoro to 18.2% among Mangyans (Evangelista et al. 2006). The factors that underlie the large prevalence discrepancy have not been fully established but are thought to relate to socioeconomic factors, including inadequate access to health services among the Mangyans (Gish et al. 2016). In Vietnam, overall national HBsAg prevalence is estimated to be 12%, corresponding to approximately ten million people with CHB (Gish et al. 2012), but prevalence varies between urban and rural areas, ranging from 10–14% in Ho Chi Minh City and Hanoi (Tran et al. 2003; Nakata et al. 1994) to 18.8% (Hipgrave et al. 2003) to 19% (Nguyen et al. 2007) in some rural areas. As with the Philippines, this prevalence discrepancy may be due, at least in part, to the reduced access to health-care services and screening programs in rural areas (Gish et al. 2012). Other high-endemicity countries in this region include Laos (8.74%) and Mongolia (9.07%) (Schweitzer et al. 2015).

Countries in the Western Pacific region with high-intermediate prevalence include China (5.49%), the Marshall Islands (7.80%), Samoa (5.53%), and Tuvalu (7.14%) (Schweitzer et al. 2015). Most other countries in this region have low-intermediate prevalence, including Brunei (4.06%), Cambodia (4.05%), Fiji (4.8%), Micronesia (3.5%), South Korea (4.36%), and Singapore (4.09%) (Schweitzer et al. 2015). The only countries with low prevalence other than Australia are Malaysia

(0.74%) and Japan (1.02%) (Schweitzer et al. 2015). Compared to the Western Pacific region, prevalence is generally lower in WHO's Southeast Asia region, with low HBsAg prevalence in Nepal (0.82%), India (1.46%), and Indonesia (1.86%); low-intermediate prevalence in Bangladesh (3.10%), Myanmar (3.40%), and Sri Lanka (2.51%); and high-intermediate prevalence only in Bhutan (5.84%) and Thailand (6.42%).

Effective infection control measures have reduced prevalence in some of the countries in these regions, particularly in people born after the widespread initiation of vaccination programs. Transmission of HBV in China has most commonly occurred through MTC vertical transmission and early childhood transmission (Lok 1992; Yao 1996a, b). Prior to implementation of universal HBV vaccination, the prevalence of HBsAg positivity among children in the 1–4 years age group equaled the level of the general population. The two most recent nationwide cross-sectional seroepidemiological surveys in China showed a reduction in HBsAg prevalence from 9.8% (high endemicity) in 1992 to 7.2% (high-intermediate) in 2006, with prevalence among children aged <5 years reduced to only 1.0% (Liang et al. 2009). The reduction was strongly associated with vaccination among all age groups. Since, historically, unsafe blood products were a major cause of HBV transmission in China, credit is also given to the improved screening of blood donors since 1999 (Yan et al. 2014). The universal infant vaccination program launched in Taiwan in 1984 has also been very successful, reducing HBsAg prevalence from 10% in 1984 to 0.9% in 2009 in people born after the initiation of the program (Ni et al. 2012). People vaccinated as infants were also shown to have significantly reduced hepatocellular carcinoma rates (Chang et al. 2009). Screening and vaccination programs have contributed to reduced prevalence in multiple other countries. Over the time periods of 1957–1989 and 1990–2013, decreases in prevalence were also noted in Thailand, India, South Korea, Malaysia, and Singapore (Schweitzer et al. 2015). In New Zealand and Australia, prevalence has increased in recent years due to immigrants from high-prevalence countries (Ott et al. 2012).

To fully achieve a reduction of CHB prevalence in Asia and the Pacific Islands, there are multiple factors that must be addressed. Although there has been an overall increase in timely birth dose coverage in this region, WHO estimates that it is only attained in 76% of the Western Pacific region overall, with multiple countries continuing to have much too low birth dose coverage (World Health Organization 2014). For example, some of the island nations noted above as having high CHB prevalence have much too low birth dose coverage, including Papua New Guinea (32%) and the Solomon Islands (65%) (World Health Organization 2016). WHO notes that in order to improve birth dose coverage in this region, it will be important to increase awareness about the importance of the birth dose, to increase deliveries that are attended by skilled birth attendants who have been educated about the need for the birth dose, and to ensure that vaccine is easily accessible (World Health Organization 2014). This also applies to other Asian countries, in some of which birth dose coverage is exceptionally low. For example, it is estimated that in India timely birth dose coverage is only 44%, in Iraq only 43%, in Afghanistan only 18%, and in Pakistan only 10% (World Health Organization 2016).

Although MTC transmission is the most common source of HBV infection throughout Asia and the Pacific Islands, it will also be important to address HBV transmission in the health-care setting. WHO estimates that in 2000 30% of injections were carried out with reused injection equipment in the Western Pacific Region (Hutin et al. 2003). Worldwide, it is thought that 21 million HBV infections annually (approximately 32% of new infections) are the result of contaminated injections (Hauri et al. 2004). In the Philippines, a 2007 survey of injection safety in 80 government health facilities discovered that in only approximately 80% of procedures were new sterile syringes and needles, lancets, or other devices taken from sterile packets or fitted caps used, including in only 65.7% of intravenous injections (World Health Organization 2007). Another study in the Philippines pointed to the need to address inadequately sterilized hospital equipment since the risk of developing HBV infection was found to be eightfold higher in patients with a history of hemodialysis and fourfold higher in patients with a history of blood donation (Tecson and Luna 2005). A meta-analysis of 32 studies has also shown that the risk of HBV infection is increased in people with a history of tattoo (Jafari et al. 2012). Because of the increasing popularity of tattoos in Asian Pacific countries, particularly among young people, it will be important both to educate the public on this and to provide guidance on eliminating unsafe practices by tattoo artists. Education of prisoners and institution-wide enforcement of guidelines and safer tattooing practices in prisons will also be important since the prevalence of CHB in correctional settings is high (Jafari et al. 2012). In addition, in many Asian Pacific countries, reuse of razors in barbershops to reduce costs is not uncommon so education of the public on this risk and guidance for barbers on unsafe practices are both needed (Gish et al. 2016).

2.3 CHB in the Americas

With the exception only of Haiti (13.55% prevalence), countries in the WHO region of the Americas are of low or low-intermediate endemicity levels (Schweitzer et al. 2015), although prevalence is substantially higher in certain population groups. Countries with low prevalence include the United States (USA), Canada, Mexico, the countries in Central America, and most of the countries in South America and the Caribbean (Schweitzer et al. 2015). Countries with low-intermediate prevalence include Belize (4.71%), the Dominican Republic (4.09%), Jamaica (3.76%), and several of the Amazon basin countries, including Colombia (2.29%), Ecuador (2.00%), Peru (2.10%), and Suriname (3.91%) (Schweitzer et al. 2015).

Although the US Centers for Disease Control and Prevention (CDC) estimates an overall prevalence in the United States of only 0.8–1.2% (805,000–1,405,000 persons) (Weinbaum et al. 2008), the basis for this estimate, the National Health and Nutrition Examination Survey (NHANES), excludes some populations with increased infection risk, including the incarcerated, the homeless, and institutionalized persons, and does not adequately represent multiple racial/ethnic groups with higher infection rates, including Native Americans, Alaska Natives, and Asians and Pacific Islanders

(APIs) (Gish et al. 2015a). HBsAg prevalence is estimated to be especially high (3.45%) in foreign-born US immigrants, a population estimated to equal 1.32 million persons (Gish et al. 2015a; Kowdley et al. 2012). A study that adjusted for this higher prevalence in the foreign-born estimated that up to 2.2 million US persons are living with CHB (Kowdley et al. 2012). In addition, the HBsAg prevalence in the Bering Sea coastal region of Alaska is estimated to be low-intermediate in the predominantly Alaska Native population there, compared to <2% in the rest of Alaska. In another area populated predominantly by indigenous peoples, Arctic Canada along the Arctic Ocean, the prevalence is also estimated to be low-intermediate.

2.4 CHB in Europe

The European WHO region is estimated to have low-intermediate endemicity overall (2.06%), but HBsAg prevalence varies widely between countries (European Centre for Disease Prevention and Control 2014) and is generally lower in Western Europe compared to Eastern Europe, with HBsAg prevalence estimated to be very low in the United Kingdom (0.01%), Norway (0.01%), Ireland (0.03%), Iceland (0.14%), and Switzerland (0.18%) and low or low-intermediate in most other European countries (Schweitzer et al. 2015). Prevalence is only estimated as high-intermediate in Albania (7.99%), Kazakhstan (6.05%), Moldova (7.38%), Romania (5.61%), Tajikistan (7.2%), and Uzbekistan (6.99%) and high in Kyrgyzstan (10.32%) (Schweitzer et al. 2015). Although considered part of the European region because it is a Danish territory and thus generally shown on prevalence maps as having low prevalence (Ott et al. 2012), Greenland actually has very high HBsAg prevalence in its population (16.6%), 89% of which is Inuit (McMahon et al. 1998).

Across all age groups, most CHB in Europe is the result of vertical MTC transmission (67%), but it is slightly more common among those aged under 30 years (70.1%) than among those aged 30 or over (65.2%) (European Centre for Disease Prevention and Control 2014). Inward migration of people with CHB from high-prevalence countries appears to account for a substantial proportion of European CHB cases, with data suggesting that most MTC infections in Europe were acquired in a country different from the reporting country (European Centre for Disease Prevention and Control 2014). The percentage of CHB cases reported as being due to injection drug use was estimated as 3.9% in 2012, while the percentage of cases classified as due to nosocomial transmission or as the result of blood or blood products is low, approximately 2% for each (European Centre for Disease Prevention and Control 2014).

3 HBV Genotypes

HBV has a number of genetic variants described as serotypes (adw, ayw, ayr, and adr) and genotypes (A, B, C, D, E, F, G, H, I, and J) (Lin and Kao 2015). Genotyping is specified by sequencing the HBV genome, using a line probe assay (capture hybridization), or by using serologically based antibody testing (Gish and Locarnini

Table 4.1 Geographic distribution of hepatitis B virus genotypes and subtypes

Genotypes	Serotypes	Subtypes	Geographic location
A	adw	A1 A2 A3	Sub-Saharan Africa and India Northern Europe and India Western Africa
B	adw, ayw	B1 B2–5 B6	Japan East Asia, Taiwan, China, Indonesia, Vietnam, and the Philippines Alaska, Northern Canada, and Greenland
C	adw, ayr, adr	C1–3 C4 C5 C6–11	Taiwan, China, Korea, and Southeast Asia Australia The Philippines and Vietnam Indonesia
D	ayw	D1–6	Africa, Europe, Mediterranean countries, India, and Indonesia
E	ayw		Restricted to West Africa
F	adw	F1–4	Central and South America
G	adw		France, Germany, and the United States
H	adw		Central America
I	adw		Vietnam and Laos
J			Japan

Reprint with permission from Lin CL and Kao JH. Cold Spring Harb Perspect Med 2015;5:a021436

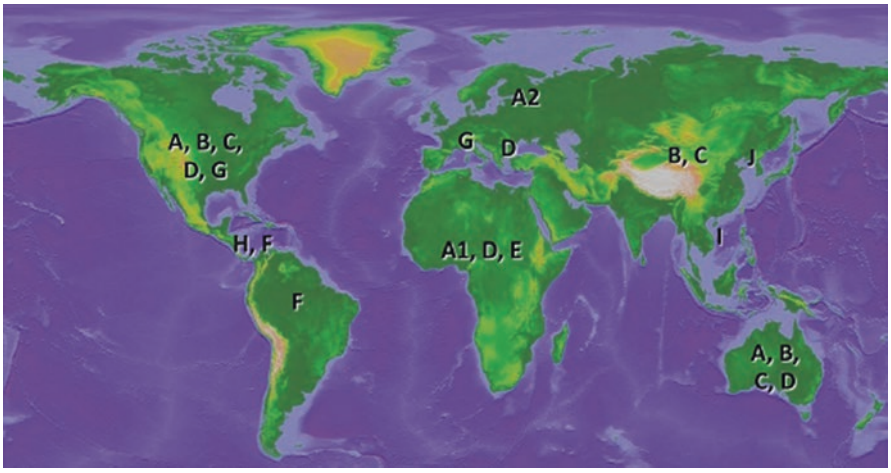

Fig. 4.2 Global distribution of HBV genotypes. Updated and adapted from Liaw YF, et al. Liver Int. 2005;25:472–489. Note: A1 is the African variant, and A2 is the European variant of HBV genotype A

2009). The distribution of HBV genotypes varies by world regions (Lin and Kao 2011) (Table 4.1 and Fig. 4.2). While genotyping of HBV is not routine practice in all settings, knowledge of HBV genotypes can provide important epidemiological and clinical information. Genotype assessment and nucleic acid sequence analysis may allow epidemiologists to track the transmission and movement of HBV strains through the world or regions of the world; to establish other epidemiological

behavior of HBV infection, including the investigation of common source outbreaks; and to establish clinical behaviors specific to each subgroup (Gish and Locarnini 2009; Lin and Kao 2011). Furthermore, HBV genotyping provides important data that help guide clinical management. For example, previous studies demonstrated that HBV patients with genotype A have higher response rates to treatment with interferon therapy (Lau et al. 2005). In addition, HBV genotype C is associated with higher risk of developing HCC (Chan et al. 2004; Kao et al. 2000, 2002), and HBV genotype D is associated with development of adefovir resistance (Gish and Locarnini 2009). While treatment outcomes with current first-line oral antiviral therapies and their success at HBV suppression and/or clearance are not well predicted by HBV genotype, knowledge of HBV genotype may be important with the advent of new HBV therapies in development. As previously discussed, mixed infections with two different genotypes can result in new recombinants (Zhou et al. 2012), but the survival of the recombinant strains varies. For instance, HBV/G is very slow to replicate as a monoinfection; however, after coinfection of mice with HBV/A, the replication of HBV/G was significantly increased (Sugiyama et al. 2007). Another study showed that coinfection with HBV/A was required for effective replication of HBV G genotype in a specific population in Japan (Tsuzuki et al. 2016). While many recombinants can potentially arise in individuals with coinfection with several genotypes, there is a strong selection power for elimination of hybrid genomes. A study of families in western China initially showed that many novel recombinants arose; however, after 18 months, only one recombinant variant had persisted (Zhou et al. 2012).

Genotypes in China have been studied extensively. While the predominant HBV genotypes in China are B2–5 and C1–3, within China there are region-specific variations. Genotype B is more prevalent in southern China, whereas genotype C is more prevalent in northern China (Lin and Kao 2011). The subgenotypes C1 and C2 are predominant in western China, and a high prevalence of CD1 and CD2 was found in a Tibetan population, indicating that the distribution of these two subgenotypes may be related to ethnic origin (Zhou et al. 2011). This is further supported by the study of recombinant hepatitis B viruses. Recombination contributes to the diversity in HBV genomes (Shi et al. 2013). A study of 15 families in which individuals were coinfected with two different HBV genotypes showed naturally occurring HBV recombinants between C2, D1, and CD1 genotypes in 3 of the 15 families (Zhou et al. 2012). Some initial products of recombination may go undetected due to the selection to remove new, deleterious mutations. Thus the recombinant nature of HBV may preclude classification into genotypes, and a new classification for HBV sequences may be required (Zhou et al. 2011).

4 Natural History

The natural history of HBV and the risk of developing chronic infection after acute exposure is affected by age and mode of transmission. The modes of transmission vary substantially in different regions of the world and in the presence of high-risk

behaviors (Kuo and Gish 2012; McMahon 2005). Chronic HBV is defined as hepatic necroinflammation due to the persistent presence of HBV infection beyond 6 months. Patients are positive both for HBsAg and for HBV DNA with serum levels of HBV greater than 2000 to 20,000 IU/ml or have positive staining for the presence of hepatitis B core antigen (HBcAg) in the liver. Liver enzyme levels are elevated for over 6 months, either persistently or intermittently. The WHO case definition of chronic HBV requires two separate reactive serum test results for HBsAg over a 6-month period.

The risk of developing chronic HBV infection after acute exposure ranges from ≤5% in adults to approximately 30% in children infected between ages 1 and 4 years to >90% in infants born to infected mothers who are positive for hepatitis B e antigen (HBeAg), a secreted protein that is detectable in the bloodstream when HBV is actively replicating (Hyams 1995; McMahon et al. 1985). Persistent and stable HBV DNA levels detected during the first 1–4 weeks following acute hepatitis B infection are strong predictors of not clearing HBV infection and progression to chronic HBV (Pan and Zhang 2005).

Perinatal transmission is a leading cause of HBV transmission, accounting for more than 60% of all childhood-acquired HBV worldwide (Gish and Locarnini 2009). However, the primary mode of transmission varies across regions. MTC vertical transmission is the most common source of infection in people with CHB in Asia and the Pacific Islands and in Europe, while early childhood horizontal transmission is most common in sub-Saharan Africa, the Mediterranean region, and Alaska (Kiire 1996; Hadziyannis 2011; Whittle et al. 1983; McMahon et al. 1985; Bortolotti et al. 2006; Dusheiko et al. 1989). In regions of low endemicity, infections most commonly occur among adolescents and adults through sexual and injection drug use exposures (Wasley et al. 2010).

For children born to CHB mothers, prevention of perinatal transmission with injection of hepatitis B immune globulin (HBIG) combined with vaccine is effective (Wong et al. 1984), but HBIG is neither available nor affordable in much of the developing world. The initiation of antiviral therapy in pregnant mothers, a much less costly approach, can also greatly reduce the risk of perinatal HBV transmission (Han et al. 2011; Shi et al. 2010; van Zonneveld et al. 2003; Xu et al. 2009; Pan et al. 2016). A randomized controlled study in which highly viremic pregnant women received antiviral therapy during the third trimester showed an 18% HBsAg seropositivity in infants born to lamivudine-treated mothers, compared with 39% seropositivity in infants born to untreated mothers (Xu et al. 2009). A study evaluating the efficacy of telbivudine for decreasing the rate of perinatal HBV transmission showed a 0% incidence of perinatal transmission at 7 months in infants born to mothers with high HBV viral load treated during weeks 20–32 of pregnancy, versus an 8% transmission rate in infants born to untreated mothers (Han et al. 2011). A recent study of HBeAg-positive pregnant women with an HBV DNA level of more than 200,000 IU/mL compared MTC transmission in women given tenofovir (300 mg daily) from 30 to 32 weeks of gestation until postpartum week 4 to women who did not receive antiviral therapy. The per protocol analysis showed transmission to none of the infants of mothers given tenofovir vs. 7% of infants of mothers who did not

receive antiviral therapy (Pan et al. 2016). Recently updated AASLD, EASL, and APASL guidelines recommend starting antiviral therapy in the third trimester in pregnant mothers with chronic HBV and viral load ≥200,000 IU/mL (Terrault et al. 2016; Liaw et al. 2008; European Association for the Study of the Liver 2012).

Adult-acquired HBsAg positivity is more common in low- and intermediate-prevalence regions and results mainly from unprotected sexual contact or injection drug use (Pan and Zhang 2005). While the majority of adult-acquired HBV infections are asymptomatic, some patients will present with acute HBV with jaundice and elevated liver tests following a high-risk sexual exposure (Gish and Locarnini 2009). In populations that acquired HBV as adults, sexual contact between heterosexuals (42%) and men who have sex with men (15%) are common modes of acute transmission (Gish and Locarnini 2009). Injection drug use accounts for about 21% of all HBV infections acquired in adulthood (Gish and Locarnini 2009). Cognizant of these modes of transmission, public health interventions targeting high-risk behaviors can impact transmission rates and reduce morbidity and mortality. For example, elimination of the practice of reusing needles in developing countries may lead to a marked reduction in childhood-, adolescent-, and adult-acquired HBV infections (Yao 1996a; Ko and Chung 1991). Nosocomial/occupational exposure and transmission is also an important issue. Health-care workers exposed to blood of patients with chronic HBV through needlestick injuries or blood splash exposures are at risk of infection (Yao 1996a; Coppola et al. 2016). Worldwide, approximately three million health-care workers annually are exposed to blood or other potentially infectious biological materials via either a mucosal-cutaneous or percutaneous route, resulting in two million exposures to HBV (Coppola et al. 2016). The risk of HBV transmission with such exposures depends on the patient's HBeAg status and the HBV DNA viral load. In exposures to blood from patients who are HBeAg-positive or who have an HBV DNA load $>10^6$ IU/mL, the risk of HBV transmission is estimated at 19–30%, compared to 5% with exposures to blood from patients who are HBeAg-negative or who have $<10^6$ IU/mL viral load (Coppola et al. 2016). To prevent infection from such exposures, hepatitis B vaccination is strongly advised for all health-care personnel (Schillie et al. 2013).

Historically, renal dialysis patients have been considered a high-risk group for acquiring or transmitting HBV since many have had extensive blood exposure in the dialysis setting. A recent study of a large multiethnic hemodialysis cohort in London found that 2% of dialysis patients had chronic HBV infection (HBsAg-positive) and 20% were anti-HBc-positive but HBsAg-negative suggesting past exposure that was cleared from the blood, but not from the liver (Sowole et al. 2015). Of the patients with past infection, 2.2% had detectable HBV DNA, albeit very low levels, thus making transmission via blood exposure unlikely. The risks of HBV exposure from inadequately sterilized medical equipment are higher in the developing world. For example, in a study in the Philippines, it was shown that the odds of developing HBV infection was eightfold higher in patients who had a history of hemodialysis (Tecson and Luna 2005). Implementation of vaccination policies and infection control measures are necessary to decrease the risk of nosocomial transmission in dialysis patients.

Household transmission has also been clearly identified as a risk for acquiring HBV (Yao 1996a). The route of exposure is not clear, but HBV is a DNA virus that can exist outside the body on fomites for prolonged periods. Current recommendations state that the sharing of household utensils that may carry blood such as toothbrushes and razor blades must be avoided (Korean Association for the Study of the Liver 2012). The transmission of HBV with common kitchen items and food sharing has not been described. All household members living with an individual positive for HBsAg or known to be a person with chronic HBV should be tested for evidence of HBV infection and vaccinated if not exposed or immune (Yao 1996a; Weinbaum et al. 2009).

Blood transfusion is a very unlikely source of HBV in developed countries where effective screening of blood takes place. Screening of all blood units for HBV by HBsAg and anti-HBc, and in many countries HBV DNA by PCR, as well as predonation screening for risk behavior should become a standard practice throughout the world. The risk of acquiring HBV through a blood transfusion in the United States is less than 1:400,000 units. The best current test used to screen blood for HBV infection is the HBV DNA by nucleic acid testing (NAT), also termed "molecular testing," as well as improved HBsAg and anti-HBc assays (Allain and Candotti 2009). The reason any risk is present from blood products relates to the fact that some patients donate blood before the onset of an immune response to HBV infection or the presence of clinical evidence of hepatitis. NAT is emerging as a method to make the blood supply even safer (Allain and Candotti 2009).

Finally, in some cases of adult-acquired HBV infection, the source of exposure is not clear. For example, approximately 20–35% of individuals with adult-acquired HBV infection in the United States have no known risk factor or easily identifiable risk factor (Gish and Locarnini 2009). Possible transmission through sexual contact, medical or dental treatment, injection drug use (IDU), sharing household utensils, or blood exposure in an occupational setting must all be considered.

5 Interpretation of Serologies

As a general principle of laboratory-based investigation for the virological cause of chronic liver disease, testing should include all the major etiological agents (HBV, HBV plus HDV, and HCV). The principal screening assay for acute and chronic hepatitis B, as well as for the screening of blood and organ donors, is detection of HBsAg in serum combined with anti-HBc (Shepard et al. 2006), although molecular testing with more advanced nucleic acid tests such as PCR and transcription-mediated amplification (TMA) is now being instituted in the United States and considered worldwide.

The serological profiles that are typically found in acute, chronic, or past HBV infection are shown in Table 4.2. The serological findings that are associated with the number of weeks post-exposure are shown in Fig. 4.3. In patients with CHB, hepatitis B core-specific IgG antibodies (IgG anti-HBc) are almost always present in serum. With MTC transmission, these antibodies may play a role in fetal and

Table 4.2 Interpretation of HBV serological tests

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Never infected and no evidence of immunization, needs vaccination
+	+	+	–	Acute infection
+	+	–	–	Chronic infection
–	+	–	–	Exposure with occult HBV, false positive (rare) or chronic infection
–	+	–	+	Exposure and clearance of HBV infection from the blood, with occult HBV

Modified from Weinbaum CM, et al. MMWR Recomm Rep. 2008;57:1–20

neonatal immunological responses to HBV (Gish and Locarnini 2009). Because these antibodies cross the placenta in utero, the neonate has high titers of maternal IgG anti-HBc at birth, but the antibodies are not neutralizing and do not appear to influence viral replication (Gish and Locarnini 2009).

Recent research has shown that with HBV exposure in utero, there are enhanced innate immune cell maturation, increased Th1 development, and lowered production of pro-inflammatory cytokines (IL-10, IL-6, IL-8, and TNF-a) along with higher production of IL-12p40, a state recently termed *trained immunity* by Hong and colleagues (Hong et al. 2015). Rather than the previous belief that HBV exploits the neonate's immature immune system and induces a state of immune tolerance in order to establish chronic infection, the findings of Hong et al. support the idea that defective priming of HBV-specific T cells may promote chronicity. Further countering the previously accepted idea of immune tolerance is the recent research by Vanwolleghem et al. showing that both B-cell responses and interferon responses are highly active during this phase of infection and that the immune system's antiviral sensing and effector machinery is working to control high levels of viral replication (Vanwolleghem et al. 2015).

The detection of IgM anti-HBc is generally diagnostic of acute HBV infection (Chau et al. 1983) (Fig. 4.3), but it is also seen in flares of HBV including reactivation (Yuan et al. 2015). Most patients with underlying inflammatory activity in the liver will show evidence of viral infection with one or more of the available tests. Relative levels of HBV DNA often correlate inversely with the degree of necroinflammatory activity in the liver, reflecting attempts by the host's immune response to control and eliminate the virus. The serum level of HBV DNA has been shown to be associated with the risk of developing HCC (Chen and Yang 2011; Chen et al. 2006; Tseng and Kao 2015). The REVEAL study, a prospective cohort study evaluating the risk factors for progression of chronic HBV, has helped researchers develop nomograms for the long-term risk of developing cirrhosis and HCC based on HBV DNA levels (Chen and Yang 2011).

HBeAg is detectable in the serum with active replication of wild-type virus or of mixed wild-type virus and HBV with core/precore mutations; however, mutant strains of HBV that replicate without producing HBeAg can be selected out (Frenette and Gish 2009). Thus, CHB patients can be divided into two subgroups,

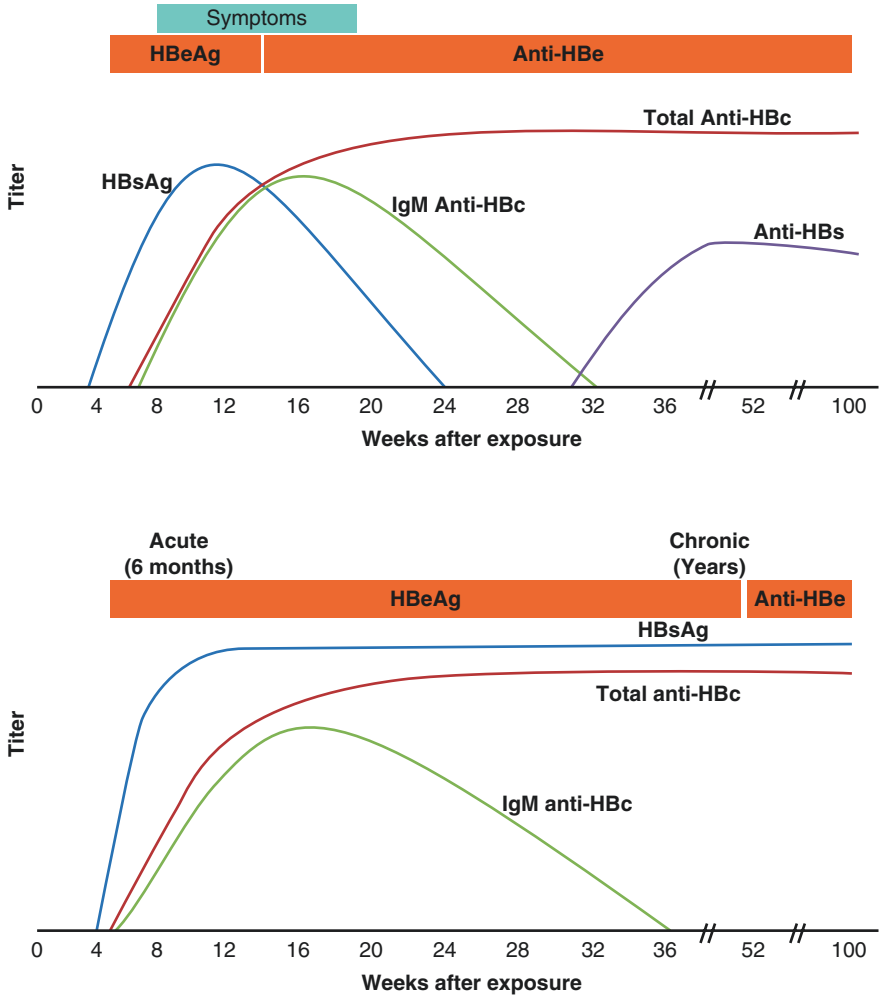

Fig. 4.3 Acute HBV infection with (**a**) recovery and (**b**) progression to chronic HBV. (**a**) Acute HBV infection with recovery: typical serologic course. (**b**) Acute HBV infection with progression to chronic HBV: typical serologic course. Adapted from Weinbaum CM, et al. MMWR Recomm Rep. 2008;57:1–20

HBeAg-positive (wild-type or mixed infection) and HBeAg-negative (basal core promoter and precore mutants) (Gish et al. 2015b). Interestingly, many adult patients who are HBeAg-positive have a mixed infection with both wild-type virus and virus with core promoter (CP) and/or, less commonly, precore (PC) mutations (Baqai et al. 2015; Takahashi et al. 1995). This may progress to a dominant (although not pure) HBeAg-negative disease. If infection is acquired from a person with mixed infection or HBeAg-negative disease, the person who becomes infected develops HBeAg-positive disease. Due to the high rate of mixed infection as well as HBeAg-negative disease, HBeAg seroconversion is no longer used as a marker for treatment

cessation (Frenette and Gish 2009). A team of researchers for the REVEAL study group found that seroclearance of HBeAg was not significantly associated with HCC risk (Liu et al. 2014). This may be associated with the high level of HBV DNA at HBeAg seroclearance. HBsAg clearance is the most favorable outcome in CHB (Yang and Kao 2016) and is the goal of treatment today (Frenette and Gish 2009). To further emphasize correct test interpretation, patients who are anti-HBs and anti-HBc-positive are not "naturally immune." Rather, they carry a low level of HBV, similar to what is seen with herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, and can have reactivation with immune suppression.

6 HBV Structure and Replication Cycle

HBV is an enveloped DNA virus with a partially double-stranded relaxed circular genome made up of 3200 base pairs. Four long open reading frames encode five proteins: HBsAg, HBcAg, HBeAg, DNA polymerase, and HBx protein (Demma and Dusheiko 2016). After internalization, the virus genome is converted into a covalently closed circular DNA (cccDNA) in the nucleus of the host hepatocytes and serves as the template for transcription of the four viral RNAs. cccDNA is a minichromosome in the nucleus of the infected hepatocytes and is multiplied by an amplification process during infection (Yan et al. 2012). Without cccDNA clearance from all cells, there is no HBV cure.

The multiple mRNAs produced from the cccDNA then produce a series of key viral proteins including the polymerase, hepatitis B x antigen (HBxAg), hepatitis B core-related antigen (HBcrAg), HBeAg, and HBsAg required for viral replication and full and partial virion formation. The capsid of HBV self-assembles into core particles that internalize the template mRNA required for the reverse transcription of HBV DNA. These capsid/DNA particles are then coated with HBsAg and liver cell membrane to form mature virus particles for release (Yan et al. 2012). This is measured in the blood with HBcrAg testing. Segments of HBV DNA are also incorporated into host DNA. This DNA incorporation is not a requirement for HBV replication; however, HBsAg is also produced from this pathway (Wooddell et al. 2015; Wooddell 2015). HBV DNA incorporation into the host genome in key areas of the genome is associated with later development of HCC (Kew 1981).

7 Phases of Infection

Chronic HBV can be divided into at least five major phases (Gish et al. 2015b) (Fig. 4.4). There are distinctive patterns of ALT, HBV DNA levels, HBeAg status, liver histology, and response to antiviral therapy that are associated with each phase (Gish et al. 2015b). The age of infection largely dictates the immune response against acute HBV infection and the subsequent natural history of chronic infection. These stages of infection are not static and may not be sequential, with movement

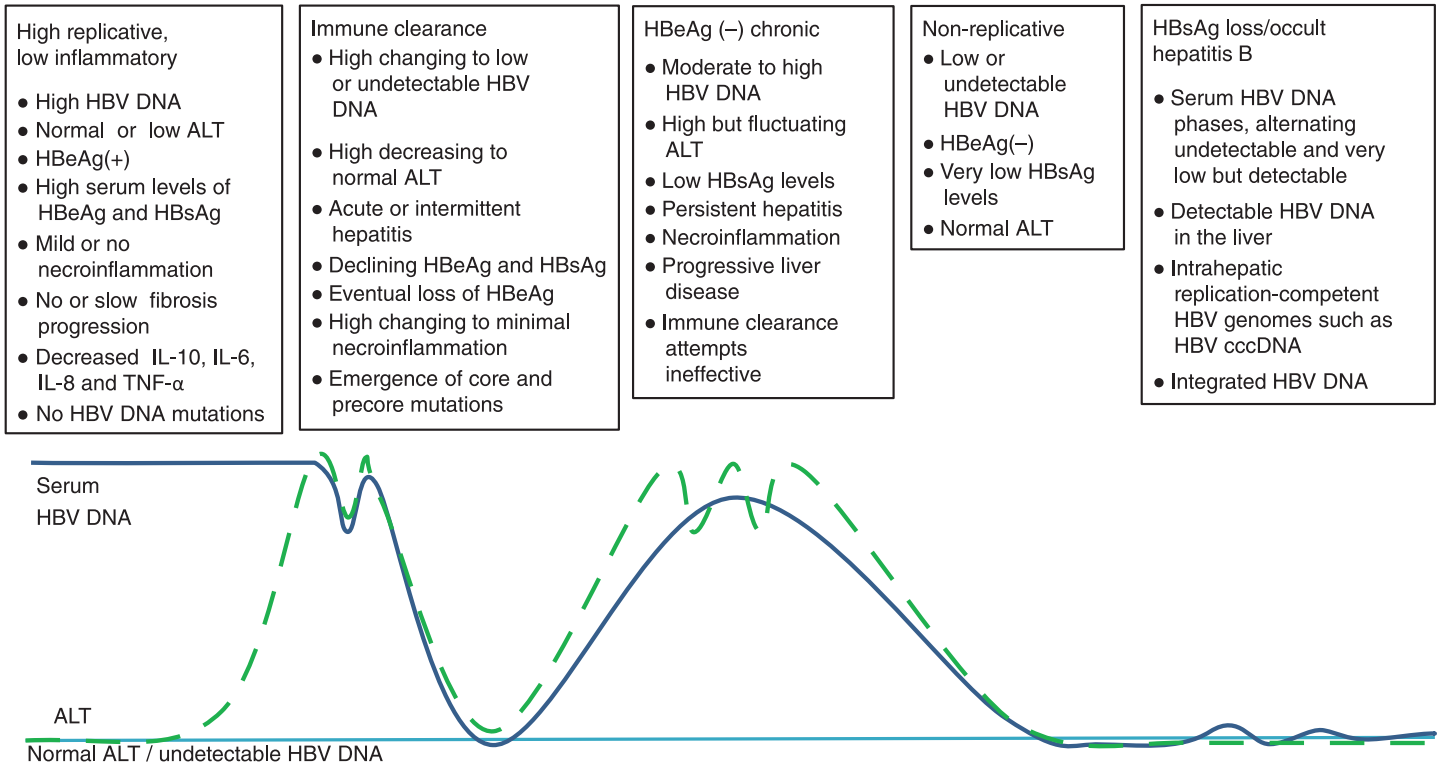

Fig. 4.4 Phases of hepatitis B infection

from one phase to another potentially occurring in any direction (Gish et al. 2015b). As recently described by Gish and colleagues, these phases can be defined as follows (Gish et al. 2015b):

- High replicative, low inflammatory phase (previously known as "immune tolerant"):
  Characterized by high HBV DNA (>20,000 IU/mL), HBeAg-positive, normal or low levels of ALT, mild or no liver necroinflammation with lower production of IL-10 and pro-inflammatory cytokines (IL-6, IL-8, and TNF-α), and no or slow progression of fibrosis. In this phase the virus induces a state of trained immunity, enhancing the maturation of the innate immune cells (Hong et al. 2015).
- Immune clearance:
  Characterized initially by wide fluctuations in serum HBV DNA and ALT, the latter resulting from acute changes in inflammation or intermittent episodes of hepatitis, with a decrease over time from high to low or undetectable DNA and from high to normal ALT (<30 IU/mL for men and <19 IU/mL for women), with eventual loss of HBeAg in wild-type infection. Liver histology ranges from high to minimal necroinflammation. In some patients, core and precore mutations and HBeAg-negative disease emerge.
- HBeAg-negative chronic hepatitis:
  Characterized by persistent hepatitis with necroinflammation where attempts at immune clearance are ineffective, serum ALT levels can reach five times their normal value, HBV DNA levels are moderate to high, and liver disease is progressive.
- Non-replicative (previously known as "inactive carrier"):
  Characterized by low or undetectable serum HBV DNA, HBeAg-negative, normal ALT, and the presence of HBsAg in serum. The clinical course of patients in this phase will be affected by the level of liver damage prior to HBeAg seroconversion to anti-HBe and the durability of the phase (Liaw et al. 2008). These patients are at risk of relapse to active liver disease and replication of virus as well as HBV DNA integration into the hepatocyte nuclear DNA (Fattovich 2003). They should be monitored at least every 6 months with serum tests for HBV replication, serology, liver enzymes, and synthetic tests (Demma and Dusheiko 2016).
- Hepatitis B surface antigen (HBsAg) loss/occult hepatitis B phase:
  In occult hepatitis B infection (OBI), HBsAg is lost, but there is intrahepatic persistence of the entire, episomal, replication-competent HBV genomes such as HBV cccDNA chromatinized episomes. There is very low to undetectable HBV DNA in serum but detectable HBV DNA in the liver; in some patients all HBV serum markers are negative (Pollicino and Raimondo 2014). In a population of 1271 Alaska Natives with chronic HBV, the rate of HBsAg clearance was found to be 0.7% per year (McMahon et al. 2001; Simonetti et al. 2010). The incidence of HCC in patients who had cleared HBsAg was significantly lower than the rate in the HBsAg-positive individuals, but the risk of HCC was still present and periodic follow-up was warranted.

There are two additional proposed phases of HBV clearance which are theoretical and would be the ultimate goal of viral control (Gish et al. 2015b):

- Clearance of cccDNA
- Clearance of cells that have integrated HBV

In patients infected with HBV perinatally, the high replicative, low inflammatory phase is generally prolonged, with patients remaining in this phase for many years without disease progression (Lok 1992; Trepo et al. 2014). However, it is during this prolonged phase in perinatally infected persons that DNA integration into the hepatocyte genome most likely occurs, with its subsequent effect on oncogenicity. In HBeAg-positive children, seroconversion usually occurs around puberty (Lok and McMahon 2009).

In regions where HBV infection in adulthood generally occurs through sexual exposure or injection drug use, chronic infection is characterized by immediate entry into the immune clearance phase. In CHB patients with elevated ALT, the rate of spontaneous HBeAg seroconversion ranges from 8 to 12% per year (McMahon et al. 2001; Fattovich et al. 1986; Hoofnagle et al. 1981; Lok et al. 1987). Of those who achieve HBeAg seroconversion, up to 80% either transition to the non-replicative phase (with normal ALT and low or undetectable HBV DNA) or transition directly to HBeAg-negative chronic HBV (Bortolotti et al. 2006; Fattovich et al. 1986; Hoofnagle et al. 1981; Lok et al. 1987; Hadziyannis and Vassilopoulos 2001; Hsu et al. 2002). Among patients in the non-replicative phase, spontaneous reactivation has been shown to occur in 17% (defined as reversion from HBeAg-negative to HBeAg-positive) (McMahon et al. 2001) to 32% (defined as elevation in ALT and reappearance of markers of HBV replication as well as, in most cases, reversion to HBeAg-positive) (Davis et al. 1984) (Fig. 4.4).

Conclusion

Chronic hepatitis B virus continues to pose a very serious health-care problem all around the world and particularly in high-endemicity countries that have not yet fully implemented a national vaccination program beginning at birth. Widespread vaccination will most likely cause a shift in the most common modes of transmission, which will in turn affect the patterns of disease and infection phases. CHB is dynamic and the phases of infection may fluctuate. The next steps will be aimed at truly universal early vaccination for disease prevention, as well as targeting specific phases in order to prevent disease progression.

References

Allain JP, Candotti D. Diagnostic algorithm for HBV safe transfusion. Blood Transfus. 2009;7(3):174–82.

Baqai SF, Proudfoot J, Yi DH, Mangahas M, Gish RG. High rate of core promoter and precore mutations in patients with chronic hepatitis B. Hepatol Int. 2015;9(2):209–17.

Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer. 1988;61(10):1942–56.

Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology. 2006;43(3):556–62.
Bosch FX, Ribes J, Cleries R, Diaz M. Epidemiology of hepatocellular carcinoma. Clin Liver Dis. 2005;9(2):191–211. v
Centre for Disease Prevention and Control of Latvia. Epidemiology of hepatitis B and C in Latvia. 2015. http://www.vhpb.org/files/html/Meetings_and_publications/Presentations/RIGA36.pdf. Accessed 15 Sept 2016.
Chan HL, Hui AY, Wong ML, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut. 2004;53(10):1494–8.
Chang MH, You SL, Chen CJ, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst. 2009;101(19):1348–55.
Chau KH, Hargie MP, Decker RH, Mushahwar IK, Overby LR. Serodiagnosis of recent hepatitis B infection by IgM class anti-HBc. Hepatology. 1983;3(2):142–9.
Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. J Gastroenterol Hepatol. 2011;26(4):628–38.
Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65–73.
Chen CH, Yang PM, Huang GT, Lee HS, Sung JL, Sheu JC. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J Formos Med Assoc. 2007;106(2):148–55.
Chu JJ, Wormann T, Popp J, et al. Changing epidemiology of hepatitis B and migration—a comparison of six Northern and North-Western European countries. Eur J Pub Health. 2013;23(4):642–7.
Coppola N, De Pascalis S, Onorato L, Calo F, Sagnelli C, Sagnelli E. Hepatitis B virus and hepatitis C virus infection in healthcare workers. World J Hepatol. 2016;8(5):273–81.
Cui Y, Jia J. Update on epidemiology of hepatitis B and C in China. J Gastroenterol Hepatol. 2013;28(Suppl 1):7–10.
Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. Gastroenterology. 1984;86(2):230–5.
Demma S, Dusheiko G. The current treatment situation and definitions of a cure for chronic HBV infection. Future Virol. 2016;11(1):79–92.
Dumpis U, Holmes EC, Mendy M, et al. Transmission of hepatitis B virus infection in Gambian families revealed by phylogenetic analysis. J Hepatol. 2001;35(1):99–104.
Dusheiko GM, Brink BA, Conradie JD, Marimuthu T, Sher R. Regional prevalence of hepatitis B, delta, and human immunodeficiency virus infection in southern Africa: a large population survey. Am J Epidemiol. 1989;129(1):138–45.
European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–85.
European Centre for Disease Prevention and Control. Hepatitis B and C surveillance in Europe. Stockholm, Sweden: European Centre for Disease Prevention and Control; 2014. Available at: http://ecdc.europa.eu/en/publications/publications/hepatitis-b-c-surveillance-europe-2012-july-2014.pdf. Accessed 26 Aug 2016
Evangelista KV, Dalmacio LMM, Wells J, Kron MA, Ramirez BL. Prevalence of hepatitis B virus (HBV) infection among Tagalogs and Mangyans in Oriental Mindoro. Philipp J Intern Med. 2006;44:161–6.
Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003;23(1):47–58.
Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology. 1986;6(2):167–72.
Frenette CT, Gish RG. To “be” or not to “be”: that is the question. Am J Gastroenterol. 2009;104(8):1948–52.
Gish RG, Locarnini S. Chronic hepatitis B viral infection. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powell DW, editors. Textbook of gastroenterology. Oxford, England: Blackwell Publishing; 2009. p. 2112–38.
Gish RG, Bui TD, Nguyen CT, et al. Liver disease in Viet Nam: screening, surveillance, management and education: a 5-year plan and call to action. J Gastroenterol Hepatol. 2012;27(2):238–47.

Gish RG, Cohen CA, Block JM, et al. Data supporting updating estimates of the prevalence of chronic hepatitis B and C in the United States. Hepatology. 2015a;62(5):1339–41.
Gish RG, Given BD, Lai CL, et al. Chronic hepatitis B: virology, natural history, current management and a glimpse at future opportunities. Antivir Res. 2015b;121:47–58.
Gish RG, Sollano JD Jr, Lapasaran A, Ong JP. Chronic hepatitis B virus in the Philippines. J Gastroenterol Hepatol. 2016;31(5):945–52.
Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol. 2005;34(6):1329–39.
Gust ID. Epidemiology of hepatitis B infection in the Western Pacific and South East Asia. Gut. 1996;38(Suppl 2):S18–23.
Hadziyannis SJ. Natural history of chronic hepatitis B in Euro-Mediterranean and African countries. J Hepatol. 2011;55(1):183–91.
Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2001;34(4 Pt 1):617–24.
Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55(6):1215–21.
Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS. 2004;15(1):7–16.
Hipgrave DB, Nguyen TV, Vu MH, et al. Hepatitis B infection in rural Vietnam and the implications for a national program of infant immunization. Am J Trop Med Hyg. 2003;69(3):288–94.
Hong M, Sandalova E, Low D, et al. Trained immunity in newborn infants of HBV-infected mothers. Nat Commun. 2015;6:6588.
Hoofnagle JH, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. Ann Intern Med. 1981;94(6):744–8.
Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002;35(6):1522–7.
Hutin YJ, Hauri AM, Armstrong GL. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. BMJ. 2003;327(7423):1075.
Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. Clin Infect Dis. 1995;20(4):992–1000.
Jafari S, Buxton JA, Afshar K, Copes R, Baharlou S. Tattooing and risk of hepatitis B: a systematic review and meta-analysis. Can J Public Health. 2012;103(3):207–12.
Jombo GT, Egah DZ, Banwat EB. Hepatitis B virus infection in a rural settlement of northern Nigeria. Niger J Med. 2005;14(4):425–8.
Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology. 2000;118(3):554–9.
Kao JH, Chen PJ, Lai MY, Chen DS. Genotypes and clinical phenotypes of hepatitis B virus in patients with chronic hepatitis B virus infection. J Clin Microbiol. 2002;40(4):1207–9.
Kew MC. Clinical, pathologic, and etiologic heterogeneity in hepatocellular carcinoma: evidence from southern Africa. Hepatology. 1981;1(4):366–9.
Khan S, Attaullah S. Share of Afghanistan populace in hepatitis B and hepatitis C infection's pool: is it worthwhile? Virol J. 2011;8:216.
Kiire CF. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa. Gut. 1996;38(Suppl 2):S5–12.
Ko YC, Chung DC. Transmission of hepatitis B virus infection by iatrogenic intramuscular injections in an endemic area. Gaoxiong Yi Xue Ke Xue Za Zhi. 1991;7(6):313–7.
Komas NP, Vickos U, Hubschen JM, et al. Cross-sectional study of hepatitis B virus infection in rural communities, Central African Republic. BMC Infect Dis. 2013;13:286.
Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of chronic hepatitis B. Clin Mol Hepatol. 2012;18(2):109–62.
Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology. 2012;56(2):422–33.
Kuo A, Gish R. Chronic hepatitis B infection. Clin Liver Dis. 2012;16(2):347–69.

Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med. 2005;352(26):2682–95.
Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat. 2004;11(2):97–107.
Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China—declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2009;27(47):6550–7.
Liaw YF, Leung N, Kao JH, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int. 2008;2(3):263–83.
Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: recent advances. J Gastroenterol Hepatol. 2011;26(Suppl 1):123–30.
Lin CL, Kao JH. Hepatitis B virus genotypes and variants. Cold Spring Harb Perspect Med. 2015;5(5):a021436.
Lin X, Robinson NJ, Thursz M, et al. Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression. J Gastroenterol Hepatol. 2005;20(6):833–43.
Liu J, Yang HI, Lee MH, et al. Spontaneous seroclearance of hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma. Gut. 2014;63(10):1648–57.
Lok AS. Natural history and control of perinatally acquired hepatitis B virus infection. Dig Dis. 1992;10(1):46–52.
Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–2.
Lok AS, Lai CL, Wu PC, Leung EK, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology. 1987;92(6):1839–43.
MacLachlan JH, Allard N, Towell V, Cowie BC. The burden of chronic hepatitis B virus infection in Australia, 2011. Aust N Z J Public Health. 2013;37(5):416–22.
Matthews PC, Beloukas A, Malik A, et al. Prevalence and characteristics of hepatitis B virus (HBV) coinfection among HIV-positive women in South Africa and Botswana. PLoS One. 2015;10(7):e0134037.
McCarthy MC, el-Tigani A, Khalid IO, Hyams KC. Hepatitis B and C in Juba, southern Sudan: results of a serosurvey. Trans R Soc Trop Med Hyg. 1994;88(5):534–6.
McMahon BJ. Epidemiology and natural history of hepatitis B. Semin Liver Dis. 2005;25(Suppl 1):3–8.
McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis. 1985;151(4):599–603.
McMahon BJ, Lanier AP, Wainwright RB. Hepatitis B and hepatocellular carcinoma in Eskimo/Inuit population. Int J Circumpolar Health. 1998;57(Suppl 1):414–9.
McMahon BJ, Holck P, Bulkow L, Snowball M. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Ann Intern Med. 2001;135(9):759–68.
Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine. 2016;34(29):3335–41.
Mohamed R, Ng CJ, Tong WT, Abidin SZ, Wong LP, Low WY. Knowledge, attitudes and practices among people with chronic hepatitis B attending a hepatology clinic in Malaysia: a cross sectional study. BMC Public Health. 2012;12:601.
Mulwa JKM. Hepatitis B situation in Botswana. J Prev Med Hyg. 1994;35:67.
Musa BM, Bussell S, Borodo MM, Samaila AA, Femi OL. Prevalence of hepatitis B virus infection in Nigeria, 2000–2013: a systematic review and meta-analysis. Niger J Clin Pract. 2015;18(2):163–72.
Nakata S, Song P, Duc DD, et al. Hepatitis C and B virus infections in populations at low or high risk in Ho Chi Minh and Hanoi, Vietnam. J Gastroenterol Hepatol. 1994;9(4):416–9.
Nguyen VT, McLaws ML, Dore GJ. Highly endemic hepatitis B infection in rural Vietnam. J Gastroenterol Hepatol. 2007;22(12):2093–100.
Ni YH, Chang MH, Wu JF, Hsu HY, Chen HL, Chen DS. Minimization of hepatitis B infection by a 25-year universal vaccination program. J Hepatol. 2012;57(4):730–5.
Otegbayo JA, Fasola FA, Abja A. Prevalence of hepatitis B surface and e antigens, risk factors for viral acquisition and serum transaminase among blood donors in Ibadan, Nigeria. Trop Gastroenterol. 2003;24(4):196–7.

Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30(12):2212–9.
Paat G, Uuskula A, Tefanova V, Tallo T, Priimagi L, Ahi K. The trends and risk factors for hepatitis B occurrence in Estonia. Cent Eur J Public Health. 2009;17(2):108–11.
Pan CQ, Zhang JX. Natural history and clinical consequences of hepatitis B virus infection. Int J Med Sci. 2005;2(1):36–40.
Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med. 2016;374(24):2324–34.
Pollicino T, Raimondo G. Occult hepatitis B infection. J Hepatol. 2014;61(3):688–9.
Poorolajal J, Majdzadeh R. Prevalence of chronic hepatitis B infection in Iran: a review article. J Res Med Sci. 2009;14(4):249–58.
Rabenau HF, Lennemann T, Kircher C, et al. Prevalence- and gender-specific immune response to opportunistic infections in HIV-infected patients in Lesotho. Sex Transm Dis. 2010;37(7):454–9.
Robinson T, Bullen C, Humphries W, Hornell J, Moyes C. The New Zealand Hepatitis B Screening Programme: screening coverage and prevalence of chronic hepatitis B infection. N Z Med J. 2005;118(1211):U1345.
Schillie S, Murphy TV, Sawyer M, et al. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep. 2013;62(RR-10):1–19.
Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546–55.
Shepard CW, Simard EP, Finelli L, Fiore AE, Bell BP. Hepatitis B virus infection: epidemiology and vaccination. Epidemiol Rev. 2006;28:112–25.
Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstet Gynecol. 2010;116(1):147–59.
Shi W, Zhang Z, Ling C, et al. Hepatitis B virus subgenotyping: history, effects of recombination, misclassifications, and corrections. Infect Genet Evol. 2013;16:355–61.
Simonetti J, Bulkow L, McMahon BJ, et al. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. Hepatology. 2010;51(5):1531–7.
Sirisena ND, Njoku MO, Idoko JA, et al. Carriage rate of hepatitis-B surface antigen (HBsAg) in an urban community in Jos, Plateau State, Nigeria. Niger Postgrad Med J. 2002;9(1):7–10.
Sowole L, Labbett W, Patel M, et al. The prevalence of occult hepatitis B virus (HBV) infection in a large multi-ethnic haemodialysis cohort. BMC Nephrol. 2015;16:12.
Sugiyama M, Tanaka Y, Sakamoto T, et al. Early dynamics of hepatitis B virus in chimeric mice carrying human hepatocytes monoinfected or coinfected with genotype G. Hepatology. 2007;45(4):929–37.
Takahashi K, Aoyama K, Ohno N, et al. The precore/core promoter mutant (T1762A1764) of hepatitis B virus: clinical significance and an easy method for detection. J Gen Virol. 1995;76(Pt 12):3159–64.
Tecson MPV, Luna JTP. Risk factors for hepatitis B infection among gynecologic patients admitted in a tertiary hospital for elective surgery: a cross-sectional study. Philipp J Obstet Gynecol. 2005;29(3):91–8.
Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261–83.
Tran HT, Ushijima H, Quang VX, et al. Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam. Hepatol Res. 2003;26(4):275–80.
Trepo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014;384(9959):2053–63.
Tseng TC, Kao JH. Treating immune-tolerant hepatitis B. J Viral Hepat. 2015;22(2):77–84.
Tsuzuki Y, Watanabe T, Iio E, et al. Virological characteristics of hepatitis B genotype G/A2 recombination virus in Japan. Hepatol Res. 2016;46(8):775–83.
United Nations General Assembly resolution A/RES/70/1 – Transforming our world: the 2030 Agenda for Sustainable Development. 2016. .Available at: http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E. Accessed 1 Aug 2016.

Unnewehr M, Stich A. Fighting hepatitis B in North Korea: feasibility of a bi-modal prevention strategy. J Korean Med Sci. 2015;30(11):1584–8.
van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. J Viral Hepat. 2003;10(4):294–7.
Vanwolleghem T, Hou J, van Oord G, et al. Re-evaluation of hepatitis B virus clinical phases by systems biology identifies unappreciated roles for the innate immune response and B cells. Hepatology. 2015;62(1):87–100.
Wasley A, Kruszon-Moran D, Kuhnert W, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. J Infect Dis. 2010;202(2):192–201.
Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57(RR-8):1–20.
Weinbaum CM, Mast EE, Ward JW. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. Hepatology. 2009;49(5 Suppl):S35–44.
Whittle HC, Bradley AK, McLauchlan K, et al. Hepatitis B virus infection in two Gambian villages. Lancet. 1983;1(8335):1203–6.
Wong VC, Ip HM, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet. 1984;1(8383):921–6.
Wong SN, Ong JP, Labio ME, et al. Hepatitis B infection among adults in the Philippines: a national seroprevalence study. World J Hepatol. 2013;5(4):214–9.
Wooddell CI. Integrated HBV DNA implicated in maintaining circulating HBsAg levels in chronically infected chimpanzees. 66th AASLD Annual Meeting, The Liver Meeting 2015; November 13–17, 2015; San Francisco, California.
Wooddell CI, Chavez D, Goetzmann JE, et al. Reductions in cccDNA under NUC and ARC-520 therapy in chimpanzees with chronic hepatitis B virus infection implicate integrated DNA in maintaining circulating HBsAg. Hepatology. 2015;62(1 Suppl):222A–3A.
World Health Organization. Temperature sensitivity of vaccines. Geneva, Switzerland: World Health Organization; 2006. Available at: http://apps.who.int/iris/bitstream/10665/69387/1/WHO_IVB_06.10_eng.pdf. Accessed 26 Aug 2016
World Health Organization. Assessment survey of injection safety and safety of phlebotomies, lancet procedures, intravenous injections and infusions in government health facilities in the Philippines. WHO (World Health Organization); 2007. Available at: http://www.wpro.who.int/health_technology/documents/docs/AssessmentSurveyofInjectionSafetyPHL.pdf. Accessed 10 Aug 2016.
World Health Organization. Hepatitis B vaccines: WHO position paper—recommendations. Vaccine. 2010;28(3):589–90.
World Health Organization. Prevention and control of viral hepatitis infection: framework for global action. Geneva, Switzerland. 2012. Available at: http://www.who.int/hiv/pub/hepatitis/Framework/en/. Accessed 1 Aug 2016.
World Health Organization. Immunization week in the Western Pacific. 2014. .Available at: http://www.wpro.who.int/world_immunization_week/celebrating_wiw2014/en/. Accessed 24 Aug 2016.
World Health Organization. WHO vaccine-preventable diseases: monitoring system. Geneva, Switzerland. World Health Organization; 2015. Available at: http://apps.who.int/immunization_monitoring/globalsummary/schedules. Accessed 22 Aug 2016.
World Health Organization. HepB birth dose: reported estimates of hepB BD coverage. 2016. .Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragehepb_bd.html. Accessed 23 Aug 2016.
World Health Organization-UNICEF. Estimates of national immunization coverage. Geneva, Switzerland. 2015. Available at: http://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/index4.html. Accessed 23 Aug 2016.

Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat. 2009;16(2):94–103.

Yan H, Zhong G, Xu G, et al. Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. eLife. 2012;1:e00049.

Yan YP, Su HX, Ji ZH, Shao ZJ, Pu ZS. Epidemiology of hepatitis B virus infection in China: current status and challenges. J Clin Transl Hepatol. 2014;2(1):15–22.

Yang HC, Kao JH. Revisiting the natural history of chronic HBV infection. Curr Hepatol Rep. 2016;15(3):141–9.

Yano Y, Utsumi T, Lusida MI, Hayashi Y. Hepatitis B virus infection in Indonesia. World J Gastroenterol. 2015;21(38):10714–20.

Yao GB. Importance of perinatal versus horizontal transmission of hepatitis B virus infection in China. Gut. 1996a;38(Suppl 2):S39–42.

Yao JL. Perinatal transmission of hepatitis B virus infection and vaccination in China. Gut. 1996b;38(Suppl 2):S37–8.

Yuan Q, Song LW, Cavallone D, et al. Total hepatitis B core antigen antibody, a quantitative noninvasive marker of hepatitis B virus induced liver disease. PLoS One. 2015;10(6):e0130209.

Zhou B, Xiao L, Wang Z, Chang ET, Chen J, Hou J. Geographical and ethnic distribution of the HBV C/D recombinant on the Qinghai-Tibet Plateau. PLoS One. 2011;6(4):e18708.

Zhou B, Wang Z, Yang J, et al. Novel evidence of HBV recombination in family cluster infections in western China. PLoS One. 2012;7(6):e38241.