

# The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B

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## Abstract

**Background** Chronic infection with hepatitis B virus (HBV) is associated with a high lifetime risk of developing hepatocellular carcinoma (HCC) and cirrhosis of the liver.

**Purpose** To review the studies published to date regarding the association of HBV genotypes and subgenotypes in the development of adverse sequelae from HBV.

**Methods** Review of the literature for articles describing studies of HBV genotype/subgenotypes and development of HCC, cirrhosis, and liver-related death.

**Results** Eight genotypes of HBV (A through H), which differ from each other in viral genome sequence by more than 8%, and multiple subgenotypes, which differ from each other by 4–8% have been identified. Recently, studies investigating the association between the risks of developing HCC and cirrhosis by specific HBV genotypes and subgenotypes have reported marked differences in outcome. Certain HBV genotypes and subgenotypes, including genotype C, B2-5, and F1, appear to be associated with a higher risk of developing HCC, and others, including genotypes B1, B6, and A2, appear to be associated with a lower risk of complications of HBV. Our understanding of the role of HBV genotypes and subgenotypes on the outcome of HBV infection is limited, as few population-based prospective studies have been performed and most studies compare only the outcome in areas where two genotypes predominate whereas others have not examined subgenotypes.

**Conclusions** Studies to date suggest that HBV genotypes/subgenotypes have important influences on the outcome of chronic HBV infection, but more population-based prospective studies examining multiple genotypes are needed.

**Keywords** Hepatitis B virus genotypes · Clinical outcome

## Introduction

Hepatitis B virus (HBV) is one of the most common chronic viral infections in the world. More than 400 million persons are chronically infected with HBV and at risk of developing hepatocellular carcinoma (HCC) and cirrhosis [1]. However, the incidence rates of developing HCC and cirrhosis vary widely around the world. Several factors have been identified that could influence the rate of these severe complications resulting from HBV infection. These include sex (with higher rates of HCC found in men than women), geographic area (with higher rates found in eastern and southeast Asia and sub-Saharan Africa than in other endemic areas), environmental factors such as the presence of aflatoxin on food stuffs, the age at infection (with perinatal infection appearing to have a higher risk of HCC than infection later in life), ethnicity, heavy use of alcohol, and smoking [2].

Several viral factors appear to strongly influence outcome in HBV infection including HBV genotype, DNA levels over time, and specific HBV viral mutations. Since HBV in immune-competent persons is not ordinarily pathogenic, it is the host's immune response to the virus that determines the extent of liver inflammation and fibrosis. However, because the virus's polymerase has reverse transcriptase properties, HBV DNA integrates

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randomly into the host's liver cell DNA throughout the course of infection. Thus, it is likely that this property of the virus independently contributes to the development of HCC. Also, liver damage that occurs leads to more rapid hepatocyte cell turnover, which may be a contributing factor to the development of HCC. The purpose of this article is to review the data available on the association of specific HBV genotypes and subgenotypes with clinical outcome of HBV. The article also discusses the role of HBV DNA levels and specific viral mutations in the context of HBV genotypes. Unfortunately, there is insufficient data available to understand the precise role of HBV genotype in liver disease progression. While some prospective population-based studies are available, many studies may suffer from biases due to the fact that they come from referral centers where patients likely have, on average, more severe liver disease than would be seen in those infected with HBV from the general population. Nevertheless, it is worth to review the existing data found in the literature on the association of HBV genotype with progression of liver disease and use these available studies to discuss what further investigations are needed to learn more about these associations.

### HBV genotypes and subgenotypes

Eight genotypes of HBV worldwide have been identified. When sequencing the entire viral genome, these genotypes differ from each other by more than 8% [3–7]. In addition, multiple subgenotypes have been and are continued to be identified, which differ from each other by 4–8%. The HBV genotypes identified to date are A, B, C, D, E, F, G, and H. Subgenotypes for each genotype have been labeled by using the nomenclature 1, 2, 3, etc. Genotype A is divided into A1, found in sub-Saharan Africa, A2, in Northern Europe, and A3 in Western Africa. The subgenotypes of HBV genotype B have been divided into two major groups: those found to be “pure” genotype B including B1 (formerly called Bj or B Japan) and B6, and those subgenotypes that have a recombination of part of the core region of HBV genotype C onto the genotype B core area including B2, B3, B4, and B5 (formerly called Ba or B Asia). Genotype B1 is found in Japan, B2–5 are found in East Asia, and B6, the newest identified B genotype, is found in indigenous populations living in the Arctic. Genotype C is divided into C1, C2, and C3 and is found in China, Korea, Southeast Asia, and in several South Pacific Island countries. Genotype D is widely spread across Eastern Europe, the Mediterranean region, including North Africa, Russia, the Middle East, the Indian subcontinent, and across the Arctic. Genotype E is found in West Africa. HBV genotype G has been found only in small areas of the

world, in the United States, Vietnam, and Southern Europe, and appears primarily to be present as a coinfection with another HBV genotype, most commonly genotype A. Genotypes F and H are the “New World” genotypes found in indigenous populations in Alaska and Central and South America. Genotype F is divided into 4 subgenotypes: F1–F4. Genotype H is very closely related to genotype F and was initially thought to be a clade of genotype F. In the 48 contiguous US states, genotypes A2, B, C, and D are more commonly found, with immigrants born in endemic areas reflecting the HBV genotype of their country of origin [8].

### HBV genotype, the mode of transmission of HBV, and the risk of developing chronic infection

Three major patterns of transmission of HBV have been observed. Each pattern is associated with a different risk of developing chronic HBV infection. Perinatal infection, which usually occurs at the time of delivery, is seen primarily in East and Southeast Asia. The risk of perinatal transmission of HBV is highest when the infant's mother is hepatitis B surface antigen (HBsAg) positive and hepatitis B “e” antigen positive (HBeAg). When the mother is HBeAg positive, infants infected at birth have virtually a 100% risk of acquiring HBV and a 90% risk of developing chronic HBV infection if hepatitis B vaccine and hepatitis B immunoglobulin are not administered shortly after birth [9, 10]. In contrast, when the mother is HBeAg negative and antibody to HBeAg (anti-HBe) positive, the infant has a less than 25% risk of acquiring HBV and only 10–15% of becoming chronically infected [9, 10]. Children in areas where HBV is endemic can become infected by inadvertent horizontal transmission of HBV thought to occur through open cuts and scratches. The risk of developing chronic HBV infection after horizontal transmission is between 30% and 50% for children infected between birth and 5 years of age but only 7–10% thereafter [11, 12]. A third mode of transmission also occurs horizontally either by sexual transmission or by needlestick transmission; the latter from illicit drug use or inoculations from inadequately sterilized needles and infection from medical procedures in which inadequate precautions to prevent transmission of bloodborne diseases have not been carried out [13]. The risk of becoming chronically infected in these circumstances is believed to be about 10% [12, 13].

It has been unclear why vertical transmission is common in some areas of the world such as Asia and horizontal transmission in children is the dominant mode in other parts of the world such as the Mediterranean region, Eastern Europe, Alaska, and sub-Saharan Africa. The age at which seroconversion from HBeAg to anti-HBe occurs in infected persons appears to be a key determinant in whether HBV is

transmitted at or after birth. When persons are HBeAg positive, they have very high levels of HBV DNA, from  $10^5$  to  $10^{10}$  copies/ml in their sera, whereas after HBeAg seroconversion, HBV DNA levels may fall below  $10^4$  copies/ml in the sera of most persons. If HBV seroconversion occurs early in a woman's life, the chances of perinatal transmission decrease dramatically. It has been shown that at least 50% of women in Eastern and Southeast Asia, where perinatal transmission is common, are HBeAg positive at the time of delivery in comparison with less than 15% in Africa and southwest Alaska, where perinatal transmission is uncommon [9, 10, 14]. A recent study from Alaska, where five of the eight HBV genotypes are present, has shed light on this mystery. While horizontal transmission of HBV in early childhood is common in southwest Alaska, perinatal transmission is frequent in northwest Alaska. In both areas, the population is composed of Alaska Native Peoples of Eskimo (Yupik and Inupiat) origin. Genotype C is the dominant genotype in northwest Alaska and genotypes A2, B6, D, and F1 are the dominant genotypes in southwest Alaska, where genotype C is rare. In this population, testing for HBeAg and anti-HBe was performed at least once yearly for 21 years and HBV genotype testing was subsequently performed on 1,158 of 1,560 HBsAg chronically infected persons. The results were used to determine the age at which HBeAg seroconversion occurred. Table 1 shows that the age at which 50% of HBeAg-positive persons cleared HBeAg was less than 20 years for those infected with genotypes A2, B6, D, and F1, but approximately 3 decades later for those infected with genotype C [15]. This shows that most women infected with genotype C would likely be HBeAg positive throughout their childbearing years, whereas women infected with the other genotypes would be likely to be anti-HBe positive. This suggests that in those areas of the world where perinatal transmission plays a major role in the transmission of HBV, genotype C is likely to predominate.

### The relationship of HBV genotype with the development of liver disease

Many studies have been published regarding the relationship between HBV genotype and serious sequelae of HBV

including cirrhosis and HCC. Most studies have been conducted in East Asia among persons infected with HBV genotypes B and C. Unfortunately, few studies are available examining other HBV genotypes for associations with adverse outcomes. Most of these studies are descriptive in nature or compare one HBV genotype to another, and few are prospective in design. Therefore, the findings of the studies regarding liver disease outcome for each one of the HBV genotypes have been summarized.

### HBV genotype A and disease outcome

Three subgenotypes of genotype A have been identified: A1–A3. The classical precore (PC) mutation, located at HBV nucleotide 1896 consisting of a G-A substitution that creates a stop codon, is not found in genotype A. Genotype A (and F2) contains a cytosine at position 1858 instead of a uracil, which is found in most other genotypes. The presence of a cytosine at position 1858 stabilizes the PC loop, not allowing the 1896 G-A PC mutation to occur. Genotype A1 has been associated with very high rates of HCC in sub-Saharan Africa [16–18]. In this part of Africa, especially in the western and southern portions, HBV genotype A1 predominates [17]. In South Africa, HCC occurs in younger men who are anti-HBe positive and often do not have accompanying cirrhosis. In a case-control study of HBsAg-positive Africans, a 4.5-fold increased risk of HCC was found in those infected with genotype A versus those infected with other HBV genotypes [16].

Genotype A2 is found in northern Europe, the United States, and the Arctic, including Alaska and Greenland [3, 8, 19, 20]. In comparison with genotype A1, liver cancer associated with A2 is found primarily in older individuals. In addition, the rate of complications, including HCC, for those infected with genotype A2 appears to be less than that found in those infected with genotype D, C, or F1 [21, 22]. A prospective study from Spain showed that genotype A (presumably A2) infection was associated with a significantly higher cumulative rate of sustained biochemical remission, HBV DNA clearance, and HBsAg clearance in patients with chronic HBV infection than genotype D infection [22]. Genotype A3 is found in West Africa [23]. Unfortunately, little is known about the

**Table 1** Age in years of the 50th and 75th percentiles of Alaskan Natives at the time of clearance of HBeAg by HBV genotype<sup>a</sup>

Genotype/ subgenotype	Number of patients	Age (years) at HBeAg clearance: 50th percentile	Age (years) at HBeAg clearance: 75th percentile
A2	34	19.4	32.1
B6	6	19.5	27.5
C2	36	47.8	58.1
D	305	18.0	27.3
F1	126	16.1	24.5

<sup>a</sup> Modified from Livingston et al. [15]

clinical outcome of persons infected with A3; other than that, HCC is a common occurrence in this area (Table 2).

### HBV genotype B

Genotype B is divided into two major groups. One group, formerly called Bj for B Japan, is a “pure” strain of genotype B, whereas the other, Ba or B Asia, contains a portion of the genome of genotype C recombined into the core region of genotype B [6]. Genotype Bj consists of two subgenotypes, B1 and B6. Genotype B1 is the original “Bj” subtype, found in Japan. Genotype B6 is a new genotype recently found in the Arctic region in indigenous populations of Alaska, Canada, and Greenland [24]. While B6 is phylogenetically related to B1, and may have originated from Japan, it is distant enough that this subgenotype is likely many centuries removed from Japan [24]. Genotype Ba consists of four distinct subtypes, B2 (China), B3 (Indonesia), B4 (Vietnam), and B5 (Philippines). HBeAg has been found significantly more frequently in persons infected with Ba than B1 [25, 26]. In fact, in persons older than 30 years, 32% vs. 9% of those infected with Ba were HBeAg positive than those infected with B1, implying that seroconversion from HBeAg to anti-HBe likely occurs at a younger age in those infected with B1 [26]. In addition, the basal core promoter (BCP) mutation, a double mutation (T1762/A1764) that has been associated with a higher risk of HCC and more severe liver disease, has been found more frequently in Ba strains than B1 [26]. In contrast, acute and fulminant hepatitis has been more frequently associated with B1 [27] (Table 3).

### HBV genotype C

HBV genotype C is found throughout the eastern and southeastern portions of Asia and the Pacific islands (Micronesia, Melanesia, and Polynesia), as well as in

immigrants from these areas in the United States, Europe, Australia, and New Zealand [6–8]. More studies have been published about genotype C than any other HBV genotype. The majority of the studies compare the disease manifestations in persons infected with genotype C in comparison with those found in persons infected with genotype B [28, 29]. Most of the published studies are cross-sectional and clinic-based. These studies can suffer from referral bias, since a higher proportion of patients with advanced disease are seen in hepatology clinics, and selection bias, a problem with all studies that are not population-based share. However, a few important population-based prospective studies have been published. Multiple cross-sectional studies have almost universally shown that patients with genotype C experience HBeAg seroconversion at an older age and are more likely to be HBeAg positive at any given age than HBV genotype B [30–32]. In most cross-sectional studies, HBV genotype C is associated with an increase risk of liver inflammation, flares of hepatitis, liver fibrosis, and cirrhosis [30, 31, 33].

Several cross-sectional studies have been conducted examining the association of genotypes C and B with HCC. In most of the studies, genotype C has been associated with an increased risk of HCC [34–36]. In two of these studies, genotype C-associated HCC occurred in significantly younger persons (<50 years) and genotype B HCC was found primarily in persons older than 60 years [35, 36]. In one of these cross-sectional studies, the overall risk of HCC was not shown to be different between HBV genotypes B and C, but risk of HCC in genotype C occurred at a younger age [36]. The BCP mutation was found to be independently associated with presence of HCC [21, 33, 37] and occurred more frequently in HBV genotype C [33]. In patients infected with HBV genotype B or C, the relationship between PC and HCC was less clear [21, 33].

Fortunately, several prospective studies compared the outcome in those infected with genotypes B and C and bolster the findings of the cross-sectional studies. These studies included between 90 and 4,841 patients followed up

**Table 2** Liver disease associated with HBV genotype A

Subgenotype	Geographic location	Liver disease association
A1	Sub-Saharan Africa	HCC in young males
A2	Northern Europe, United States, the Arctic	HCC and cirrhosis in older persons
A3	West Africa	Not studied

**Table 3** Liver disease associated with HBV genotype B

Subgenotype	Geographic location	Liver disease association
B1	Japan	HCC and cirrhosis in older persons
B2–5	China, Indonesia, Vietnam, Philippines	HCC and cirrhosis occur at younger age than B1
B6	Alaska, Northern Canada, Greenland	No serious sequelae identified to date

for up to 14 years [33, 38–42]. They confirmed that HBeAg seroconversion occurred at a significantly younger age for those infected with genotype B than genotype C [15, 38, 40, 42] and that increased risk of fibrosis was associated with genotype C [39, 40]. The two largest studies, consisting of 426 and 4,841 patients followed up for a mean of 4.8 and 14 years, respectively, showed a significant increase in risk for HCC in genotype C in comparison with genotype B [33, 38–42]. Two smaller studies did not find any difference [39, 42]. Taken together, the majority of the cross-sectional and the largest prospective studies with the longest follow-up show that persons infected with HBV genotype C seroconvert from HBeAg later in life and have an increased risk of liver inflammation, liver fibrosis, and HCC.

Increased HBV viral level in several prospective studies in Asia has been shown to be associated with an increased risk of both cirrhosis and HCC [43–45]. In one of these studies, infection with genotype C was also found to be an independent risk factor for the development of HCC [45]. These studies suggest that genotype C might be the most deadly of the HBV genotypes, and there are two possible explanations for this finding. First, persons infected with HBV genotype C clearly have higher levels of HBV DNA, as evidenced by prolonged HBeAg positivity, than those infected with genotypes A1, A2, B1–6, D, and F1. Those infected with genotype C experience prolonged viremia throughout much of their lives, which means more time for HBV integration to occur and more opportunity for liver inflammation and fibrosis. Second, certain mutations such as the BCP mutation, which independently may be associated with higher risk of HCC, appear to occur more frequently in those infected with genotype C.

Within HBV genotype C, there is not much information regarding differences between subgenotypes and disease

outcome. However, a recent prospective study from Hong Kong of 1,006 patients with chronic HBV infection followed up for a median of 7.7 years showed that the highest risk of developing HCC was in persons infected with HBV genotype C2 (Ce) and the next highest in C1 (Cs) than those infected with genotype B (presumably Ba) [45]. However, more studies comparing the risk of HCC among HBV subtypes of genotype C are needed (Table 4).

### HBV genotype D

HBV genotype D is distributed widely throughout the Middle East, Eastern Europe, Russia, Northern Asia, and the Mediterranean region, including southern Europe and North Africa located above the Sahara desert. It is also commonly found in the United States as well as in indigenous populations of the Arctic (Alaska and Greenland). Persons infected with genotype D usually convert from HBeAg to anti-HBe in adolescence or early adulthood. The PC mutant is frequently associated with HBV seroconversion in this genotype [46]. While it appears that many persons go into and remain in the inactive carrier phase [47, 48], some persons develop HBeAg-negative/anti-HBe-positive chronic hepatitis B. This can lead to cirrhosis and HCC [48–51]. In an acute liver failure study in the United States, genotype D was found to be an independent risk factor for fulminant hepatitis [52]. A study from India reported that genotype D was associated with more severe liver disease and HCC in younger patients than genotype A [53]. A study from Alaska showed that genotype D was significantly associated with HBV-associated vasculitis (polyarteritis nodosa) in comparison with genotypes A2, B6, C2, and F1 [54] (Table 5).

**Table 4** Liver disease associated with HBV genotype C

Subgenotype	Geographic location	Liver disease association
C1	Vietnam, Thailand, Myanmar	High rates of HCC
C2	China, Korea, Japan	Increased risk of HCC and cirrhosis in comparison with genotype B: all subgenotypes
C3	Pacific Islands (Micronesia, Melanesia, and Polynesia)	Not studied

**Table 5** Liver disease associated with HBV genotype D

Subgenotype	Geographic location	Liver disease association
D1	Europe, Middle East, Egypt, India, Asia	HBeAg-negative chronic hepatitis and cirrhosis <sup>a</sup>
D2	Europe, Japan	HBeAg-negative chronic hepatitis and cirrhosis <sup>a</sup>
D3	Europe, Asia, South Africa, United States	HBeAg-negative chronic hepatitis and cirrhosis <sup>a</sup>
D4	Australia, Japan, Papua New Guinea	Not studied

<sup>a</sup> Studies from Europe on HBeAg-negative hepatitis have not delineated which subgenotypes are associated with this finding

## HBV genotypes E and G

HBV genotype E is found throughout the West Africa and into Central Africa. This genotype is characterized by a low genetic diversity among strains from throughout this region of the world [55–57]. Both PC and BCP mutations are found commonly in persons infected with genotype E [55]. Other than that, nothing is known about the influence of this genotype on disease outcome.

Genotype G is the most uncommon of all HBV genotypes. Genotype G has been found in France and the United States in only a few patients [58]. This genotype is almost exclusively found in persons coinfecting with another HBV genotype, most commonly genotype A [59]. The only exception is a single report of a transfusion-associated case [60]. One possible explanation for this finding was found in an experimental model of combined immunodeficient mice carrying human hepatocytes, which suggested that HBV genotype G may have difficulty establishing an infection without another HBV genotype present. When these animals were monoinfected with genotype G alone, HBV replicated poorly and did not produce HBV DNA in the sera. However, when these mice were subsequently superinfected with HBV genotype A, genotype A began to replicate but was rapidly replaced by genotype G [61]. In a study from France of 104 patients coinfecting with HBV and HIV, 25 of 73 patients with genotype A were coinfecting with genotype G. Presence of HBV genotype G was an independent risk factor for fibrosis score. No other articles describing an association of genotype G with outcome were found in the literature [62].

## HBV genotypes F and H

HBV genotypes F and H are the “New World” genotypes found primarily in indigenous population of North and South America [63]. Genotype F is divided into four subtypes: F1–F4 [64].

Genotype F2 codes for C at position 1858 and therefore PC mutation does not occur, whereas F1 does not and thus PC mutation can occur [7]. There is very little data on clinical outcome in those infected with HBV genotype F. In a prospective study of 258 Spanish patients followed for a mean of 94 months that included both interferon-treated and untreated patients, those infected with genotype F (subgenotype not stated) were reported to have lower cumulative probability of sustained biochemical remission and HBV DNA loss and a significantly higher cumulative liver-related death rate than those infected with genotype D or A [22]. In a nested case-control study of a cohort of 1,176 Alaskan Natives with chronic HBV infection followed up for 20 years, a significantly higher proportion of

persons infected with either genotype F1 or genotype C2 developed HCC than those infected with genotype A2, B6, or D [21]. Furthermore, in this study, the median age of patients at diagnosis of HCC for those infected with HBV genotype F was significantly lower than those infected with genotype A2, C2, or D (22.5 years vs. 60 years). In addition, BCP mutations were negatively associated with HCC in Alaskan Natives infected with genotype F compared with age- and sex-matched persons infected with genotype F without HCC. In controls, there was a positive association of BCP mutations in those infected with genotype A2, C2, or D who developed HCC. This suggests that genotype F might affect the development of HCC through a different molecular mechanism than other HBV genotypes, such as A2, B, C, and D. Finally, a study from Venezuela found that outbreaks of fulminant hepatitis were associated with coinfection with HBV genotype F and hepatitis delta virus (HDV), but it is not clear whether both viruses together play a role or this severe outcome is due primarily to the HDV [65].

HBV genotype H is found in Central America, primarily Mexico and Nicaragua [66]. It has also been found in immigrants from this region to the United States, especially in California [67]. Genotype H is most closely related to genotype F and likely evolved from this genotype after it established itself in the New World, although its complete genome differs by more than 8% and thus is a separate genotype [67]. There are no reports of the relationship of HBV genotype H to disease outcome in HBV (Table 6).

## Recombinant HBV genotypes and coinfection with more than one HBV genotype

Recombinations between a part of the genome of one HBV genotype into the genome of another HBV genotype are probably common and have been reported in most HBV genotypes [5, 7, 68]. However, there is little information about the clinical outcome of these recombinations with the exception of the recombination of a portion of the genotype C core gene region to genotype B, which occurs in subtypes B2–5 (described in detail earlier). Coinfection with more than one HBV genotype may also be a more common occurrence than was previously thought [5, 68]. One large study of a convenience sample of 375 Vietnamese, 38 European, and 47 African HBV-infected persons found HBV genotype admixtures in 29.8% of Africans, 15.7% of Asians, and 13.2% of Europeans [69]. Among the Asian patients from Vietnam, significantly higher associations were found between mixed genotype infections and acute hepatitis B, liver cirrhosis, and HCC. However, there were 15 different admixtures (A/C, A/D, A/G, C/D, C/G, and D/G, and 9 others), making it impossible to identify which

**Table 6** Liver disease associated with HBV genotypes E, F, G, and H

Genotype/subgenotype	Geographic location	Liver disease association
E	West Africa	Not studied
F1	Alaska, Argentina, Bolivia	HCC in young patients in Alaska
F2	Venezuela, Brazil	Fulminant hepatitis with HDV coinfection
F3	Venezuela, Columbia, Panama	Fulminant hepatitis with HDV coinfection
F4	Argentina	Not studied
G	France, United States, Vietnam	Usually found in coinfection with genotype A; increased association with acute hepatitis, liver fibrosis, and HCC in Vietnam
H	Mexico, Nicaragua, California	Not studied

specific combinations, if any, are associated with more severe liver disease.

### Areas for future research in the relationship of HBV genotypes and subgenotypes with disease outcome

While it is clear that HBV genotypes and subgenotypes play an important role in the outcome of chronic HBV infection, more research is needed to define specific relationships between individual genotypes/subgenotypes and risk for development of cirrhosis and HCC. Ideally, these investigations should be population-based studies that compare persons with different genotypes, conducted prospectively over a long period of time to precisely identify the risk of sequelae associated with each genotype and subgenotype, such as have been done in Asia and Alaska [15, 21, 33, 38–42]. At this time, several HBV genotypes and subgenotypes, such as genotypes A1 and D, that have been associated with increased risk of cirrhosis and HCC in cross-sectional studies have not been evaluated in prospective longitudinal studies. Furthermore, there are many genotypes and subgenotypes, including A3, E, F4, and H, for which we have no data whatsoever regarding clinical outcome. Prospective longitudinal studies are best conducted through collaboration among multiple institutions in several countries. In addition, molecular investigations of sequences, both cross-sectional and prospective, need to be conducted. These studies should examine full genome sequences of genotype and subgenotype isolates from patients with and without serious complications. These investigations should search for specific mutations that might be significantly associated with the development of HCC and advanced liver fibrosis. Identification of viral mutations that increase the risk of severe sequelae could help identify patients who might benefit from earlier intervention with antiviral medications and increased surveillance for HCC. Finally, since the immune response to HBV determines the amount of liver damage that results, studies should be undertaken to evaluate genotype- and

subgenotype-specific peptides that are exhibited and the immune response to these specific peptides such as cytotoxic T cells and regulator cells.

In conclusion, the evidence available strongly suggests that HBV genotype and subgenotype are strong factors in predicting outcome of chronic HBV infection. On the basis of available studies, we might conclude from studies to date that HBV genotypes A1, C, B2–5, F1, and perhaps D are associated with an increased risk of developing serious complications of HBV in comparison with genotypes A2, B1, and B6. However, further prospective epidemiology studies, as well as molecular examinations of full HBV genome sequences and host immune response studies to genotype-specific peptides, are needed to define these relationships. A better understanding of the role of HBV genotypes and subgenotypes could lead to early intervention with antiviral therapy in those identified to be at the highest risk of developing advanced liver fibrosis and HCC.

**Disclaimer** The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Alaska Native Tribal Health Consortium.

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