

Review

Epidemiology and Prevention of Hepatitis B Virus Infection

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Hepatitis B is one of the most common infectious diseases globally. It has been estimated that there are 350 million chronic hepatitis B virus (HBV) carriers worldwide. The prevalence of chronic HBV infection varies geographically, from high (>8%), intermediate (2-7%) to low (<2%) prevalence. HBeAg-negative chronic hepatitis B (e-CHB) and occult HBV infection are two special clinical entities, and the prevalence and clinical implications remain to be explored. The predominant routes of transmission vary according to the endemicity of the HBV infection. In areas with high HBV endemicity, perinatal transmission is the main route of transmission, whereas in areas with low HBV endemicity, sexual contact amongst high-risk adults is the predominant route. HBV has been classified into 7 genotypes, i.e. A to G, based on the divergence of entire genome sequence and HBV genotypes have distinct geographical distributions. Three main strategies have been approved to be effective in preventing HBV infection. They are behavior modification, passive immunoprophylaxis, and active immunization. The implement of mass HBV immunization program is recommended by the WHO since 1991, and has dramatically decreased the prevalence of HBV infection and HCC in many countries.

Key words

Hepatitis B infection, Epidemiology, Prevention, HBV immunization

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1. Introduction

Hepatitis B virus (HBV) is a serious public health problem worldwide and major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). It was estimated that approximately 2 billion people have serological evidence of past or present HBV infection. More than 350 million are chronic carriers of HBV [1]. Approximately 75% of chronic carriers live in Asia and the Western Pacific [2]. It was reported that 15-40% of HBV infected patients would develop cirrhosis, liver failure, or HCC [3], and 500,000 to 1.2 million people die of HBV infection annually [4,5]. Because of the high HBV-related morbidity and mortality, the global disease burden of HB is substantial.

2. Epidemiology

The prevalence of chronic HBV infection varies greatly in different part of the world (Figure 1). The prevalence of chronic HBV infection worldwide could be categorized as high, intermediate and low endemicity. The age at the time of infection is associated with the endemicity of HBV infection (Table 1).

High Endemicity

The prevalence of HBV infection varies markedly throughout regions of the world [6]. Hepatitis B is highly endemic in developing regions with large population such as South East Asia, China, sub-Saharan Africa and the Amazon Basin, where at least 8% of the population are HBV chronic carrier. In these areas, 70–95% of the population shows past or present serological evidence of HBV infection. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [7].

Intermediate Endemicity

Hepatitis B is moderately endemic in part of Eastern and Southern Europe, the Middle East, Japan, and part of South America. Between 10–60% of the population have evidence of infection, and 2-7% are chronic carriers. Acute disease related to HBV is common in these areas because many infections occur in adolescents and adults; however, the high rates of chronic infection are maintained mostly by infections occurring in infants and children [8]. In these areas, mixed patterns of transmission exist, including infant, early childhood and adult transmission.

Low Endemicity

The endemicity of HBV is low in most developed areas, such as North America, Northern and Western Europe and Australia. In these regions, HBV infects 5–7% of the population, and only 0.5–2% of the population are chronic carriers [9]. In these areas, most HBV infections occur in adolescents and young adults in relatively well-defined high-risk groups, including injection drug user, homosexual males, health care workers, patients who require regular blood transfusion or hemodialysis.

3. HBV Transmission

HBV is spread through contact with infected body fluids and the only natural host is human. Blood is the most important vehicle for transmission, but other body fluids have also been implicated, including semen and saliva [10,11]. Currently, three modes of HBV transmission have been recognized: perinatal, sexual and parenteral/percutaneous transmission. There is no reliable evidence that airborne infections occur and feces are not a source of infection. HBV is not transmitted by contaminated food or water, insects or other vectors.

Perinatal Transmission

Transmission of HBV from carrier mothers to their babies can occur during the perinatal period, and appears to be the most important factor in determining the prevalence of the infection in high endemicity areas, particularly in China and Southeast Asia. Before HBV vaccine was integrated into the routine immunization program, the proportion of babies that become HBV carriers is about 10-30% for mothers who are HBsAg-positive but HBeAg-negative. However, the incidence of perinatal infection is even greater, around 70-90%, when the mother is both HBsAg-positive and HBeAg-positive [12,13]. There are three possible routes of transmission of HBV from infected mothers to infants: transplacental transmission of HBV in utero; natal transmission during delivery; or postnatal transmission during care or through breast milk. Since transplacental transmission occurs antenatally, hepatitis B vaccine and HBIG cannot block this route. Epidemiological studies on HBV intrauterine infection in China showed that intrauterine infection occurs in 3.7-9.9% pregnancy women with positive HBsAg and in 9.8-17.39% with positive HBsAg/HBeAg [14-21] and it was suggested that a mother with positive HBeAg (OR = 17.07) and a history of threatened premature labor (OR = 5.44) are the main risk factors for intrauterine infection. The studies on transplacental transmission of HBV suggested two possible mechanisms (1) hemogenous route: a certain of factors, such as threaten abortion, can make the placental microvascular broken, thus the high-titer HBV maternal blood leak into fetus' circulation [20,22]; (2) cellular transfer: the placental tissue is infected by high-titer of HBV in maternal blood from mother's side to fetus' step by step, and finally, HBV reach fetus' circulation through the villous capillary endothelial cells [14-18].

For neonates and children younger than 1 year who acquire HBV infection perinatally, the risk of the infection becoming chronic is 90% [23], presumably because neonates have an immature immune system. One of the possible reasons for the high rate of chronicity is that transplacental passage of HBeAg may induce immunological tolerance to HBV in fetus.

Sexual Transmission

Sexual transmission of hepatitis B is a major source of infection in all areas of the world, especially in the low endemic areas, such as North America. Hepatitis B is considered to be a sexually transmitted disease (STD). For a long time, homosexual men have been considered to be at the highest risk of infection due to sexual contact (70% of homosexual men were infected after 5 years of sexual activity) [24]. However, heterosexual transmission accounts for an increasing proportion of HBV infections. In heterosexuals, factors associated with increased risk of HBV infection include duration of sexual activity, number of sexual partners, history of sexual transmitted disease, and positive serology for syphilis. Sexual partners of injection drug users, prostitutes, and clients of prostitutes are at particularly high risk for infection [25].

Parenteral/percutaneous Transmission

The parenteral transmission includes injection drug use, transfusions and dialysis, acupuncture, working in a health-care setting, tattooing and household contact. In the United States and Western Europe, injection drug use remains a very important mode of HBV transmission (23% of all patients) [6]. Risk of acquiring infection increases with duration of injection drug use. Although the risk for transfusion-associated HBV infection has been greatly reduced since the screening of blood for HBV markers and the exclusion of donors who engage in high-risk activities, the transmission is still possible when the blood donors are asymptomatic carrier with HBsAg negative [26]. Obvious sources of infection include HBV-contaminated blood and blood products, with contaminated surgical instruments and utensils being other possible hazards. Parenteral/percutaneous transmission can occur during surgery, after needle-stick injuries, intravenous drug use, and following procedures such as ear piercing, tattooing, acupuncture, circumcision and scarification. The nosocomial spread of HBV infection in the hospital, particularly in dialysis units, as well as in dental units, has been well described [6], even when infection control practices are followed. As with other modes of transmission, high viral titers have been related to an increased risk of transmission. People at high-risk of infection include those requiring frequent transfusions or hemodialysis, physicians, dentists, nurses and other healthcare workers, laboratory technicians, intravenous drug users, police, firemen, laundry workers and others who are likely to come into contact with potentially infected blood and blood products.

The risk of chronicity is low (less than 5%) for transmission through sexual contact, intravenous drug use, acupuncture, and transfusion [23]. Individuals at risk for these transmission modes usually acquire HBV infection during adolescence or adulthood without immune tolerance. Instead, the disease progresses directly to the immune clearance phase and is of short duration, which probably accounts for high spontaneous recovery.

4. HBV Genotype and Its Clinical Significance

Based on an intergroup divergence of 8% or more of the complete genomes, HBV can be classified into 7 genotypes, i.e. A-G [27-30]. Genotype H was recently identified in central America [31]. It is well known that HBV genotypes have distinct geographical distributions. The geographical distributions of HBV genotypes are summarized in Table 2. The prevalent HBV strains in China are genotype B and C [32], but the two genotypes distribute unevenly in China. We studied 1096 Chinese chronic HBV carriers from 9 provinces in Mainland China. Four major genotypes A, B, C and D were found and their prevalence were 1.2%, 41%, 52.5% and 4.3%, respectively. In northern China, genotype C is predominant (85.1%), while in southern China, genotype B is predominant (55.0%) [Hou, et al., unpublished data]. Genotypes A and D are also found in other areas of China. However, the genotypes E-H have not been reported in China. Recently, genotype C/D hybrid was identified in Tibet [33] and genotype B was found recombined with preC/C region of genotype C in China [34]. Accumulated data suggest the importance of genotype, subgroup and recombination that may influence the biological characteristics of virus and clinical outcome of HBV infection. Several studies reported a correlation of HBV genotypes with HBeAg clearance, liver damage, and the response to IFN treatment. It was reported that HBeAg carrier status tends to be longer and the prevalence of HBeAg appears higher in patients with genotype C than with genotype B [35,36]. HBV carriers with genotype B have lower histologic activity scores [37], and genotype C is more prevalent in patients with cirrhosis [38,39]. Furthermore, a retrospective study showed that HBV genotype B is associated with a higher rate of IFN-induced HBeAg clearance compared with genotype C [40]. However, whether patients with genotype B differ from those with genotype C in development of hepatocellular carcinoma remains controversial. The response of different HBV genotypes to interferon- α treatment is of increasing interest because the benefit of interferon- α or its pegylated form in combination with other antiviral agents is being explored in the treatment of chronic hepatitis B. In a homogeneous group of prospectively followed patients from Europe, a recent study demonstrates that genotype A responds better than other HBV genotypes to standard interferon therapy and represents an independent predictor of a therapeutic success, with a greater impact than other pre-treatment characteristics, such as HBV DNA or ALT levels [41].

5. Occult Hepatitis B

Occult hepatitis B is defined by the presence of HBV DNA in serum or liver in the absence of HBsAg [42,43]. Serum HBV level is usually less than 10^4 copies/ml. Although occult HBV infection has been identified in patients with chronic liver disease two decades ago [44], its precise prevalence remains to be defined. Occult HBV infection has been found in patients with HCC, past HBV infection, or chronic hepatitis C, and individuals without HBV serological markers. The frequency of the diagnosis depends on the relative sensitivity of HBV DNA assays and the prevalence of HBV infection in the population. Collectively, around 30% to 35% of HBsAg-negative subjects with chronic hepatitis with or without HCC have positive serum HBV DNA (range from 5% to 55%). The prevalence of HBV DNA is higher in anti-HBc-positive, but anti-HBs-negative patients, ranging from 7% to 60% in populations highly exposed to HBV [45]. HBV DNA is much less frequently identified in HBsAg-negative patients with acute, and particularly fulminant hepatitis at around 10% and 7% in serum and liver samples [45]. Viral DNA persistence is not, however, restricted to patients with liver disease and may be observed in subjects with normal liver parameters, including blood and/or organ donors. Overall, occult HBV infection is seen in 7%-13% of anti-HBc-positive and/or anti-HBs-positive subjects, and in 0% to 17% of blood donors.

The clinical significance of occult HBV infection remains unclear. Occult HBV infection represents a potential transmission source of HBV via blood transfusion or organ transplantation. In addition, occult HBV infection has been associated with cryptogenic chronic hepatitis and hepatocellular carcinoma. Furthermore, some studies suggested that occult hepatitis B might affect responsiveness of chronic hepatitis C to interferon therapy and disease progress.

6. HBeAg-negative CHB

HBeAg-negative chronic hepatitis B (e-CHB), characterized by HBV DNA levels detectable by nonamplified assays and continued necroinflammation in the liver, has been reported worldwide, but is more common in Mediterranean countries and Asia. The prevalence of e-CHB is 33% in the Mediterranean, 15% in Asia Pacific, and 14% in the United States and Northern Europe [46]. Although the presence of e-CHB is more common in the Mediterranean, its clinical impact appears greatest in China where a

prevalence of 15% among HBsAg carriers equals to approximately 15 million cases of e-CHB. It is expected that the prevalence of e-CHB tends to increase. This is supported by data from a few studies in South-east Asia. Of the 743 successive patients with CHB in our Liver Unit, 267 (35.9%) were HBeAg-negative [47]. A cross-sectional study performed in Hong Kong showed that e-CHB might be present in up to 17% of HBeAg-negative patients [48]. Another study conducted in Korea found that among the 413 consecutive HBeAg-negative patients, 17.7% of HBeAg-negative patients had e-CHB [49].

Most patients with e-CHB harbor HBV variants in the precore or core promoter region. The most common precore mutation, G₁₈₉₆A, creates a premature stop codon in the precore region thus abolishing production of HBeAg [50]. The variant is commonly found in association with HBV genotype D, which is prevalence in the Mediterranean area and is rarely detected in the United States and North-West Europe [51,52]. The most common core promoter mutations, A₁₇₆₂T+G₁₇₆₄A, decrease transcription of precore messenger RNA and production of HBeAg [53]. There are also clinical differences between HBeAg-positive and HBeAg-negative chronic hepatitis B [54]. Patients with e-CHB tends to have lower serum HBV DNA levels and are more likely to have a fluctuating course characterized by persistently elevated or fluctuating ALT levels [54,55]. Although there has been a great deal of interest in these HBV variants, the clinical significance of these mutant viruses, particularly those described in association with severe liver disease, remains controversial.

7. HBV and Hepatocellular Carcinoma

Epidemiologic studies have demonstrated that there is a consistent and specific causal association between HBV infection and HCC [56-58]. In patients with persistent HBV infection, the risk of HCC was 100 times higher than in non-infected individuals [56]. The global distribution of hepatocellular carcinoma correlates with the geographic prevalence of chronic carriers of HBV, who number 400 million worldwide. The highest rates are in Southeast Asia and sub-Saharan Africa, with the HCC incidence >50/100,000 population [59].

Virological factors in the pathogenesis of hepatocellular carcinoma have recently been defined. Both retrospective and prospective studies strongly supported the relation between positive HBeAg and the risk of HCC [60-62]. A prospective study in Taiwan [62] showed that relative risk of HCC among men who were positive for both HBsAg and HBeAg (RR=60.2) were much higher than that among men who were positive for HBsAg alone (RR=9.6). HBV DNA was identified as the most important predictor of the development of hepatocellular carcinoma in HBsAg-positive patients with different clinical conditions [63-65]. Therefore, efforts at eradicating or reducing the viral load may reduce the risk for HCC. Additionally, HBV genotype might play a role in the development of HCC. The data from Taiwan showed that genotype C is associated with more severe liver disease including cirrhosis and hepatocellular carcinoma (HCC), whereas genotype B is associated with the development of HCC in young noncirrhotic patients.

8. Prevention of HBV Infection

Three main strategies are available for the prevention of HBV infection: (1) behavior modification to prevent disease transmission, (2) passive immunoprophylaxis, and (3) active immunization.

Behavior Modification

Changes in sexual practice and improved screening measures of blood products have reduced the risk of transfusion-associated hepatitis. Behavior modification is thought to be more beneficial in developed countries than in developing countries, where neonates and children in early childhood are at the greatest risk of acquiring infection. In these groups, immunoprophylaxis, both passive and active, will be more effective.

Passive Immunoprophylaxis

Hepatitis B Immune Globulin (HBIG) is a sterile solution of ready-made antibodies against hepatitis B. HBIG is prepared from human blood from selected donors who already have a high level of antibodies to hepatitis B and used in passive immunoprophylaxis. Passive immunoprophylaxis is used in four situations (1) newborns of mothers infected with hepatitis B; (2) after needlestick exposure, (3) after sexual exposure, and (4) after liver transplantation. Immunoprophylaxis is recommended for all infants born to HBsAg positive mothers. Current dosing recommendations are 0.13ml/kg HBIG immediately after delivery or within 12 hours after birth in combination with recombinant vaccine. The combination results in a higher-than-90% level of protection against perinatal acquisition of HBV [66]. Between 3.7% to 9.9% of infants still acquire HBV infection perinatally from HBV-infected mothers, despite immunoprophylaxis [14-21]. Failure of passive and active immunoprophylaxis in this setting may be the result of in utero transmission of HBV infection, perinatal transmission related to a high inoculum, and/or the presence of surface gene escape mutants. To study the interruptive effect of HBIG before delivery in attempt to prevent intrauterine transmission of HBV, a large-scale, random-control study was conducted in China [67]. In this study, nine hundred and eighty HBsAg carrier pregnant women were randomly divided into HBIG group and control group. Each subject in the HBIG group received 200 IU or 400 IU of HBIG intramuscularly at 3, 2 and 1 month before delivery, in addition to newborns receiving HBIG intramuscularly. By this way, the rate of intrauterine transmission in this group fell to 5.7%, compared to 14.3% in control group. ($P < 0.001$). However, the preventive effect of HBIG administration before delivery needs to be confirmed by more study in the future.

Hepatitis B immune globulin remains a central component of prophylaxis in HBV-infected patients undergoing liver transplantation. HBIG monotherapy given at a high dosage can prevent recurrence in 65% to 80% of patients. Because the cost of long-term prophylaxis with high-dose HBIG is extremely high and combination therapy using HBIG with a nucleoside analog is more uniformly effective, the current protocol is combination HBIG with a nucleoside analog after liver transplantation. These combination protocols have reduced the rate of virologic breakthrough to 10% or less [68].

Active Immunization

Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications. The first-generation hepatitis B vaccine, an inactive plasma-derived vaccine, became available in 1982. Consequently, the second generation of HB vaccine, a DNA recombinant HB vaccine was also available for general use in 1986. Both of the vaccines were proven to be safe and efficacious in preventing HBV infection. In 1991, the World Health Organization

(WHO) recommended that hepatitis B vaccination should be included in national immunization system in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. By May 2002, 154 countries had routine infant immunization with hepatitis B vaccine [69].

The world's first universal vaccination program for HBV infection was launched in 1984 in Taiwan [70-73]. During the first 2 years of the program, coverage was provided mainly for infants whose mothers were carriers of HBsAg. Vaccination was subsequently extended, first to all newborns and then to unvaccinated preschool-age and elementary school-age children. Since 1991, catch-up vaccinations have been given to children in the first grade. This program reduced the overall HBsAg prevalence rate from 9.8% in 1984 to 1.3% in 1994 among children <15 years of age. The HBV carrier population was further reduced through improved maternal screening [71]. In 1999, vaccination rates were 80–86% for young children and higher than 90% for older children; the prevalence of HBsAg was reduced to 0.7% for children younger than 15 years of age [70]. To evaluate the long-term efficacy of hepatitis B (HB) vaccination in newborns, one of the longest HB vaccine follow-up studies in the world was conducted in Shanghai, China [74]. Children who were born in 1986 and immunized with hepatitis B vaccine at birth were followed up at least once a year. Serum HBsAg, anti-HBc and anti-HBs were tested. The positive rates of HBsAg in the vaccine group with the period of 16 years were 0.46%-0.97%, the average being 0.61%, which was much lower than those of baseline before vaccination and external control. The long-term efficacy of newborn vaccination was 85.42%. In countries such as Italy and the United States, the incidence of acute hepatitis B has declined dramatically during the past decade after vaccination program for HBV infection, particularly among persons in younger age group [75,76].

Universal HB vaccination was proven to be effective in the prevention of HCC in several large cohort studies in Southeast Asia. Chang et al [77] reported that the average annual incidence of HCC in children 6 to 14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 ($P < 0.01$) in the first vaccinated cohort in Taiwan. The corresponding rates of mortality from hepatocellular carcinoma also decreased. After universal vaccination against HB in 1987 in Long'an, Guang Xi, a highly endemic area in Southern China, a birth cohort study was used to evaluate the efficacy of hepatitis B vaccination. The incidence of HCC dropped from 3.27/10,000 to 0.17/10,000, a 94.8% decrease, in the group of 0-19 year-olds. The average incidence of HCC in general population for the period from 1996 to 2002 dropped to 27.86/100,000 from 48.18 for the period from 1969 to 1988 [78]. The protective effect of HBV vaccination against liver cancer in adults was investigated in a cohort study in Korea. This study suggested that the immunization with HB vaccine, even in adulthood, could reduce the risk of liver cancer [79]. The decrease in the rate of HCC after universal vaccination against hepatitis B provides further evidence that HBV is a cause of HCC.

Considering anti-HBs may disappear in a substantial proportion of vaccinee after initially successful vaccination, a booster dose of vaccine, following the administration of the primary course, is recommended by most national bodies. However, is it necessary to boost after initially successful vaccination? The results of long-term follow-up studies, together with assessment of the role of immunological memory among vaccinees, now question the necessity of providing booster doses following a successful course of primary immunization. In China, a long-term follow up study on HB vaccine immune efficacy showed that within the period of 16 years, the positive rate for HBsAg of the children born in 1986 ranged between 0.46 %~0.97 % with the average being 0.61 %, which was much lower than those of the background group before vaccination, despite the rate of HBsAg positive and the geometric mean titer declined [74]. It was suggested that the newborns who had been vaccinated completely by HBV vaccine at their birth are unnecessary to take the booster again within 16 years. The studies in other countries also show that protection is still maintained among vaccinees, even in HBV endemic countries, despite waning or undetectable anti-HBs levels [80-82]. Long-term B-cell memory has been confirmed by demonstrating either the presence of anamnestic anti-HBs responses, or the presence of circulating B cells to produce anti-HBs by a spot-enzyme-linked immunosorbent assay (ELISA) [83]. The accumulated data indicate that protection is dependent on immune memory, rather than declining anti-HBs responses. European Consensus Group on hepatitis B immunity recommend that following a complete course of vaccination, booster doses are unnecessary in immunocompetent persons [84].

The effectiveness of routine infant hepatitis B immunization in significantly reducing or eliminating the prevalence of chronic HBV infection has been demonstrated in a variety of countries and settings. However, there are still many challenges to achieve the goal of universal childhood immunization against hepatitis B, such as poor immunization delivery infrastructure, low coverage and lack of financial sustainability. Therefore, to continue to promote access to hepatitis B vaccines worldwide, great efforts are needed to support countries to ensure sustained funding for immunization programs.

9. Research Direction

On epidemiology of HBV, additional research using population based samples of adequate size on a consensus definition of e-CHB and using standard HBV DNA assays is needed to estimate the true prevalence of e-CHB and its associated HBV variants and the precise prevalence of occult HBV infection remains to be defined. The conventional three-dose HBV vaccine schedule is not optimal in terms of ease of implementation, record keeping, and compliance. A more immunogenic HBV vaccine that could be used in a single dose or abbreviated schedule would be a major advance and might prove useful in reducing nonresponsiveness in immunosuppressed individuals. Additionally, because the current vaccine must be given by injection, the development of an effective and safe oral HBV vaccine would be advantageous.

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Conflict of interest

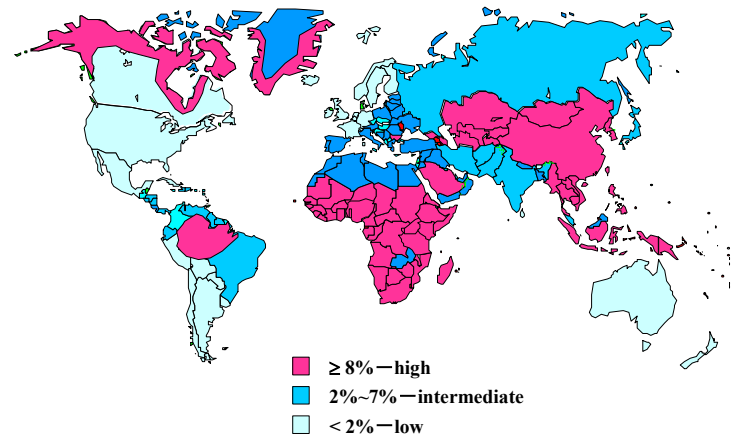
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Tables and Figures

Figure 1. Geographic distribution of chronic hepatitis B infection, shown as HBsAg prevalence. Source of Figure: available on request from D. Lavanchy, World Health Organization, Communicable Diseases Surveillance and Response (CSR).

Table 1. Characteristics of endemic patterns of hepatitis B virus infection. Source: adapted from Ref.[7].

Characteristic	Endemicity of infection		
	Low (%)	Intermediate (%)	High (%)
Chronic infection prevalence	0.5-2	2-7	≥8
Past infection prevalence	5-7	10-60	70-95
Perinatal infection	Rare (<10)	Uncommon (10-60)	Common (>20)
Early childhood infection	Rare (<10)	Common (10-60)	Very ommon (>60)
Adolescent/adult infection	Very common (70-90)	Common (20-50)	Uncommon (10-20)

Table 2. Geographic Distribution of HBV Genotypes

Genotypes	Distributions
A (Aa, Ae)	White Caucasians in Europe, Black Americans in US (Ae), Black Africans, South Africa (Aa), Asia (Aa), India
B (Ba, Bj)	Southern China (Ba), Taiwan (Ba), Vietnam (Ba), Asians in the USA, Japan (Bj)
C	China (Mainland and Taiwan), Japan, Thailand, Asians in the USA
D	White Caucasians (Southern Europe), Arabs (North Africa and the Middle East), India
E	West Africa
F	Central and South America
G	United States, France
H	Central America