3 Epidemiology of Viral Hepatitis B, C, and D: A Global View

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Abstract

Viral hepatitis constitutes a great burden of public health in the world. In 2016, the World Health Assembly approved a global strategy to achieve elimination of this threat by 2030. To achieve this goal, countries and regions need to reduce incidence and mortality by 90% and 65%, respectively, by 2030. Five strategic directions have been proposed, with understanding the epidemiology of viral hepatitis being the first step toward elimination. Hepatitis B and C are responsible for 96% of all hepatitis mortality. Hepatitis D is an important cofactor of hepatitis B virus infection.

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The World Health Assembly adopted the first *Global Health Sector Strategy on Viral Hepatitis, 2016–2021* in 2016, which has a vision of eliminating viral hepatitis as a public health problem. The targets for the year 2020 include a 30% reduction in new cases of chronic viral hepatitis B and C infections and a 10% reduction in viral hepatitis B deaths. By 2030 the global targets are to reduce new viral hepatitis infections by 90% and reduce mortality due to viral hepatitis by 65% (Fig. 3.1).

To achieve the 2030 goals, five strategic directions are proposed. These strategic directions include (1) information for focused action (what is the situation); (2) interventions for impact (what service should be delivered); (3) delivering for equity (how can these services be delivered); (4) financing for sustainability (how can the costs of delivering the package of services be met); and (5) innovation for acceleration (how can the trajectory of the response be changed). This strategy helps outline the priority actions to be taken by countries and by the World Health Organization (WHO), with respect to region-specific hepatitis epidemics, national priorities, and country contexts and taking national policies, jurisdiction, and legislation into consideration.

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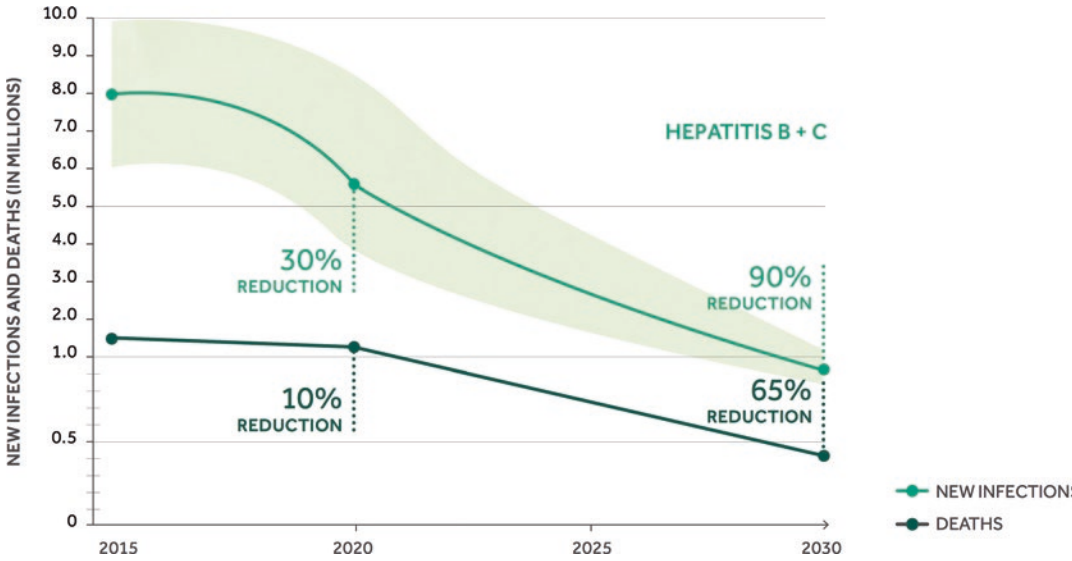

Fig. 3.1 World Health Organization (WHO) targets for reducing new cases of and deaths from chronic viral hepatitis B and C infection. (From WHO, global health sector strategy on viral hepatitis 2016–2021, June 2016)

Understanding the epidemiology of viral hepatitis is the first step toward elimination. A total of five hepatitis viruses have been identified, referred to as types A, B, C, D, and E, which caused 1.34 million deaths in the human population in 2015. The five hepatitis viruses are distinct with regard to modes of transmission, populations affected, and health outcomes (Fig. 3.2). Hepatitis A and E are typically caused by ingestion of contaminated food or water. Hepatitis B, C, and D usually occur as a result of parenteral contact with infected body fluids. All the hepatitis viruses can cause acute hepatitis, while only hepatitis B, C, and D viruses cause chronic hepatitis, which may progress to cirrhosis and primary liver cancer. Hepatitis B and C are of greatest concern as they are responsible for 96% of all hepatitis mortality. This chapter focuses on the epidemiology and global view of hepatitis B, C, and D.

3.1 Epidemiology and Global View of Hepatitis B

Hepatitis B virus (HBV) infection is a severe global health issue due to its geographically widespread distribution and its potential to cause advanced liver diseases such as cirrhosis and hepatocellular carcinoma (HCC). Understanding of the epidemiology and the natural history of HBV infection is necessary for disease prevention and intervention.

3.1.1 Global Distribution of HBV Infection

Worldwide estimates suggest that more than 2 billion people have been infected with HBV, and among them, 248 million are suffering from chronic HBV (CHB) infection, which is defined as being hepatitis B surface antigen (HBsAg)

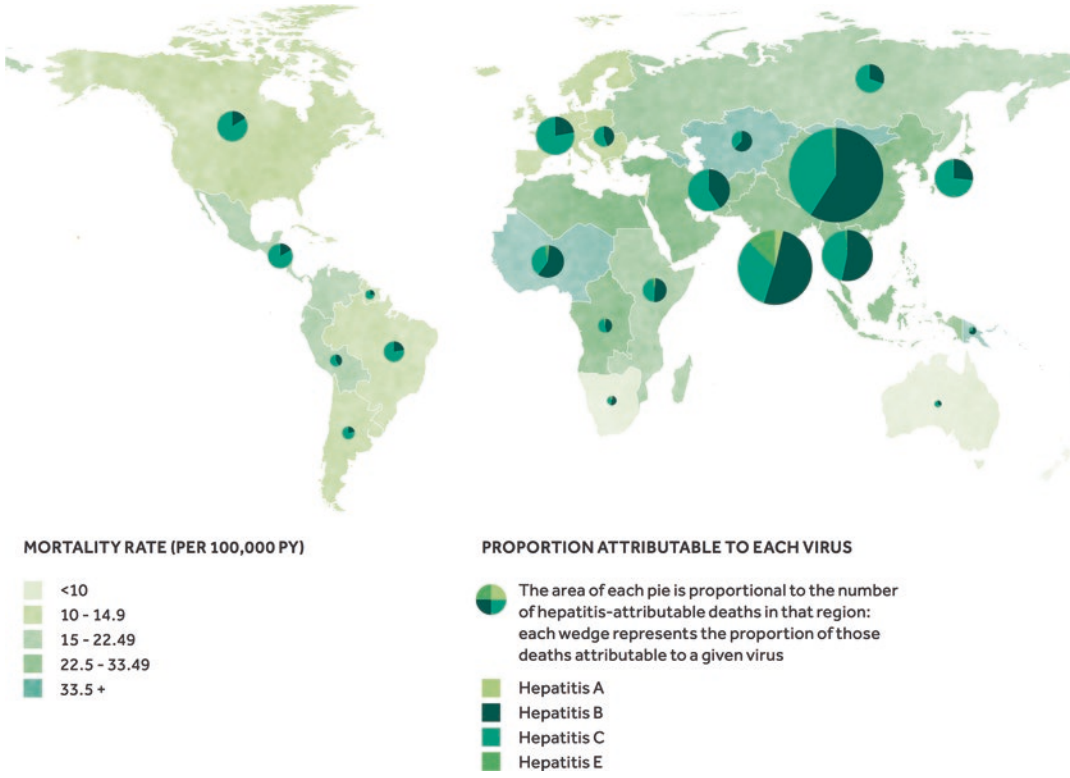

Fig. 3.2 Regional distribution of deaths from viral hepatitis. (From WHO, global health sector strategy on viral hepatitis 2016–2021, June 2016)

positive [1]. Globally, CHB infection accounts for approximately 30% of all cirrhosis and 53% of all HCC cases, [2] and 15–25% of CHB patients eventually die from these two advanced diseases [1]. In addition, it has been estimated that 600,000 deaths per year can be attributed to HBV infection [3].

The worldwide prevalence of HBsAg positivity is estimated to be 3.61% [1]. However, the prevalence varies greatly from one WHO region to another (Fig. 3.3). The highest prevalence can be found in most African (especially Sub-Saharan Africa), Western Pacific (including China, Taiwan, and most Pacific Islands), and Southeastern Asian regions, where the prevalence is as high as 8–15%. About 45% of HBV-infected individuals reside in these regions, and their lifetime risk of infection is more than 60%. The prevalence of HBsAg positivity is moderate in Eastern Mediterranean (including South-Central and Southwestern Asia), European (Southern and Eastern regions), and American (Central and Southern) regions, where prevalence rates range from 2% to 7%. Forty-three percent of HBV-infected individuals live in these regions, and their lifetime risk of infection is between 20% and 60%. The remaining 12% of HBV-infected individuals are located in low-prevalence areas, where the prevalence is less than 2%, and their lifetime risk of infection is less than 20%. These low-prevalence areas include the United States, Western Europe, and Australia [1, 4–6].

Over time, there has been an overall decrease in the prevalence of HBsAg positivity in most WHO regions and countries [4]. The Eastern Mediterranean region has seen a strong decrease in prevalence, while Eastern and Western Europe show stable high and low prevalences, respectively. Meanwhile,

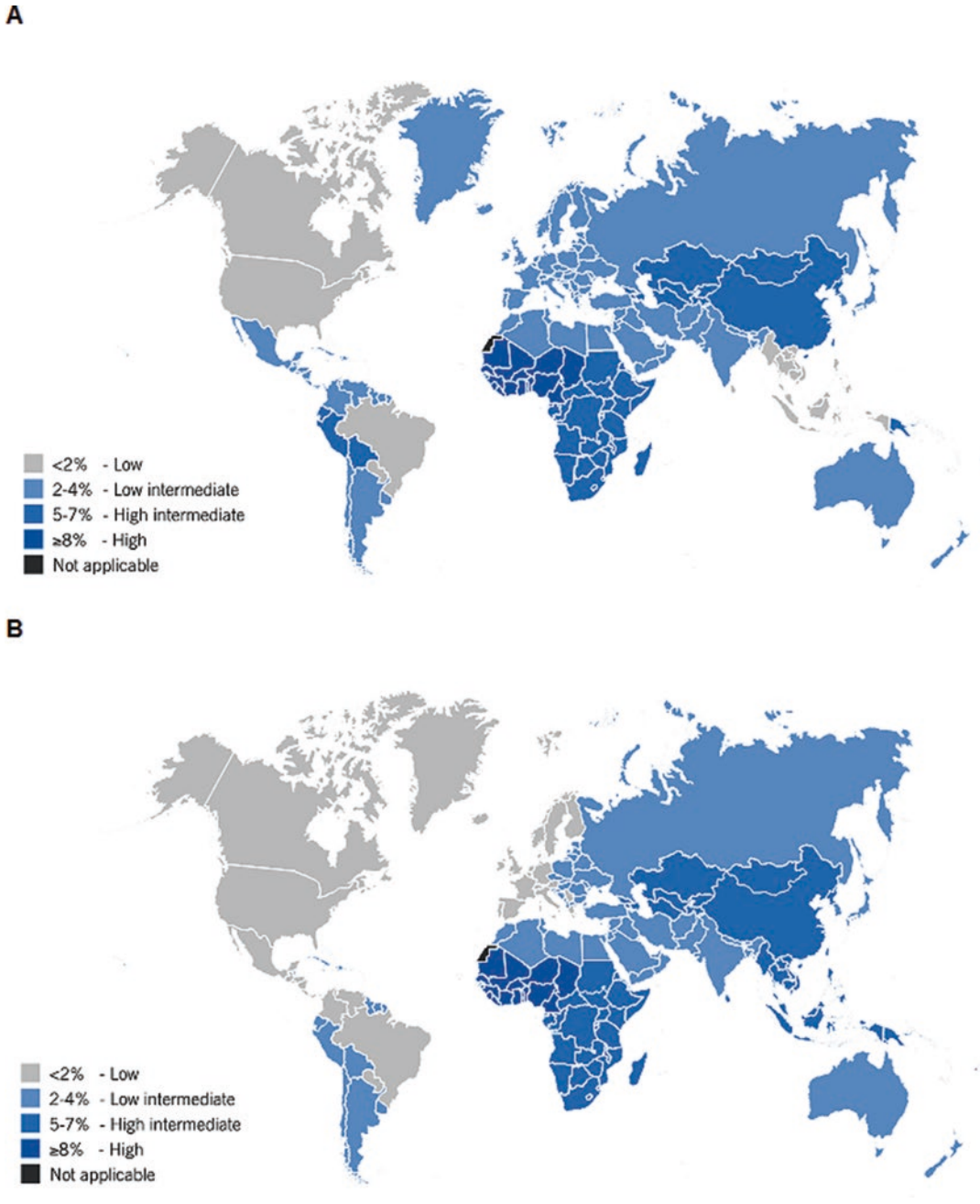

Fig. 3.3 Prevalence of chronic hepatitis B infection (**a**) in children 5–9 years old and (**b**) in adults 19–49 years old in 2005. (From WHO, guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection, March 2015)

Southeastern Asian and Western Pacific regions have seen low to medium reductions in prevalence, with the most prominent reductions occurring in China and Malaysia [1, 7]. However, there has been a notable increase in prevalence in African and Eastern European regions [1].

3.1.2 Global Distribution of HBV Genotypes

Due to the lack of a proofreading function in the HBV reverse transcriptase, transcription errors occur during viral replication, which result in different HBV genotypes, subgenotypes, mutants, and recombinants. To date, ten HBV genotypes, which are dispersed across different geographical regions, have been identified [8]. Genotype A is commonly found in Western and Sub-Saharan Africa, Northern and Northwestern Europe, North America, and India. Genotypes B and C are endemic to Asian regions. Genotype D is widespread in Africa, Eastern Europe, Mediterranean countries, the Middle East, Central Asia, and India. Genotype E is prevalent in Western Africa, while genotypes F and H are common in South and Central America. Genotype G is most predominant in France, Germany, Mexico, and the United States. Recently, genotype I was reported in Vietnam and Laos, and genotype J was identified on Japan's Ryukyu Islands [5, 6, 8–13].

In addition to different geographical distributions, HBV genotypes also have different impacts on disease and clinical progression, response to antiviral treatment, and prognosis [8]. Several studies have shown that HBV genotypes A and D have higher rates of progression from acute to chronic infection than genotypes B and C and that genotype A is significantly associated with chronicity [10, 14]. In Asian regions, it was reported that the rate of chronicity was higher in genotype B than in genotype C [15]. A Taiwanese study showed that the spontaneous HBV e antigen (HBeAg) seroconversion rate is higher in genotype B than in genotype C [16]. Regarding response rates to interferon treatment, they have been reported to be greater for genotypes A and B than for genotypes C and D, while genotype E is the most difficult to treat [17, 18]. For severe liver diseases, genotype C is widely accepted to be associated with higher risks of cirrhosis and HCC [19].

3.1.3 Transmission Routes and Risk of Chronic HBV Infection

There are two major routes of HBV transmission. Perinatal transmission, in which HBV is passed from infected mothers to their newborns, accounts for the majority of worldwide transmissions. It has been reported that 85% of infants born to HBeAg-seropositive mothers as well as mothers with high viral loads became chronically infected, while 32% of those born to HBeAg-seronegative mothers became chronically infected [20]. Another route of HBV transmission is horizontal transmission, which occurs through open wounds or scratches, blood transfusions, unprotected sexual contact, or risky behaviors such as sharing of unsterilized needles, tattooing, and body piercing during childhood or adulthood [4]. It has been widely reported that the probability of becoming chronically infected increases with decreasing age of first infection. Up to 90% of individuals with perinatal infections become chronically infected, while approximately 20–60% of individuals infected during early childhood become chronic carriers, and only 5–10% of infected adults become chronic carriers [21, 22]. Therefore, in endemic regions, 40–50% of chronic HBV infection originates from perinatal transmission. In areas with moderate endemicity, chronic HBV infection is usually caused by transmission during early childhood. In areas with low HBV prevalence, however, chronic HBV infection is typically acquired through transmission during adulthood [6, 23, 24].

3.1.4 Long-Term Consequences of Hepatitis B Virus Infection

Infection with the hepatitis B virus is a particularly serious threat to global public health, due to its widespread geographical distribution and its potential for serious clinical consequences such as cirrhosis, HCC, and liver-related death [24–26]. In addition, based on the comprehensive assessment of both epidemiological and mechanistic

evidence, the International Agency for Research on Cancer (IARC) has notably also classified the HBV as a Group 1 human carcinogen with sufficient evidence to prove its causation of HCC [27]. In a landmark study of 22,707 Taiwanese men, men that were seropositive for HBsAg had a 223-fold increased risk of developing HCC, compared to non-infected men [25, 28]. Among individuals that are chronically infected with HBV, however, results from long-term prospective studies have shown that the progression of hepatitis B infection toward long-term clinical consequences is typically characterized by interactions between crucial viral, environmental, and host factors [29–32].

3.1.4.1 Cirrhosis

Specifically, risk factors that have been shown to affect progression of HBV-infected individuals to cirrhosis include age, male sex, viral genotypes, HBeAg serostatus, HBV DNA, HBsAg levels in the serum, and ALT levels [30, 31, 33, 34]. Studies from the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HBV (REVEAL-HBV) study and other long-term prospective studies have shown that HBV DNA levels are a major driver of disease progression. Specifically, the risk for cirrhosis has been shown to increase with higher HBV DNA levels among HBV carriers, even after adjustment for age, sex, and other viral factors and stratification by sex, alcohol consumption, and cigarette smoking [33]. More recently, prediction models incorporating quantitative HBsAg levels have also been able to increase prediction accuracy for cirrhosis [31].

3.1.4.2 HCC

Many studies have examined cofactors of HBV-related HCC. Viral factors shown to affect progression to HCC include age, male sex, viral genotypes, HBeAg serostatus, HBV DNA, HBsAg levels in the serum, and seroclearance of HBeAg, HBV DNA, and HBsAg [29–32, 35–37]. An early study of individuals with chronic hepatitis B found that HBeAg seropositivity was associated with significantly increased risk for HCC, implying that active viral replication was a relevant determinant for HCC [37]. In a later landmark study, this was confirmed when a strong biological gradient of HCC risk was observed across serum HBV DNA levels. The corresponding relative risks with 95% confidence intervals were 1.0 (referent), 1.1 (0.5–2.3), 2.3 (1.1–4.9), 6.6 (3.3–13.1), and 6.1 (2.9–12.7), respectively, for serum HBV DNA levels of <300, 300–9999, 10,000–99,999, 100,000–999,999, and ≥ 1,000,000 copies/mL [38]. In addition, several studies in recent years have confirmed the role of quantitative HBsAg levels in predicting HCC risk, independent of conventional risk factors such as ALT and HBV DNA viral load. Specifically, higher serum HBsAg levels have been able to predict higher risk for HCC, even among individuals with low viral loads [31, 36]. Thus, as higher levels of seromarkers have been shown to predict higher HCC risk, it is important to also highlight the importance of the seroclearance of HBeAg, HBV DNA, and HBsAg, each of which has been shown to predict a decreased risk of HCC, while persistence of each is also predictive of an increased risk for HCC [32].

In addition to viral factors, studies have also shown that environmental factors such as a positive family history, increased alcohol consumption, and metabolic syndrome are also associated with increased risk for developing HCC [39–42]. Lastly, more recent studies have also focused on the role of host genetic factors in predicting a host's risk for HBV-related HCC. Notably, the role of the S267F variant on NTCP, the putative receptor for HBV, in modulating HBV infection and risk for HCC has been recently confirmed in the REVAL-HBV cohort [43].

3.1.5 The Era of Personalized Medicine

With the confirmation of a myriad of risk factors for HBV-related clinical outcomes such as cirrhosis and HCC, recent research has begun to focus on the establishment of risk calculation tools, which would allow for a personalized assessment of risk based on the clinical profile of

each HBV-infected patient. Several tools have been created, both for the prediction of HBeAg, HBV DNA, and HBsAg seroclearance and for the prediction of cirrhosis and HCC [31, 44–49]. To date, only risk calculators for HCC have been robustly developed and externally validated in clinical settings. The easy-to-use REACH-B risk score is based on noninvasive clinical characteristics and has helped clinicians and HBV carriers to stratify their HCC risks according to their personal profiles, including age, sex, family history, alcohol consumption, serum ALT levels, HBeAg serostatus, serum HBV DNA, HBsAg levels, and HBV genotypes, and has recently been revised to incorporate quantitative HBsAg levels [48–50].

In conclusion, it is clear that infection with the hepatitis B virus poses a serious threat to global public health, and even with the availability of an effective vaccine and significantly low rates of new infection, high rates of chronic infection continue to plague highly endemic areas, and the long-term consequences of HBV infection are being seen with high rates of cirrhosis and HCC in HBV-endemic areas. With such robust and clinically applicable tools being developed through sound epidemiological research, the hope is that the dangerous consequences of HBV infection can be better anticipated, or even prevented, reducing the global disease burden resulting from the hepatitis B virus.

3.2 Epidemiology and Global View of Hepatitis C

Hepatitis C virus (HCV) is recognized as a major cause of chronic liver disease. Generally, liver cirrhosis occurs in 20 to 30% of patients with chronic HCV infection after two to three decades [51]. Once cirrhosis occurs, HCC develops in 1–4% of these patients per year [52]. In addition, HCV is estimated to be attributable for one third of HCC cases globally [53], representing a great public health burden. The transmission of HCV primarily occurs through blood contact.

3.2.1 Prevalence of HCV Infection

The global prevalence of HCV infection is estimated to be 2–3%, which equates to 130–180 million people living with HCV infection [54]. The seroprevalence of HCV has considerable geographical variation [55]. The estimated prevalence of HCV infection in economically developed countries is relatively low at 1–2% of the adult population, whereas it is up to 5–10% in less developed countries [56, 57]. Regions with the highest HCV prevalence include African, Eastern Mediterranean, Southeast Asian, and Western Pacific regions [56, 57], while areas with lower prevalence include the North American, Northern and Western European, and Australian regions. In Africa, countries with the highest HCV prevalence include Egypt and Cameroon, where the prevalence rates are reported to be higher than 10% [58, 59].

The estimated absolute number of individuals with HCV infection is 29.8 million in China, 18.2 million in India, 11.8 million in Egypt, 9.4 million in Pakistan, and 9.4 million in Indonesia [58]. Although many countries in Asia have a low to intermediate prevalence of HCV, highly endemic areas have at least 50% of people with HCV infection [60].

3.2.2 HCV Transmission Routes

3.2.2.1 Injection Drug Use

The prevalence of HCV infection among intravenous drug users ranges from 31% to 98% [61]. Illicit injection drug use is a primary transmission route for HCV infection in developed countries and accounts for approximately 60% and 80% of HCV infection in the United States [62] and Australia [63], respectively. For example, anti-HCV seroprevalence among injection drug users in the San Francisco Bay Area was higher with each decade of drug use, rising from 66.2% among subjects who had injected drugs for less than 10 years to 98.7% among those who had been injecting for 30 years or longer [64]. Drug users who had ever borrowed a nee-

dle had a 2.56 (95% CI = 1.2–5.5)-fold increased risk to be infected by HCV [65].

Sharing contaminated injection equipment among injection drug users was the main HCV transmission route. Injection drug users who never used syringe exchanges had a lower cumulative incidence of HCV than those who used the exchange (15% vs. 21–26%) [66]. Drug solutions mixed with a syringe previously used for injection, clean syringes drawing solutions from containers or filters previously used by HCV-infected injectors, or cleaning syringes, containers, or filters with contaminated rinse water may result in the cross-contamination of drug preparation and injection equipment [67].

3.2.2.2 Recipients of Blood and Blood Products

In the mid-1970s, it was discovered that the blood supply was contaminated with an unidentified agent causing posttransfusion non-A and non-B hepatitis [68]. Patients with hemophilia, thalassemia, cardiac surgery, or chronic renal disease had increased risk for posttransfusion hepatitis [69–71]. However, these days, posttransfusion hepatitis C has become relatively rare in developed countries. The incidence of transfusion-associated hepatitis from 1970 to 1998 decreased from 33% to nearly nonexistent HCV transmission due to effective blood donor screening [72]. One multicenter study conducted in Baltimore showed a reduction of posttransfusion hepatitis from 45 per 100,000 units transfused in 1985 to 3 per 100,000 units transfused in 1990 [73]. Compared to individuals who received a transfusion after 1992, patients who had a transfusion history or high volume of blood loss related to surgery before 1992 had a higher risk of being anti-HCV seropositive [74, 75].

HCV screening in blood products has not been feasible in developing countries, and receiving infected blood products remains a major source of HCV infection. Most of these countries are located in Africa and Asia, where blood safety is threatened by poverty, insufficient instruments and laboratory reagents, limited numbers of trained professionals, traditional cultural barriers, and difficulties in mobilizing volunteer donors [76, 77]. According to the Human Development Index (HDI), which ranks countries on the basis of life expectancy, literacy, and gross domestic product, countries with low HDI had 63% paid donors in their blood donor systems and only 51.3% of units screened for anti-HCV, compared with only 4% paid donors and nearly 100% of units screened for anti-HCV in countries with high HDI [78].

3.2.2.3 Unsafe Medical Injections

Unsafe medical injection, which is defined as the reuse of syringes or needles from patient to patient without sterilization, is also one of the primary modes of HCV transmission. Unsafe injections resulted in approximately 2.3–4.7 million HCV infections annually [79]. Transmission of HCV through contaminated injection equipment has been a major transmission source in most developing countries. One of the most well-known cases of unsafe medical injections was the massive Egyptian anti-schistosomal treatment campaign, later discontinued in the 1980s, which became the world's largest iatrogenic transmission of a blood-borne pathogen known to date and resulted in a large reservoir of chronic HCV infection and a high HCV seroprevalence [80]. More than 3 million injections were given per year to over 300,000 individuals between 1964 and 1969, and by the mid-1980s, the campaign had infected 10% of the entire adult population in Egypt with hepatitis C [80, 81].

Medical injection played an important role in the spread of HCV in the past. The age-specific prevalence is low in younger adults but is increased in older people [82–85], implying that the risk of infection was greatest around 30–50 years ago [86]. A community-based study found that the population attributable risk of medical injection for HCV infection was 57% [85]. Receiving injections by non-licensed practitioners was also more common in anti-HCV seropositives [87], suggesting that unlicensed or nonprofessional healthcare providers may have given medical injections without standard sterilization procedures.

3.2.2.4 Mother-to-Infant Transmission

In a landmark study in which HCV infection was observed in three generations of one family, vertical transmission of HCV was confirmed by molecular evolutionary method [88]. The mother-to-infant transmission rate ranges from 0.6% to 19.4% [89]. In the vast majority of cases, infants passively acquire the maternal antibody at birth. The antibody continues to be detectable in infants and then gradually clears by 12–18 months of age [90]. Testing for HCV RNA is generally used as a marker for the detection of HCV-infected infants [91]. Mothers with detectable HCV RNA or elevated serum HCV RNA levels had a higher likelihood to transmit HCV to their babies than those with undetectable HCV RNA [92]. There is also no obvious association between different HCV genotypes and the rate of vertical transmission [90, 93]. Moreover, there are no significant associations between mode of delivery and breastfeeding on HCV vertical transmission in HCV-infected mothers [94].

3.2.2.5 Sexual Transmission

Sexual transmission, which involves the exchange of bodily secretions or infected blood across mucosal surfaces, is one other possible mode of HCV transmission. Spouses with HCV-infected partners have a twofold higher risk of being HCV seropositive than spouses without HCV-infected partners [95]. In some studies, HCV genotypes were used to evaluate anti-HCV antibody-concordant couples, and the concordance rate was 50–82% in couples who both had detectable HCV RNA for HCV genotyping [95–97]. Moreover, among commercial sex workers, the prevalence of anti-HCV seropositivity ranged from 1% to 10% and was 2.9% to 13% among men who have sex with men [98]. The risk of HCV infection was highly correlated with the intensity of sexual exposures, including years of sexual exposure or numbers of sexual partners [99]. Similar to vertical transmission, individuals with high serum HCV RNA levels [100] or who were coinfected with HIV [101] had high rates of HCV transmission to their sexual partners. Partners of persons with chronic hepatitis C should be tested for anti-HCV and should be advised not to share percutaneous exposures to blood items.

3.2.2.6 Other Potential Risk Factors

There are several other biological routes associated with HCV transmission because of various human activities involving potential percutaneous exposure to blood or bodily fluids. These transmission routes include acupuncture [85], tattoos [102], cosmetic procedures [103], body piercings, commercial barbering, and religious or cultural practices such as circumcision [104].

3.2.3 Long-Term Consequences of HCV Infection

3.2.3.1 HCV Infection and Hepatic Diseases

The ability of HCV infection to increase the risk for liver-related outcomes is well documented, and clinical outcomes after HCV infection are highly variable. Among individuals with HCV infection, around 1.3–51% may develop liver cirrhosis and 0.1–5.3% may develop HCC over the course of 3.9–25 years [105, 106]. Based on the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer in HCV (REVEAL-HCV) study cohort, the cumulative lifetime (30–75 years old) incidence of HCC for men and women is 23.7% and 16.7%, respectively [107]. Elevated serum levels of HCV RNA and alanine aminotransferase (ALT) increase the risk for HCC after long-term follow-up [108]. The lifetime risk for HCC is 3.6% for those who have had spontaneous viral clearance (undetectable HCV RNA) and 24.8% for those who have continued chronic HCV infection (detectable HCV RNA). In addition, for individuals with serum ALT levels ≦15 U/L, 16–45 U/L, and >45 U/L, the cumulative lifetime risk for HCC is 11.6%, 18.5%, and 34.3%, respectively [109]. Compared with other subtypes, individuals infected by HCV subtype 1b have further increased risk of HCC. The cumulative lifetime

risk for HCC is 19.2% and 29.7% for subtypes non-1b and 1b ($p < 0.001$), respectively [110]. These seromarkers could also predict long-term development of HCC and had the potential to be used for risk stratification of HCV-infected patients in order to identify those in need of intensive care.

In order to integrate several important risk factors and predict the incidence of HCC, risk prediction models were developed for HCV-infected subjects [111]. Patients' risk profiles used in the prediction models include age, ALT, the ratio of aspartate aminotransferase to ALT, serum HCV RNA levels, the presence of cirrhosis, and HCV genotypes. Using patients' clinical profiles, risk scores are calculated, and the corresponding predicted risk for HCC can be determined. These risk prediction models are validated in another external HCV-infected community-based cohort, and results show the predictive accuracy of the prediction models to be around 70–73% [111]. In a hospital-based cohort that enrolled HCV-infected patients with antiviral treatment and compared their risk of HCC at baseline and after treatment using the risk prediction model [112], the authors found a significant reduction in the risk for HCC after treatment-induced RNA clearance. However, the risk for HCC did not change from baseline to after treatment among patients who did not experience treatment-induced RNA clearance. These findings suggest that the risk of HCC could be reduced with effective antiviral treatment.

3.2.3.2 HCV Infection and Extrahepatic Diseases

The large community-based prospective REVEAL-HCV study also found that patients with chronic hepatitis C infection, defined as having detectable serum HCV RNA, had increased risk of death from both hepatic and extrahepatic diseases, when compared to patients either seronegative for anti-HCV or seropositive for anti-HCV but with undetectable HCV RNA [113]. For example, HCV infection was reported to be associated with the incidence of cryoglobulinemia [114] and non-Hodgkin's lymphoma [114, 115].

Several studies have also shown that patients with HCV infection have a higher risk of diabetes mellitus than uninfected patients, suggesting that HCV may interfere with the insulin signaling pathway [116]. The National Health and Nutrition Examination Survey found that subjects with HCV infection have an increased likelihood of having diabetes, with an odds ratio of 3.8 (95% CI: 1.8 to 7.8), after controlling for potential risk factors [117]. Another large-scale study enrolled 10,975 subjects in an HBV- and HCV-endemic area and showed that the prevalence of HCV viremia was significantly different among diabetic and nondiabetic patients (6.9% vs. 4.5%, $p < 0.001$) [118]. Long-term follow-up studies have also showed that individuals seropositive for anti-HCV and HCV RNA have increased risk of developing diabetes [119].

Lastly, HCV infection is also associated with cardiovascular diseases. A large cross-sectional study found that patients with the presence of plaque and carotid intima media thickening, which are the early and asymptomatic signs of carotid atherosclerosis, had a twofold risk of being anti-HCV seropositive [120]. Another study, which was conducted using Australia's national registration database, found that 75,834 hepatitis C-diagnosed patients had a significantly increased risk of dying from cardiovascular diseases, compared to the general population [121]. In a similar retrospective study that compared 10,259 anti-HCV seropositive and 10,259 anti-HCV seronegative blood donors, anti-HCV seropositives had higher cardiovascular mortality rates, with a hazard ratio of 2.21 (95% CI: 1.41–3.46) [122]. In addition, a recent meta-analysis that included several observational studies found that HCV-infected patients have increased risks of cardiovascular-related mortality (OR = 1.65, 95% CI = 1.07–2.56), carotid plaques (OR = 2.27, 95% = 1.76–2.94), and cerebrovascular events (OR = 1.30, 95% CI = 1.10–1.55) [123]. Lastly, a community-based cohort study found that elevated serum HCV RNA levels increase the risk for cerebrovascular deaths, even after considering conventional risk factors. The dose-response relationship seen in this study

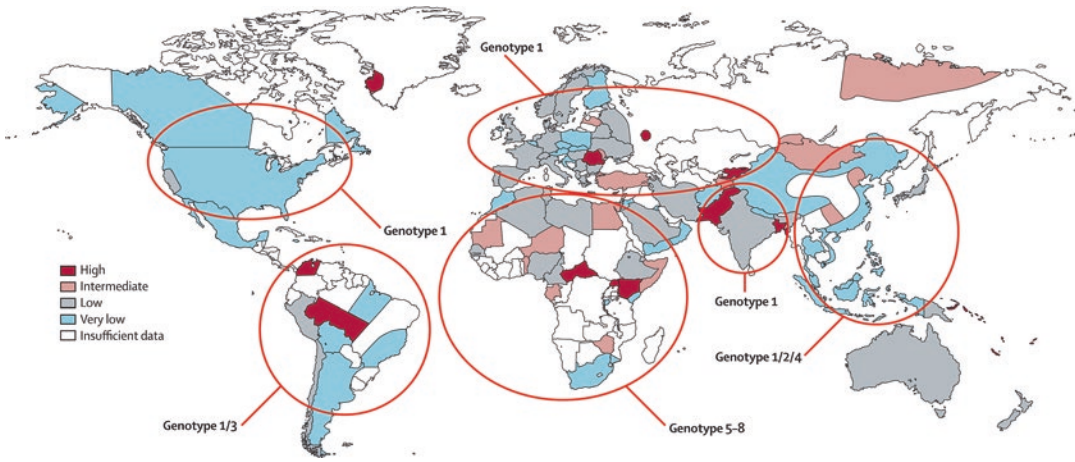

Fig. 3.4 Worldwide prevalence of HDV and the geographic distribution of its genotypes. (Reproduced with permission from Ref. [22])

supports a causal link between HCV infection and atherosclerotic changes [124].

3.3 Epidemiology and Global View of Hepatitis D

Hepatitis D virus (HDV) is the only member of the family *Deltaviridae* [125]. It appears to be a 36-nm spherical particle and consists of a circular RNA genome, a single HDV nucleocapsid antigen, and a lipoprotein envelope from HBV. HDV is a defective virus that requires HBV for its life cycle. Therefore, it is only possible to have coinfection or superinfection of HDV with HBV, which has been shown to cause a more severe disease than HBV mono-infection.

3.3.1 Geographical Distribution

The seroprevalence of antibodies against HDV (anti-HDV) in chronic HBV carriers demonstrates that HDV infection has a worldwide but nonuniform distribution. It is estimated that globally, 5% of HBsAg-seropositive individuals are coinfected with HDV, which corresponds to approximately 15–20 million people worldwide. High-prevalence areas include the Mediterranean, Middle East, and Central and Northern Asia, including Mongolia, Greenland, Sub-Saharan Africa, the Amazon basin, and some areas of the Pacific (Fig. 3.4). In some countries within these endemic areas, anti-HDV seropositivity is found in as many as 30% of CHB patients [126]. However, the prevalence of HDV is low in North America and Northern Europe, South Africa, and Eastern Asia. Interestingly, although there is a high HBV prevalence in Southeast Asia, HDV infection is relatively rare in areas other than Vietnam and the Pacific Islands. In the Amazon area, high HDV antibody prevalence rates have been found among children younger than 4 years [127].

The decline in the prevalence of HDV has been reported in Italy, Spain, Turkey, and Taiwan [128–132], mainly due to the availability of universal HBV vaccination, improvements in public health and hygiene, and increased awareness of transmission routes [133]. However, despite declining rates in some areas, some studies have reported an alarming prevalence of HDV infection in Northern California, Europe, Brazil, the Mediterranean Basin, and Vietnam, with rates ranging from 3.7% to 27.8% in CHB patients [134–138]. The epidemiology of HDV infection in children is similar with that in adults. Identical HDV strains in members from the same family had been reported, which

highlights the importance of the intrafamilial spread of HDV in endemic areas [139, 140].

Eight major genotypes of HDV have been classified, based on the heterogeneity in viral genome sequences [141–143]. Genotype 1 is the most predominant, which presents throughout the world (Fig. 3.4). Genotype 2 is more commonly found in Eastern Asia such as Japan and Taiwan, while genotype 3 has been reported to cause outbreaks in Venezuela and Peru [144].

3.3.2 Transmission

HDV shares the same transmission routes with HBV: percutaneously or sexually through contacting infected blood or other body fluids of an infected person. Vertical transmission from mother to child is possible but considered to be rare [145]. Recent evidence showed a higher prevalence of HDV infection in patients aged 20–40 than the overall prevalence, implicating that sexual transmission might be a factor with higher importance in the spread of the disease than previously thought [136, 146]. Vaccination against HBV can prevent HDV coinfection. However, an increasing HDV prevalence has been observed in injection drug abusers [147] or in immigrants from areas where HDV is endemic.

3.3.3 Disease Progression and Long-term Consequences of HDV Infection

The risk of disease progression depends on the mode of infection. Coinfection with HBV and HDV usually results in mild, self-limited hepatitis and subsequent clearance of both viruses, with less than 10% of coinfected patients progressing to chronic HDV infection [144, 148]. However, some patients may develop severe fulminant hepatic failure [149]. Superinfection occurs when individuals with established chronic HBV are superinfected with HDV. Three phases are usually seen: acute, chronic, and late phases. The acute phase is characterized by high alanine aminotransferase (ALT) levels, active HDV replication, and suppression of HBsAg and HBV DNA. During the chronic phase, ALT levels decrease but may remain moderately elevated, HDV replication decreases, and HBV reactivation at low levels may occur. The late phase is characterized by reduced levels of both viruses or the replication of either virus that causes cirrhosis or HCC [150, 151]. Superinfection leads to chronic HDV in 70–90% of cases [150, 152] and can accelerate progression to a more severe disease than HBV mono-infected persons [153]. However, it is still unclear why HDV causes more severe hepatitis and a faster progression of fibrosis than HBV alone. It has been reported that superinfection of HDV may increase the risk of cirrhosis three times higher than those with HBV infection alone [149]. The association between HDV infection and HCC risk is controversial; some studies show that HDV infection is associated with increased risk of HCC, while others do not show an association [149, 154].

Several risk factors that affect disease progression of HDV infection have been identified. A Taiwanese study showed that among 194 patients with dual infection of HBV and HDV, 24 and 41 progressed to cirrhosis and HCC, respectively, during a median follow-up of 135 months. Older age, genotype 1 HDV, and genotype C HBV were found to be associated with adverse outcomes [155]. Another study from Italy tracked the course of 299 HDV-infected individuals for a mean period of 20 years. This study showed that persistent HDV replication was an important predictor of disease progression, which could lead to cirrhosis and HCC at annual rates of 4% and 2.8%, respectively. HDV replication was also the only predictor of liver-related mortality [156]. In addition, coinfection with other viruses such as HIV and HCV was shown to impact the course of HDV-related liver disease [157, 158].

HDV genotype can also influence outcomes of HDV infection. HDV genotype 1 has been shown to be associated with a higher incidence of acute liver failure following acute hepatitis D, a lower remission rate, and an increased incidence of adverse outcomes compared to genotype 2 [150,

155, 159]. Genotype 3 was reported to be associated with outbreaks of acute hepatitis D with a high incidence of fulminant hepatic failure in South America [160, 161].

3.3.4 Hepatitis D in Children

Although the incidence of HDV infection in children has decreased due to the implementation of the universal hepatitis B vaccination programs, there are still outbreaks reported in children in endemic areas of HBV infection [162].

HDV superinfection has profoundly modified the natural history of CHB in children, transforming a usually mild disease into progression toward severe hepatitis [163]. Severe cases of hepatitis, such as fulminant hepatic failure in children, are mainly caused by HDV superinfection [161]. One study in Turkey reported that although HDV infection was rare among HBV-infected children in the Western region of Turkey, all three children infected with HDV had biopsy-proven cirrhosis. In addition, there was a positive correlation between histological cirrhosis and the number of years following acute HDV infection [164]. Another Turkish study reported that 6 out of 206 children who had CHB were also infected with HDV. Among these children, three had cirrhosis, two had a moderate degree of hepatitis, and one had minimal inflammation [165]. However, a study from Taiwan found that high levels of HBV replication may result in the suppression of HDV and that HDV infection did not largely affect the natural course of HBV infection in Taiwanese children [139].

The baseline-event-anticipation score (BEA score) has been developed for predicting risk of liver-related morbidity or mortality (including decompensation, HCC, liver transplantation, and/or death) for patients with HDV infection and incorporates age, sex, region of origin, bilirubin, platelets, and international normalized ratio (INR) [166]. The accuracy of the BEA score was evaluated in two independent validation cohorts followed in Barcelona and Düsseldorf and may be used to assist with prognostication of HDV infection.

3.3.5 Seromarkers

The presence of HBsAg is a prerequisite for the diagnosis of HDV infection. Several seromarkers including HDV antigen (HDAg), anti-HDV, and HDV RNA may be used for the screening and diagnosis of HDV infection. Testing for serum HDAg in the acute phase may yield negative results, and repeat testing may be necessary [167]. In the chronic phase, as HDAg is complexed with high titers of anti-HDV, levels of HDAg are usually low.

Anti-HDV antibodies develop in every individual infected with HDV [126]. Low titers of anti-HDV may persist for years after recovery from infection and should not be used as an indication of active infection. Several commercial tests are available for total anti-HDV antibody. HDV RNA is an early and sensitive marker of acute HDV infection and is useful for assessing the resolution of HDV infection. However, there still is no standardized HDV RNA assay, and in-house assays can only be performed in specialized laboratories. In individuals seropositive for anti-HDV, the HDV RNA assay should be used for confirming active HDV infection. HDV genotyping may help to identify patients at increased risk of developing end-stage liver disease. However, its usage is not recommended in routine clinical practice.

3.4 Prevention and Treatment of Hepatitis B, C, and D

The hepatitis B vaccine is the most important tool for the prevention of hepatitis B virus infection. WHO recommends that all infants receive the hepatitis B vaccine within 24 hours after birth. Vaccination has reduced the rate of chronic infection to less than 1% among immunized children in countries in which 15% of children used to become chronic carriers. The implementation of a nationwide hepatitis B vaccination program in Taiwan in 1984 shows that vaccination of newborns has not only reduced the risk of infection but has also led to significant reduction in the incidence of childhood liver cancer [168, 169].

It is recommended by WHO that all children and adolescents younger than 18 years old who live in countries with low or intermediate endemicity and who are not previously vaccinated receive the vaccine. Some high-risk people, including those who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, those who inject drugs, those with multiple sexual partners, household and sexual contacts of people with chronic HBV infection, those who will be travelling to endemic areas, and healthcare workers, are also recommended to be vaccinated. As the protection can last at least 20 years and is probably lifelong in those who complete vaccine series, WHO does not recommend booster vaccination for persons who have completed the three-dose vaccination schedule. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%. However, the coverage with the initial birth dose vaccination is still low at 39%.

In addition to vaccination, blood safety strategies such as screening of donated blood and blood components used for transfusion can prevent transmission of HBV. In 2013, 97% of blood donations were screened and quality assured worldwide; however, there exist gaps for improvement. Furthermore, eliminating unnecessary and unsafe injections and minimizing the number of partners and using barrier protective measures are also important strategies for protection against HBV transmission.

WHO also recommended the use of simple, noninvasive diagnostic tests to assess the stage of liver disease and eligibility for treatment; to prioritize treatment for those with most advanced liver disease and at greatest risk of mortality; the preferred use of the nucleos(t)ide analogues with a high barrier to drug resistance for first- and second-line treatment; lifelong treatment in those with cirrhosis; and regular monitoring for disease progression and toxicity of drugs and early detection of liver cancer.

As there is no vaccine for hepatitis C, the prevention of HCV infection depends mainly on reducing the risk of exposure in higher-risk populations and through sexual contact. Therefore, the provision of effective harm-reduction services to people who inject drugs, including sterile injecting equipment, and the promotion of correct and consistent use of condoms are important. Primary preventive interventions are also suggested for healthcare settings including testing of donated blood for hepatitis C, safe and appropriate use of healthcare injections, safe handling and disposal of sharps and waste, and training of health personnel.

For people infected with HCV, WHO recommends early and appropriate medical management including antiviral therapy if appropriate and regular monitoring for early diagnosis of chronic liver disease. The assessment for antiviral treatment should be implemented for all adults and children with chronic HCV infection. All patients with hepatitis C are recommended by WHO to be treated with direct-acting antivirals (DAA)-based regimens, except for a few specific groups of people in whom interferon-based regimens can still be used.

WHO does not have specific recommendations for hepatitis D. However, the WHO suggests that prevention of HBV transmission by hepatitis B immunization, safe injection practices, blood safety, and harm-reduction services with clean needles and syringes are effective in preventing HDV transmission. Currently, the vaccine against HBV is the method of choice to prevent HDV infection; however, it does not protect against HDV infection for those already infected with HBV. Passive immunoprophylaxis with hepatitis B immunoglobulin does not confer any protection against HDV infection, unless it controls the spread of HBV infection. In children, universal vaccination remains the fundamental method of prevention. It is prudent to check for adequate immunity to HBV after vaccination in children with household members known to have HDV infection, in order to inhibit intrafamilial transmission.

There is still no specific treatment for acute or chronic HDV infection. Although persistent HDV replication is the most important predictor of mortality and the need for antiviral therapy, the ultimate goal for eradication of HDV should be the clearance of HBsAg [170]. Oral antivirals against HBV showed little or no effect on HDV

replication when used alone. Interferon-alpha-based therapy is the only drug effective against HDV [146, 171]. However, the overall rate of sustained virological response remains low, and most patients relapse after discontinuation of therapy. The optimal duration of therapy is not well defined, and more than 1 year of therapy may be necessary. Patients with fulminant hepatitis due to coinfection or superinfection with HDV did not respond to interferon-alpha therapy, and liver transplant is the only option for such patients [172]. New therapeutic agents and strategies for HDV infection are needed.

3.5 Summary

This chapter has provided a global view for hepatitis B, C, and D, in terms of worldwide distribution, transmission route, long-term consequences, and preventive measures.

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