Global Epidemiology of Hepatitis B Virus (HBV) Infection

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Abstract

Hepatitis B virus (HBV), a DNA virus with a human-only reservoir, is a worldwide public health problem. Hepatitis B is transmitted through parenteral or mucosal exposure to infected blood and body fluids. The mode of transmission is usually vertical or horizontal in highly endemic areas early in life, resulting in a high chronicity rate. In low endemic countries, transmission is usually in adulthood with self-limiting infection in most. The prevalence of chronic HBV infection is highly variable, ranging from 0.1% in the United States to 20-30% in some Pacific Island nations. There are an estimated 360 million people who are chronically infected, of whom almost one million people die annually of HBV-related liver disease. Chronic hepatitis B is the major cause of hepatocellular carcinoma in the world. Safe and effective HBV vaccines have been available since 1982. The implementation of effective vaccination programs has resulted in a significant decrease in the incidence of chronic hepatitis B infection. Nevertheless, hepatitis B remains an important cause of morbidity and mortality among the chronic carriers worldwide. Understanding the epidemiology of the disease is essential in developing programs to prevent and treat this global infection.

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Worldwide Prevalence

Of the 2 billion people or one-third of the world's population that has been infected with HBV, it is estimated that 360 million people are chronic carriers.[1] The global epidemiology of HBV is best reviewed according to the six regions defined by the World Health Organization (WHO): the Americas, Europe, Africa, Eastern Mediterranean, South-East Asia, and the Western Pacific (**Figure 1**). Each geographical area can then be described by its endemicity, which is defined as the prevalence of hepatitis B surface antigen (HBsAg) in the general population of that particular geographical area (**Figure 2**).

In countries of high HBV endemicity, where the prevalence of HBsAg is ≥8%, the usual mode of transmission is vertical at the time of birth from a chronically infected mother or horizontal in early childhood from bites, skin lesions or unsanitary habits. Approximately 45% of the world's population, including those who live in many African and Asian countries, the Amazon Basin and parts of the Middle East, are considered to live in areas of high endemicity with a lifetime risk of infection of more than 60%. Only about 12% of the world's population live in areas of low endemicity, such as the United States, Western Europe and Australia, where the prevalence of HBsAg is < 1% and the lifetime risk of infection is < 20%. The most common mode of transmission in areas of low endemicity is horizontal in adulthood, usually through sexual transmission and the use of contaminated needles in medical procedures or injection drug use. The remainder of the world's population lives in areas of intermediate endemicity, such as Eastern and Southern Europe, Russia, Central and South America, where the prevalence is 1-7% and the lifetime risk of infection ranges from 20-60%.[2]

Disease Burden

Hepatitis B virus infection is estimated to be the cause of 30% of cirrhosis and 53% of liver cancer in the world.[3] Approximately 15-40% of patients with chronic HBV will develop cirrhosis, end-stage liver failure or hepatocellular carcinoma (HCC) in their lifetime. [4] Mathematical modeling for the year 2000 estimated the annual number of HBV-related deaths to be more than 600,000 worldwide. Most of the deaths (94%) were attributed to complications of chronic infection, such as cirrhosis and HCC, and only 6% were attributed directly to acute hepatitis B.[5]

Figure 1. The six regions of the World Health Organization (WHO).
Data from the World Health Organization website, available at http://www.who.int/about/regions/en/index.html. Accessed July 14, 2010.

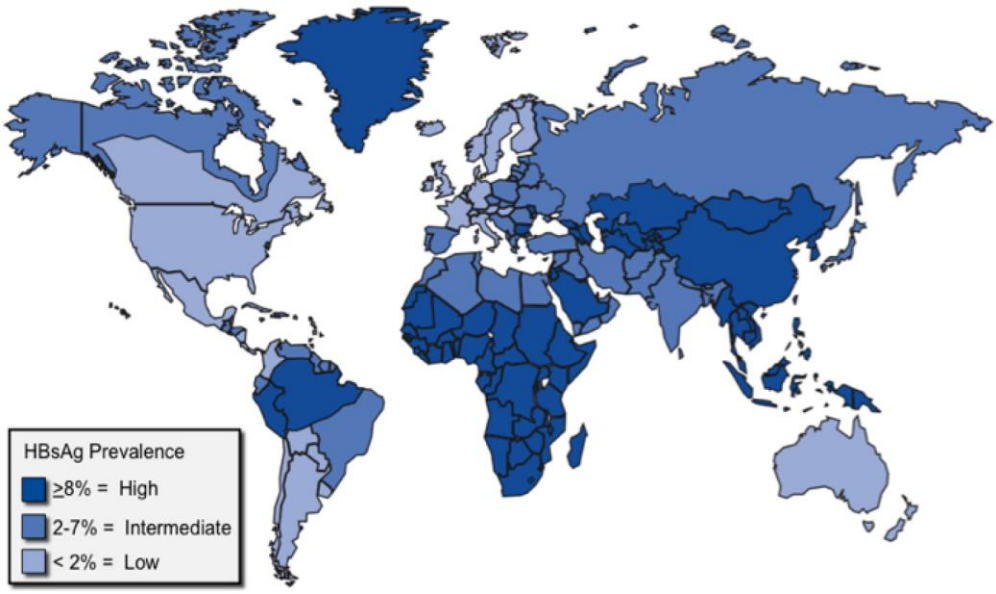

Figure 2. Prevalence of hepatitis B virus infection in the world by country.
Data from the World Health Organization website, available at http://www.who.int/csr/disease/hepatitis/en/. Accessed July 14, 2010.

Hepatocellular carcinoma is the sixth most common cancer and the third most common cause of cancer death in the world.[6] Chronic HBV infection is the most common cause of HCC, accounting for 50% of HCC cases worldwide and up to 80% of cases in high HBV endemic regions.[7] The risk of developing HCC is greatly increased with the development of cirrhosis. Thus, the ideal way to decrease HBV-related deaths is to first prevent the infection through vaccination and strategies to reduce transmission and second, to prevent progression to cirrhosis and HCC in those already infected. Although anti-viral therapies can suppress HBV and delay liver disease progression, most people with chronic HBV infection reside in developing countries with limited health care resources. Thus, HBV-related HCC incidence is projected to increase for at least two decades due to the high prevalence of chronic HBV infection throughout the world.[8]

Impact of Prevention of Transmission

Prevention strategies include primary prevention of new infections (i.e. vaccines and post-exposure prophylaxis), secondary prevention of HBV transmission by appropriate sexual and sanitary practices, and tertiary prevention of the pathological consequences of chronic HBV by anti-viral treatment. The risk of progression from acute to chronic infection is inversely proportional to the age of infection. Up to 90% of infants who acquire HBV infection from their mothers at birth become chronically infected, whereas in adults, only 5% of acute HBV cases remain chronically infected.[9] Thus, the highest risk of developing chronic HBV is in high endemic areas where perinatal and early childhood infection is most common, making universal immunization the highest yield strategy for prevention. According to model-based predictions, universal HBV infant immunization would prevent up to 75% of global deaths from HBV-related causes. Adding a birth dose, where the first dose of HBV vaccine is administered within the first 24 hours of birth, would prevent perinatal transmission in up to 84% of infants.[5]

Safe and effective HBV vaccines have been available since the 1980s. The plasma-derived HBV vaccine was first commercially available in the United States in 1982, and continues to be used today, mostly in the less affluent countries. Recombinant DNA vaccines were then licensed in 1986 and 1989.[10] After the introduction of recombinant vaccines and the subsequent drop in cost of the plasma-derived vaccines, the WHO set a goal in 1992 for all countries to introduce the HBV vaccine into their national routine infant immunization programs by 1997. By 2006, 162 of 193 countries had introduced the vaccine into their national infant immunization schedules. As of 2008, 177 countries had incorporated the vaccine as part of their national infant immunization program and an estimated 69% of all newborns had received all 3 doses of the HBV vaccine.[11]

In 2010, the WHO recommended universal administration of a birth dose regardless of the level of endemicity.[12] As of 2006, 81 of 193 countries (42%) reported using a vaccination schedule with a birth dose; however, only 36% of all newborns in countries with high endemicity and 27% of newborns worldwide received a birth dose.[11] Although these relatively low percentages were partly due to missing data from logistical and financial issues, they emphasize the need to improve newborn hepatitis B vaccination programs.

Following a full course of vaccination (3 doses of the vaccine given at 0, 1 and 6 months after birth), almost 100% of children and 95% of healthy young adults developed protective levels of antibody against hepatitis B surface antigen (anti-HBs). People who are elderly, obese, heavy smokers, undergoing hemodialysis or immunocompromised have suboptimal antibody responses when vaccinated.[10] For that reason, the key is to vaccinate the youngest populations as broadly as possible to allow for maximal prevention.

Hepatitis B immune globulin (HBIG), combined with hepatitis B vaccine or active post-exposure prophylaxis with hepatitis B vaccine alone, is effective in preventing transmission after exposure to HBV from mother to newborn or after sexual exposure. Post-exposure prophylaxis with hepatitis B vaccine is recommended first-line; if available and feasible from a logistic and financial standpoint, HBIG is also recommended for infants born to HBsAg-positive mothers, unvaccinated infants whose mothers or primary caregivers have acute hepatitis B, sexual contacts of people with acute hepatitis B, and people without immunity who have been occupationally exposed to HBsAg-positive blood.[13]

Genotypes

There are 8 genotypes of HBV, A through H, each with a distinctive geographical distribution. The HBV genotypes, except for genotype E and G, can be further divided into sub-genotypes. Genotype A is more prevalent in North America, Northern and Western Europe, India, Sub-Saharan Africa, and in some regions of South America. Genotype B and C are most common in Asia. Genotype D is endemic to the Mediterranean region and Eastern Europe, although it can also be found all over the world. Genotype E exists in Western Africa. Genotype F is present in South America. Genotype G has been reported in France, Germany, Central America, Mexico and the United States. Lastly, genotype H can be found in Central America.[14]

The different HBV genotypes exhibit diverse clinical and virologic manifestations. For example, genotypes A and B have better responses to interferon therapy than genotypes C and D.[15] In a prospective study done in India, genotype D was found to be associated with more severe liver disease and HCC in young patients than genotype A.[16] There are also clinical differences among sub-genotypes. Studies in Taiwan showed that more than 50% of HBV-related HCC patients were infected with HBV genotype B. Furthermore, a high proportion of younger patients with HCC had HBV genotype B compared to genotype C.[17,18] In contrast, a study done in the Okinawa Islands of Japan showed that genotype B in Japan is rarely associated with the development of HCC, and only in older age.[19] This disparity could be explained by the difference in sub-genotypes—Japan is infected with sub-genotype B1, whereas Taiwan is predominantly infected with sub-genotype B2.[20]

Epidemiology by WHO Region

HBV in the Americas

The WHO Americas region is comprised of the countries of North America, Central America and South America. Hepatitis B prevalence in the Americas region needs to be considered in the context of 2 distinct subgroups: (1) the United States and Canada, which have low prevalence rates, and (2) Mexico, Central America and South America, which have areas of significantly higher prevalence.

North America (United States and Canada). In the United States, the National Health and Nutrition Examination Study (NHANES) found the age-adjusted prevalence of past and present infection to be 4.8% from data collected between 1996 and 2006. The prevalence of active chronic HBV infection was 0.3%, or about 730,000 total infected persons.[21] Before hepatitis B vaccines were licensed in 1982, an estimated 200,000-300,000 persons became infected with HBV in the United States each year, with rates of infection peaking in the mid-1980s.[22] However, since the initiation of increased vaccine coverage in 1991 targeting prenatal screening of infected pregnant women and universal vaccination of infants, adolescents and adults at risk for HBV, the incidence has declined. The Centers for Disease Control and Prevention (CDC) estimated that there were 13,000 acute clinical cases and 43,000 newly infected patients in the year 2007, which is significantly less than pre-vaccination prevalence rates.[23] The incidence of HBV varies greatly, with the highest rate in immigrants or refugees from areas of high endemicity, followed by the Native Alaskans and blacks. Among whites, Hispanics have a higher rate of infection than non-Hispanics**.** The incidence and prevalence rates are generally higher in urban settings and among adults, particularly males, ages 25-44 years.[24]

In Canada, the prevalence of hepatitis B varies greatly depending on the population. The overall prevalence in the general population is low, about 0.5-1.0%; however, assessments based on distinct populations can range from as low as 0.1% in people born in Canada to 6.9% in the Inuit population and 7.4% in immigrants from highly endemic countries.[25] In 1999, the incidence of acute HBV infection was estimated to be 2.3/100,000 population, approximately 700 cases per year.[26] The rate is higher among males than females and peaks at the age of 30 to 39 years.[27] As in the United States, adult horizontal transmission is the most common route of transmission, except for recent immigrants, native Alaskans and native northern Canadians, where vertical and childhood horizontal transmissions are more common.[28]

Mexico, Central America and South America. Hepatitis B is considered to be highly prevalent in this region, but there is variability among and within each country. The estimated prevalence ranges from 0.5-8.0%, with the total number of carriers approaching 11 million.[29,30] Mexico and most of Central America have low-intermediate endemicity ranging from 1.0-2.0%, except for Honduras, the Dominican Republic and Haiti where there is a higher prevalence of 3-4%. In South America, the rate of HBsAg carriage is as high as 8% in the native population of the Western Amazon Basin (Brazil, Colombia, Peru and Venezuela). With increasing distance from this area, the HBsAg prevalence decreases with Chile, Uruguay, Paraguay and Argentina having the lowest HBsAg prevalence ranging from 0.5-1.0%.[31]

Routes of transmission are highly variable in Latin America. The highest prevalence has been reported to be among 20 to 40 year olds and the lowest prevalence in children younger than 12 years, supporting adult horizontal transmission as the most common route of infection in this area. In addition to the expected means of adult transmission by sexual or parenteral practices, there are significant rates of infection through cultural practices such as tattooing. However, vertical transmission and childhood horizontal transmission are still important in areas of high endemicity such as the Amazon Basin.[31]

HBV in Europe

The prevalence of HBV is heterogeneous in this region with rates ranging from < 0.1% to as high as 12%.[28, 32] Europe can be divided into three types of epidemiological patterns. The first pattern occurs in Northern Europe (Scandinavian countries and the United Kingdom) and is generally characterized by a low HBsAg carrier rate of < 0.1%. The second pattern exists in most Western European countries, where the carrier rate ranges between 0.1% and 0.5%. The final pattern can be found in Southern Europe (countries bordering the Mediterranean Sea) and Eastern Europe where the carrier rates in some parts can be greater than 8%.[33, 34]

Overall, the highest incidence of HBV in Europe is in the 25 to 44-year old age group, followed by the 15 to 24 year-old age group. The infection is more common in males (1.33 cases per 100,000) than females (0.58 cases per 100,000).[35] The European countries follow the general rules of transmission. In countries with intermediate to high endemicity, vertical and childhood horizontal transmission within infected households are the most common routes of infection, whereas in low endemic areas, intravenous drug use and sexual activity are the predominant means. For example, in the Netherlands where the prevalence rate is low, sexual transmission is the most frequent mode of infection.[36] In Central and Eastern Europe, where the prevalence rates are higher, vertical and childhood horizontal transmission contribute to the high endemism in the former USSR.[37] Additionally, after the introduction of dry heat sterilization in the 1970s which was insufficient to eliminate HBV, multiple studies in Poland showed that nosocomial infections from blood transfusions and medical procedures accounted for up to 60% of HBV infections in adults and 80% in children.[34] Today, strict blood screening, vaccination and improved sanitation practices have led to a declining trend of HBV prevalence in most countries.

HBV in the Eastern Mediterranean

The WHO Eastern Mediterranean region extends from the countries of North Africa through the Middle East to Pakistan. The WHO estimates that the HBsAg prevalence in this region ranges from 1-10%, making it a region of intermediate to high endemicity.[28] A study of village populations in Egypt, published in 1985, revealed an overall HBV prevalence rate of 11.7% and a higher prevalence rate of 20.8% in young adults between the ages of 14-18 years. In these populations, antibodies to hepatitis B core antigen (anti-HBc) were found in nearly 90% of both men and

women.[38] More recent studies, published in 2009 and 2010, show that prevalence rates have decreased in Egypt. A study of 616 barbers and their clients in a mixed urban and rural setting revealed a HBsAg prevalence rate of 4.2%.[39] Another study screened almost 56,000 asymptomatic blood donors, mostly from rural areas, and found the seroprevalence rate to be only 1.3%.[40]

In a 2002 Pakistani study, the prevalence of HBV infection was found to be 3.3% from a sample of over 100,000 voluntary blood donors.[41] In 2005, a study in the obstetric and gynecological population in Pakistan found a 4.6% prevalence in women of childbearing age.[42] A recent population-based study in Iran showed a prevalence rate of hepatitis B surface antigen to be 2.6% in 6,583 randomly subjected subjects from three provinces in Iran, namely Tehran, Golestan, and Hormozgan.[43]

Throughout the Eastern Mediterranean region, transmission occurs through childhood horizontal and adult horizontal routes, and less commonly, vertical routes. Risk factors associated with infection include residence in a rural area, overcrowding, poor sanitary conditions, parenteral drug use, exposure to blood products, medical procedures, ear piercing and scarification.[38]

HBV in Africa

This region covers all of Sub-Saharan Africa and Algeria. Africa has the second largest number of chronic carriers after Asia and is considered a region of high endemicity. The exact burden of hepatitis B in Africa is difficult to assess due to inaccurate records and under-reporting, but between 70 and 95% of the adult population show evidence of past exposure to HBV infection and the estimated HBsAg seroprevalence ranges from 6-20%.[44,45]

Western Africa has the highest rates of endemicity within Africa with as many as 95% of the adult population displaying markers of past HBV exposure. The prevalence rate in Gambia and Senegal are about 15%, with age-specific prevalence as high as 20% in 10- to 20-year olds. Not surprisingly, this region also has one of the world's highest rates of HCC. In Gambia, HCC is the most common cancer among men and the second most common cancer among women.[6,46,47]

Different areas of Africa have varying prevalence rates. Some of the variability lies in the size of the study and the geographical location in Africa, but it appears that in general, higher prevalence rates are encountered in rural areas compared to urban areas. A study of chronic HBV infection among 2364 urban black children in Soweto, Johannesberg, South Africa showed an HBsAg positivity of 1%. This low carrier rate applied equally to children from the lowest and the highest socioeconomic groups in Soweto. This is in contrast to the established prevalence rate of 15% in rural black children in southern Africa. This significant difference in HBV carrier rate could be attributed to poor hygiene and greater chances of HBV transmission through skin abrasions, insect bites, use of contaminated needles, tribal scarification and ear piercing using contaminated equipment.[48,49]

In contrast to Asia where perinatal transmission is most common, horizontal transmission in childhood is thought to be the predominant mode of infection in Africa. For example, in Western Africa, HBV infection is uncommon in newborns, but then infection rates rise with age. By the age of 2 years, 30% of West African children have been infected with HBV and 15% have developed persistent infection. By the age of 10 years, 90% of children have become infected and 20% have become chronic carriers. A major reason for the relatively low rate of perinatal transmission is the lower prevalence of HBeAg positivity, which is considered a marker of active viral replication. A lower prevalence of HBeAg positivity has been observed in mothers from Sub-Saharan Africa compared with mothers in Asia, suggesting a lower potential for vertical transmission.[45]

HBV in South-East Asia

This region is comprised of Bangladesh, Bhutan, North Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste. It is considered to be of intermediate to high endemicity with prevalence rates ranging from 1-10%.[28]

In India, the national prevalence rate has been estimated to be 4% with approximately 36 million carriers overall.[50] An extensive review by the Indian National Association for the Study of Liver Diseases estimated the average national prevalence rate to be 4.7%.[51] However, as with other countries that cover a large geographic area, the prevalence of hepatitis B is variable throughout the country with a gradient of generally increasing prevalence from north to south. The lowest prevalence is 2.3% in a large cohort of 20,000 blood donors in northern India.[52] The highest reported rate is 5.7% in a community based study in almost 2000 people from southern India.[53] Transmission is mostly through childhood horizontal spread due to sub-optimal hygiene and crowded living conditions.

The impact of universal vaccination can clearly be observed in Thailand. Prior to universal vaccination, there was a prevalence rate of 8.2% in blood donors in Thailand.[54] In 2004, twelve years after the initiation of universal vaccination, the prevalence of HBsAg carriers decreased to 4% among the 6213 subjects studied.[55] This trend was also witnessed in a hepatitis B screening program of healthy Thai workers going abroad. In 1996, the annual prevalence in almost 25,000 workers was 6.1%; by 2001, the prevalence had decreased to 2.8%.[56]

HBV in the Western Pacific

The Western Pacific region includes: Australia, Brunei Darussalam, Cambodia, China, Cook Islands, Fiji, Japan, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Mongolia, Nauru, New Zealand, Niue,

Palau, Papua New Guinea, Philippines, South Korea, Samoa, Singapore, Solomon Islands, Tonga, Tuvalu, Vanuatu and Vietnam. The Western Pacific and South-East Asia regions are the largest and most populous of the six WHO regions and have the highest rates of hepatitis B in the world, comprising more than 75% of the world's estimated 350 million carriers.[57]

The prevalence of HBsAg in the Western Pacific region ranges from < 1% to 30%. The prevalence is lowest, about 0.1%, in the non-Aboriginal populations of Australia and New Zealand. The Northern and Central Asian countries have a HBsAg prevalence rate ranging between 7 and 12%.[57] Rates are highest in the small South Pacific island nations, reaching up to 30%.[58,59]

Evidence from China, Taiwan and South Korea demonstrate the importance of universal vaccination. In 1992, the Chinese National Hepatitis Epidemiological Survey determined that the prevalence of HBsAg was 9.8%. The Chinese government first implemented infant vaccination 1992, but parents had to pay for the vaccine, so vaccine coverage was predictably higher in urban and high socioeconomic areas. In 2002, China integrated the HBV vaccine into the national immunization program with a small surcharge to parents. In May 2005, the government then began to provide all infant vaccinations at no charge to parents. In 2009, the age-adjusted prevalence of hepatitis B was found to be 7.2%, but more importantly, the prevalence in children less than age 5 was found to be 1.0%, clearly demonstrating the success of the national immunization program.[60] Similarly, a nationwide HBV vaccination program launched in Taiwan in 1984 has reduced the HBsAg carrier rate in all six-year olds from 10.5% in 1989 to 1.7% in 1999.[61] In South Korea, the HBsAg prevalence rate has decreased from 10% in the 1980s to 3.8% in 2007 in the general population. The rate was found to be even lower at 0.4% in teenagers and 0.2% in children younger than 10 years of age.[62]

Perinatal transmission is widely thought to be the reason for high endemicity in the Western Pacific region. In Taiwan, an overall 30% of HBsAg positive women of childbearing age had positive HBeAg, indicative of active replication.[63] However, a study from China showed that childhood horizontal transmission may be the most important mode of infection, accounting for up to 80% of all HBV infection.[64] Furthermore, a study of rural sites in the Philippines suggests variable patterns of transmission in other parts of Asia. In some villages in the Phillipines, HBsAg seroprevalence peaks in the 2 to 9-year old age group, while other villages have relatively consistent seroprevalence peaking in the 30 to 49-year old age groups, providing evidence for vertical, childhood horizontal and adult horizontal transmission.[65] Regardless of the mode of infection, the Western Pacific region continues to be a highly endemic region of HBV infection with a need for continued prevention and treatment strategies.

Summary

The prevalence of chronic hepatitis B infection is variable throughout the world, ranging from < 1% in areas of low endemism up to 30% in highly endemic areas. There has been an overall decline in the prevalence of the disease due to global infant and childhood vaccination programs, post-exposure prophylaxis and anti-viral therapy. As a result of global vaccination programs, many countries in Asia that once had high rates of HBV infection are now classified as intermediate endemic areas. However, vaccination programs have still not been implemented in all countries, thereby maintaining reservoirs of infection and continued HBV transmission. Global efforts will need to be made in improving infant vaccination programs and in preventing the morbid consequences of hepatitis B infection, such as cirrhosis and hepatocellular carcinoma, with appropriate and affordable anti-viral therapy.

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