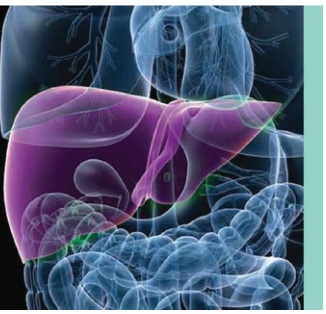

# Epidemiology of Hepatitis C

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Chronic infection with hepatitis C virus (HCV) is a major cause of cirrhosis and hepatocellular carcinoma (HCC) in the United States and globally. More than 3.5 million Americans have chronic hepatitis C infection, with the majority being older Americans born between 1945 and 1965.[1] Initially, new cases in the United States decreased by more than 90% with HCV screening of blood products. But this has again increased dramatically since 2009 with transmission among young Americans in the second or third decade of life due to injection drug use (IDU).[2] New cases of hepatitis C infection increased from close to 10,000 per year in 2005 to more than 40,000 per year in 2016.

Previous estimates placed an estimated 2.8% (range of estimates 2.6%-3.1%) of the world population—more than 184 million persons—as being infected with HCV.[3] Worldwide prevalence of hepatitis C infection varies widely, and precise global estimates are hampered by high rates of undiagnosed disease and lack of appropriate data collection. More recent epidemiology estimates viremic hepatitis C as 1.0% of the world population, corresponding to a lower number of 71 million active cases.[4] Globally, Egypt has the highest estimated prevalence—30,000 per 100,000 persons (30%)—likely because of injection procedures associated with eradication of schistosomiasis. Prevalence is also high in India, Pakistan, China, and Indonesia but markedly lower in Japan, Northern and Western Europe, North America, and Australia.[5] Data from much of Asia, Africa, and South America are limited.

In the mid-1980s, incidence of acute HCV infection in the United States peaked; rates then declined sharply in the 1990s as a result of human immunodeficiency virus (HIV) prevention efforts, such as needle exchange programs.[1] Since the early 2000s, incidence again rose, likely because of increases in injection opioid use.[1] Although increases were observed across all demographic groups, the largest

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use.

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increases were among individuals aged 18 to 29 and 30 to 39 years. IDU was reported in more than 60% of cases.

Clinical diagnosis of acute hepatitis C is frequently missed because it is often asymptomatic. The majority of persons with acute hepatitis C do not clear the virus by 6 months, resulting in chronic disease, although this development of chronic infection varies by a number of factors, including sex, ethnicity, and liver synthetic dysfunction during initial infection. Patient age is a significant factor in development of chronic disease; although roughly 75% of persons older than 20 years will progress to chronic HCV infection,[6-8] only one-third of persons younger than 20 years will experience chronic disease. African Americans appear to have higher rates of development of chronic hepatitis C than whites. Development of chronicity is thought to be less likely among those who have jaundice during acute infection, perhaps because it represents a stronger immune response to the virus. In contrast, HIV-positive persons with evidence of immune suppression are more likely to experience chronic hepatitis C after an acute infection.

In the United States and most developed countries, chronic hepatitis C prevalence is low, but there are marked differences based on age and transmission factors.[1,9] Prior estimates placed 7 million persons in the United States as HCV-positive, a prevalence rate of 1,800 per 100,000 individuals (1.8%).[9] More recent estimates of viremic hepatitis C in the United States report a prevalence rate of 0.9%, or 2,936,000.[1] The largest proportion of patients with chronic HCV in the United States were born between 1945 and 1965,[10] a pattern attributed to high rates of prior IDU in this age cohort. Prevalence in Northern and Western European countries is similar or slightly lower than in the United States, although there have been some recent increases attributed to immigration from countries where HCV is endemic. Prevalence in Southern and Eastern Europe is somewhat higher, likely due to iatrogenic spread and IDU.

HCV demonstrates great genetic diversity, far greater than hepatitis B virus (HBV) or HIV, with 7 genotypes and at least 67 subtypes. Distribution of these genotypes and subtypes varies by region.[4,11,12] (Table 1) In turn, pathogenicity, rate of progression to liver fibrosis, and treatment response can be influenced by genotype. Overall, genotype 1 dominates with 44% of infections, followed by genotypes 3 (25%) and 4 (15%).[4] Genotype 1 makes up 60% of cases in high- and upper-middle-income nations, and genotype 3 (36%) is seen more in lower-middle-income nations, whereas genotype 4 (45%) is seen more in low-income nations. Genotypes 1 to 3 are widespread globally, whereas genotype 4 is endemic to the Middle East and Africa,[13] genotype 5 is most commonly reported in South Africa, genotype 6 is most common in Southeast Asia, and the recently described genotype 7 appears to be confined to Central Africa.

**TABLE 1. PREDOMINANT GENOTYPES BY REGION**

| Region | 1a | 1b | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| North America | X | X | X | | | | | |
| Caribbean | X | X | | X | | | | |
| South America | | X | X | X | | | | |
| Europe | X | X | | X | | | | |
| Middle East | X | X | | | X | | | |
| West Asia | | X | X | X | | | | |
| South Asia | X | X | | X | | | | |
| East Asia | | X | X | | | | | |
| Australia | X | X | | X | | | | |
| North Africa | | | X | | X | | | X |
| South Africa | X | | | X | | X | | |

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Among persons who progress to chronic HCV, many will develop liver fibrosis and ultimately cirrhosis.[14] Over a mean of 6.5 years, 57.4% progress by at least one fibrosis stage, 16.1% progress by at least two stages, and 5.82% of patients progress from not having cirrhosis to having cirrhosis. Specific host factors and external cofactors can accelerate this progression, including alcohol use, viral coinfection (HIV or HBV), age older than 40 years at infection, nonalcoholic steatohepatitis, insulin resistance, and immunosuppression (Table 2). Chronic HCV infection is also the leading cause of HCC in North America, underlying more than one-third of HCC cases in the United States[15] and roughly 8% of cancers globally. Cirrhosis greatly increases risk for HCC. In Japan, the HCV epidemic preceded that of the United States by several decades; high rates of HCC among individuals with HCV in this population suggest that HCC incidence in the United States could continue to increase as the population ages. Race also appears to impact HCC; Asian Americans and African Americans are at greatly increased risk for development of liver cancer compared with whites.

The past several years have seen the emergence of direct-acting antiviral treatments for HCV, which achieve extremely high rates of sustained virological response (SVR) without the side effects that hampered previous treatment

**TABLE 2. RISK FACTORS FOR PROGRESSION OF LIVER FIBROSIS**

| |
|---|
| Age older than 40 years at infection |
| Excessive alcohol consumption (>20 g/day female, >30 g/day male) |
| Male sex |
| Coinfection with HIV |
| Coinfection with hepatitis B |
| Immunosuppression |
| Insulin resistance |
| Nonalcoholic steatohepatitis |
| Hemochromatosis |
| Schistosomiasis |

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options. Recent research has shown that persons who achieve SVR are at much lower risk for liver fibrosis and cirrhosis as well as serious extrahepatic outcomes, such as type 2 diabetes and cardiovascular diseases.[16,17] The larger challenges for the goal of global HCV eradication include increasing screening and diagnosis, education of treating providers, and the assurance that these highly effective treatments are accessible. Efforts to reduce the incidence of acute infection among drug users and through iatrogenic contamination are essential.

## CORRESPONDENCE

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