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Prevalence of Chronic Hepatitis B Virus Infection in the United States

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Chronic hepatitis B virus (HBV) infection represents a major global health problem, affecting an estimated 257–291 million persons worldwide and is associated with substantial morbidity and mortality because of clinical complications, such as liver cirrhosis and hepatocellular carcinoma. Despite existing resources for vaccination, screening, and treatment, the burden of chronic HBV remains significant within the United States (US). Both the World Health Organization (WHO) and US Department of Health and Human Services (DHHS) have articulated formal hepatitis elimination plans, although an updated assessment of the epidemiology and prevalence of chronic HBV is needed to inform these initiatives. The Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease, partnered with a panel of leading US hepatologists to conduct an updated literature review to develop a contemporary HBV prevalence range estimate. Panel members researched and evaluated the peer-reviewed literature on HBV prevalence and, in May 2019, discussed their findings during a live HBV epidemiology workshop. The panel proposed an overall estimated prevalence for chronic HBV infection in the US of 1.59 million persons (range 1.25–2.49 million). This review provides a summary of the workshop findings and conclusions, which may serve to inform future initiatives focused on HBV screening and prevention in the US.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection has a worldwide prevalence of 257–291 million affected persons (1). Patients often remain asymptomatic for years but may unknowingly transmit the infection to others via perinatal, percutaneous, and sexual exposure or close person-to-person contact (e.g., open cuts and sores) (2). An estimated 15%–40% of HBV-infected patients may develop complications such as liver cirrhosis, liver failure, and hepatocellular carcinoma, which represent the common causes of HBV-related death (3).

In the United States (US), current policies exist to prevent HBV transmission through immunization of newborns, school-aged children, and other at-risk populations. Three HBV monovalent vaccines are widely available and are highly effective at preventing infection with the completion of 2 or 3 dose schedules. Furthermore, screening and diagnosis of chronic HBV is available with standard serologic tests, including hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). Among individuals confirmed to have chronic infection (i.e., presence of HBsAg for at ≥ 6 months) and who meet the American Association for the Study of Liver Diseases (AASLD) guideline criteria for antiviral therapy (2), there are several oral antiviral agents that are highly effective in achieving long-term

virologic suppression, which in turn have been demonstrated to reduce the risk of liver-related complications (4).

Chronic viral hepatitis, including both chronic HBV and hepatitis C virus (HCV) infection, is responsible for approximately 1 million deaths worldwide and 20,000 in the US (5). Although no virologic cure is currently available for HBV, the WHO has recommended a combination of prevention and treatment strategies to achieve its goal of hepatitis B and C elimination by 2030. If achieved, these efforts would reduce the incidence of chronic infections by 90%, decrease mortality by 65% (~7.1 million deaths), and exclude HBV and HCV as public health threats (6,7).

In response to this call for global action, the US Department of Health and Human Services (DHHS) formed the Committee on a National Strategy for the Elimination of Hepatitis B and C to establish national goals for improving hepatitis prevention and care and to expand hepatitis surveillance. Elimination of viral hepatitis was considered a more ambitious, yet feasible objective but would require addressing multiple disease-related barriers. The first barrier the committee identified was a lack of understanding of the true burden of viral hepatitis in the US population, which was deemed necessary to develop targeted screening and prevention strategies (6).

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The Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease, partnered with a panel of US hepatologists, who are recognized as leaders in the field of HBV, to conduct an updated literature review to develop a contemporary HBV prevalence range estimate. Each panel member was invited by the CLDF to research and evaluate the peer-reviewed literature on the prevalence of HBV in specific populations and at-risk groups. Their findings were presented during a live HBV epidemiology workshop in May 2019. This review represents a summary of the workshop, which includes a critical evaluation of the published data addressing global and US HBV prevalence, with particular attention to specific at-risk-populations within the US (Figure 1) to generate an updated estimate of US HBV prevalence range. Furthermore, the consensus panel identified multiple evidence gaps for HBV prevalence in high-risk groups for which additional investigation is needed to address evolving patterns in HBV epidemiology and transmission.

GLOBAL AND UNITED STATES EPIDEMIOLOGY OF HBV

Global prevalence

Hepatitis (all types) represents the seventh leading cause of worldwide mortality (8). Current global prevalence of HBV estimates range from 257 to 293 million and are derived from the 2015 WHO Global hepatitis report and 2016 Polaris Observatory study. The 2015 WHO Global hepatitis report estimated a global prevalence of 3.5% of the general population, an estimate of 257 million persons, with 68% of infected persons living in sub-Saharan African and Western Pacific regions (9).

The 2016 Polaris Observatory study reported a global prevalence of 3.9% or 292 million persons based on a country- and region-level modeling study of 120 countries; the collaborators furthermore estimated that only 10% (29 million) of infected persons were diagnosed and only 1.4% (1.8 million) were in children younger than 5 years. Similar to the WHO report, the Polaris Observatory study concluded that 3 regions represented 80% of the global burden, including the African, Western Pacific, and Southeast Asia regions (1).

US prevalence

The WHO and Polaris Observatory study reports are relevant prevalence estimates in the US because of the contribution of foreign-born persons from endemic regions to HBV prevalence. The most commonly cited data estimate for HBV prevalence are derived from the National Health and Nutrition Examination Survey (NHANES), an ongoing epidemiologic survey of vital and health statistics for the noninstitutionalized general civilian population of the US. Table 1 summarizes the HBV prevalence data from 3 different NHANES studies, spanning from 1988 to 2016. The first study, examining the HBV prevalence from 1988 to 2012, reported a chronic HBV prevalence of 0.3% and revealed that US-born individuals had a lower HBV prevalence than foreign-born individuals and that the prevalence in Asians was much higher than other groups, although the Asian sample size was small ($n = 926$) (10). The second NHANES study used the 2011–2014 data and reported a similar chronic HBV prevalence of 0.34% and again confirmed a higher prevalence in foreign-born individuals of Asian origin based on a cohort which included a larger sampling of non-Hispanic Asians ($n = 1,740$) (11). Most recently, a third NHANES study analyzed the NHANES data from 1999 to 2016 and reported an overall chronic HBV prevalence of 0.35%, with a lower

prevalence (0.15%) among US-born persons than foreign-born persons (1.28%), particularly among non-Hispanic Asians (3.85%) (12).

Although the prevalence of chronic HBV infection seems to be stable within US NHANES, the prevalence of HBV exposure (anti-HBc or HBsAg positivity) has decreased from 5.80% (95% confidence interval [CI], 4.51–7.42) during 1999–2000 to 4.69% (95% CI, 3.89–5.65), which carries significant clinical implications because of the potential for either spontaneous and/or immune-mediated HBV reactivation with associated hepatitis flares or life-threatening liver failure (13,14). Le et al. (14) additionally identified key deficits in the care continuum, including poor awareness of personal liver disease among HBsAg positive individuals (15%) and low receipt of antiviral therapy among HBsAg positive individuals reporting awareness (25%). These findings are consistent with a recent real-world study reporting experience from several subspecialty and primary care practices (15).

Similarly, in addition to epidemiologic surveys which provide essential population-level estimates of HBV prevalence, real-world data sets have helped provide a clearer window into the demographics of the infected population. A retrospective study analyzed a US healthcare claims database of 44,026 patients with chronic HBV and 121,568 matched controls to characterize the changing epidemiology of comorbid medical conditions between 2004 and 2015. Patients with HBV were older (mean age increased from 48.1 to 51.8 years for commercial/Medicare patients and from 44.1 to 50.2 years for Medicaid patients; both $P < 0.001$) and experienced more medical comorbidities than matched controls, including cardiovascular disease, hypertension, hyperlipidemia, diabetes, renal impairment, and osteoporosis fractures (16); similar findings have been reported in Asian cohorts of patients with chronic HBV from Asia (17).

Summary of global and United States epidemiology

- The global burden of HBV is most largely represented in the African, Western Pacific, and Southeast Asia regions.
- In the US, foreign-born persons, particularly non-Hispanic Asians, consistently have a higher prevalence of HBV than US-born persons.

HBV PREVALENCE IN FOREIGN-BORN PERSONS LIVING IN THE UNITED STATES

US immigration statistics

“Foreign born” and “immigrant” are the terms used interchangeably to refer to persons with no US citizenship at birth. This population includes naturalized citizens, lawful permanent residents, refugees and asylees, persons on certain temporary visas, and the unauthorized.

The Migration Policy Institute (MPI), which is considered a leading international institution in the field of immigration research, estimates that the US foreign-born population was approximately 44.5 million (about 1 in 7 US residents) in 2017 (18).

A series of changes in federal immigration policy after the events of September 11, 2001 led to a significant decrease in the number of refugees and asylees entering the US (19). Although most foreign-born persons in the US were of European origin pre-2001, an increasing proportion of immigrants from Asia and Latin America has been observed from 2002–2017. As of 2017, immigrants of Mexican origin represented the largest foreign-born group in the US (25%, Figure 1), although increasing

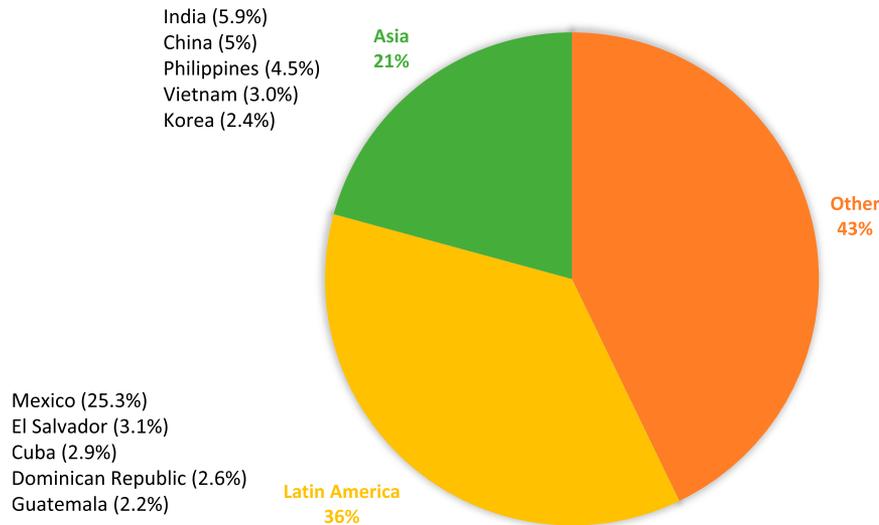


Figure 1. Top 10 US immigration groups in 2017 (ref. [18]).

expansion of immigration from Asia (predominantly China and India), the Dominican Republic, the Philippines, Cuba, El Salvador, and Venezuela has been reported (18).

Major studies on HBV prevalence data in foreign-born individuals

An increasing influx of immigrants from HBV endemic regions of the world may help account for the overrepresentation of foreign-born individuals among patients with chronic HBV in the US. Our understanding of HBV prevalence in foreign-born individuals is largely derived from 2 major studies. A study by Mitchell et al. used imputation methods (i.e., multiplying country-specific prevalence estimates by the yearly number of immigrants from each country) to estimate the contribution of foreign-born persons to chronic HBV prevalence in the US. Based on an estimate of 27.9 million immigrants who entered the US during the period 1974–2008, of whom 63% were born in countries of intermediate or high HBV prevalence, the authors estimated that an average of 53,800 persons with chronic HBV cases entered the US annually. This study reported an estimated prevalence of chronic HBV of 4.6% among foreign-born individuals and identified several countries with the greatest contribution of immigrants with HBV, including the Philippines, China, and Vietnam (20).

Kowdley et al. also reported their results of an imputation study based on a systematic review of HBsAg prevalence rates in 102 countries, using data from 256 seroprevalence surveys from 52 countries (n = 689,078 persons) and 1,797 surveys from 98 countries (n = 17,861,035 persons). These data were used to derive country-specific pooled HBV rates, which were then multiplied by US Census Bureau population data of foreign-born individuals by country of birth. According to these calculations, the authors estimated an overall prevalence of 1.32 million (95% CI: 1.04–1.61) foreign-born individuals with chronic HBV in the US as of 2009. Similar observations were reported regarding countries of origin, with a focus on foreign-born persons from endemic regions with high pooled prevalence, including those from Africa (10.3%) and Asia (7.27%), and specifically refugee populations from East Africa (12.4%) (21).

The US epidemiologic NHANES have consistently reported lower HBV prevalence in the US in both foreign-born and US-born individuals compared with imputation-based estimates,

likely reflecting differences in the methodology. The NHANES uses systematic sampling methods to conduct laboratory testing and surveys within counties, communities, and households which are determined to be representative of the overall US population. Owing to the small proportion of foreign-born individuals in the US and the lower likelihood of participation because of the language and/or cultural barriers, the NHANES surveys may be limited by inadequate sampling of foreign-born persons from endemic countries and therefore may significantly underestimate the HBV prevalence among foreign-born individuals. Conversely, imputation-based studies may overestimate prevalence because of intrinsic limitations, including reliance on prevalence studies that may be enriched with high-risk individuals who may not be representative of the general population or the cohort who immigrate to the US and are of variable methodologic quality relative to population-based survey studies such as NHANES.

Additional data on HBV prevalence in foreign-born individuals and high prevalence rates in Non-Hispanic Blacks

Viral hepatitis surveillance data from the Centers for Disease Control (CDC) indicated that, in 2016, the country of origin was unknown for most HBV-infected individuals living in the US (78%). However, among those with a known country of origin, more than two-thirds were foreign-born (14.7%) and one-third were US born (6.7%). Asian/Pacific islanders and non-Hispanic blacks were identified as having the highest rates of HBV-related death (22). Similarly, an analysis by Ugwu et al. of 8,754 refugees to Minnesota with known HBV status from 1998 to 2001 revealed an overall prevalence of 7.1%, with the highest HBsAg positive rates observed in individuals of African (8.36%) and Asian origin (7.08%) (23). These results largely corroborate previous NHANES data confirming a two-fold higher chronic HBV prevalence among non-Hispanic Blacks than the general population, particularly among those who were foreign-born vs US-born (10).

Summary of HBV prevalence in foreign-born persons living in the United States

- An increasing proportion of people from Asia and Latin America have immigrated to the US between 2002 and 2017.

Table 1. NHANES HBV prevalence data from 1988 to 2016^a

| NHANES study | Study population | Overall prevalence % (95% CI) | US-born population prevalence % (95% CI) | Foreign-born population prevalence % (95% CI) | Ethnic-specific prevalence % (95% CI) |
|--------------------------------|--|-------------------------------|--|---|---|
| 1988–2012, Roberts et al. (10) | Total: 73,446 non-institutionalized adults ≥ 6 years old 1988–1994 (21,260); 1999–2008 (29,828); 2007–2012 (22,358) | 0.3% (0.2–0.4) | 0.1 | 1.1 | Mexican Americans: 0.066 African Americans: 0.6 Asian Americans: 3.1 |
| 2011–2014, Kim et al. (11) | 16,733 persons ≥ 6 years old | 0.34 (0.2–0.4) | n/a | n/a | Asians: 2.74 (1.72–3.76) NH Blacks: 0.64 (0.35–0.92) Non-Asian, Non-Blacks: 0.1 (0.06–0.24) |
| 1999–2016, Le et al. (14) | 47,618 ≥ 18 years old | 0.35% (0.24–0.38) | 0.15 (0.10–0.24) | 1.28 (0.95–1.73) | US-Born NH White: 0.08 (0.03–0.22) NH Black: 0.52 (0.32–0.85) Mexican: 0.14 (0.03–0.61) Hispanic: 0 NH Asian: 0.79 (0.17–3.59) Other: 0.46 (0.14–1.54) Foreign-Born NH White: 0.64 (0.14–2.93) NH Black: 0.64 (0.14–2.93) Mexican: 0.19 (0.04–0.88) Hispanic: 0.09 (0.01–0.53) NH Asian: 3.85 (2.97–4.97) Other: n/a |

CI = confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NH = Non-Hispanic.

^aPrevalence data derived from HBsAg positivity.

- An increasing influx of immigrants from HBV endemic regions of the world may help account for the overrepresentation of foreign-born individuals among patients with chronic HBV in the US.
- Foreign-born prevalence estimates are not without limitations. The NHANES may significantly underestimate HBV prevalence; conversely, imputation-based studies may overestimate HBV prevalence.
- However, trends in these observations indicate that most foreign-born persons with HBV are from endemic regions with high pooled prevalence, particularly Africa and Asia.

HBV PREVALENCE IN THE UNITED STATES IN ADDITIONAL HIGH-RISK GROUPS

Every unvaccinated person in the US may be at risk of HBV throughout their lifetime. However, there are the groups that are considered higher risk than others for various reasons; for example, as previously discussed, certain countries of birth are associated with an extremely high risk of HBV. Other individuals may be at a high risk for other reasons, such as occupation or lifestyle choices, and HBV prevalence in these groups warrants further study (24). In addition to the details provided below, Table 2 summarizes the prevalence of HBV in these high-risk groups.

Veterans

US veterans are considered to be at increased risk for HBV infection because of the potential exposure in military contexts (25). The NHANES 1988–2012 reported that the prevalence of chronic HBV among 1,906 veterans among 22,358 total surveyed population was similar as the general population (0.3%) (10). By contrast, a recent study examining a national VA data set in 2013 revealed that 1.51 million (29.5%) veterans in US Veterans Health Administration (VHA) care had been tested for HBV, of whom 12,632 (0.84%) had confirmed chronic HBV infection based on HBsAg positivity, an estimate nearly 3-fold the general population. Within this cohort, the highest prevalence was observed among veterans who self-designated as of Asian ethnicity (4.94%) and veterans coinfecting with human immunodeficiency virus (HIV) (5.14%) (26).

Similarly, a cluster sample epidemiology study using stored sera from 1,146 US veterans receiving care 1998–2000 revealed an overall chronic HBV prevalence of 0.7% (95% CI, 0.3–1.5) and HBV exposure of 13.6% (95% CI, 11.5–16.1). Patients with traditional risk factors (such as drug use or high-risk sexual practices) had the highest risk of HBV infection, although service in a combat zone (odds ratio [OR] 1.56, 95% CI, 1.01–2.41) and history of wound in combat (OR 1.79, 95% CI, 1.04–3.08) were also independently associated. The prevalence of chronic

HBV within a cohort of 62,290 HCV-infected veterans undergoing direct-acting antiviral therapy was similar (377, 0.7%) (27).

Healthcare professionals

Because healthcare professionals are at risk for occupational injuries including needlestick exposures, they are considered at risk for bloodborne infections, such as HBV. However, the incidence of acute HBV exposure and prevalence of chronic HBV is poorly described. Most US literature addressing HBV epidemiology in healthcare professionals are historic and from the pre-vaccine and early vaccine eras of the 1970s–1990s (28–32) and may not reflect contemporary HBV risk.

One US study examined the prevalence of HBV and HCV from 1998 to 2008 and reported 448 individual cases of hepatitis transmission (173 incident HBV, 275 incident HCV) and 33 hepatitis outbreaks among healthcare workers (33). In contrast to an estimated chronic HBV prevalence of 6%–10% in Asian and African countries (34,35), a recent report estimated a US HBsAg prevalence of 0.1%–8.1% and anti-HBc positivity prevalence of 6.2%–7.3% in healthcare workers (36).

Men who have sex with men

According to the CDC, HBV is 50–100 times more infectious than HIV and is easily transmitted during sexual activity (37). Therefore, men who have sex with men (MSMs) are considered high risk for HBV infection if they engage in unprotected sexual behavior. However, national prevalence data specific to MSMs in the US are not available. One analysis of serologic data from the National HIV Behavioral Surveillance (NHBS) system for a sample of LA County residents (N = 345) revealed that 19% (95% CI 15%–24%) of MSMs had serologic evidence of current or past infection (38). Non-US data from Amsterdam revealed an estimated prevalence of HBV exposure of 23% within a cohort of 1,862 MSMs who underwent testing for anti-HBc, HBsAg, and HBV DNA (39).

Prisoners

Incarcerated individuals are considered a high-risk group for HBV infection because of a higher prevalence of established risk factors for transmission, including injection drug use and high-risk sexual exposures including commercial sex. A CDC analysis from 2008 revealed an estimated chronic HBV prevalence of 1.0%–3.7% among US prisoners (40). A 2009 systematic review of 23 studies from US-incarcerated populations reported a wide chronic HBV prevalence range of 0.9%–11.4% (41). Despite the higher prevalence observed in this at-risk population, no recent data sets with contemporary estimates have been reported.

Homeless patients

Limited data are available to define the prevalence of chronic HBV among homeless populations in the US. This represents an important evidence gap because of the exclusion of this group within epidemiologic surveys, such as NHANES. Historical studies suggest HBsAg positivity in 1.17% (42) and either current or past HBV infection in 30.8% (43) of homeless patients receiving residential or domiciliary services. A recent examination of national Department of Veterans Affairs (VA) Corporate Warehouse Data revealed that within a cohort of 242,740

Table 2. Summary of HBV prevalence estimates in high-risk groups^a

| High-risk group | HBV prevalence estimate |
|---------------------------------------|-------------------------|
| Veterans (10,27) | 0.3%–0.84% |
| Healthcare professionals (36) | 0.1%–8.1% |
| Men who have sex with men | Not available |
| Prisoners (41) | 0.9%–11.4% |
| Homeless patients (42,44) | 0.4%–1.17% |
| People who inject drugs (46) | 11.8% |
| Patients with HCV coinfection (63–67) | 0.7%–5.8% |
| Patients with HIV coinfection (68,69) | 3.0%–8.4% |

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus
^aPrevalence data derived from HBsAg positivity.

homeless veterans in VA care in 2015, the estimated population prevalence of chronic HBV was 0.99% (2,395/242,740), in contrast to 0.40% (21,611/5,424,685) among nonhomeless veterans (44). Additional studies in nonveteran populations are needed to further clarify HBV prevalence in homeless individuals in the US.

People who inject drugs

People who inject drugs (PWID) are additionally considered a high-risk group for HBV because of known bloodborne virus transmission through sharing of needles and/or drug preparation equipment (45). Prevalence estimates in PWID have a stronger evidence base in context of more extensive and systematic examinations of communicable diseases in this population. A large 2011 systematic review of 1,125 studies revealed a pooled estimate for HBsAg prevalence of 11.8% (46). A more recent global systematic review in 2017 of 1,147 studies revealed a pooled HBsAg prevalence estimate of 4.8% (95% CI 3.0–7.2) in North America (47). Furthermore, analysis of 2001–2016 NHANES data revealed an anti-HBc+ prevalence of 19.7% (95% CI, 16.0%–24.0%) among those with a history of intravenous drug users vs 4.6% among those without a history of intravenous drug users, although HBsAg-positive prevalence could not be estimated because of the small sample size (48). Chronic HBV prevalence estimates vary widely across both HCV (0.7%–5.8%) and HIV (3.0%–8.4%) cohorts.

Patients with HIV or HCV coinfection

Owing to shared routes of transmission, HBV infection is more common among patients with chronic HCV and/or HIV infections, as summarized in Table 3.

Summary of HBV prevalence in the United States in additional high-risk groups

- Veterans with the highest risk of HBV infection include those of Asian descent and HIV coinfection and with high-risk sexual practices.
- Although healthcare professionals are at risk for this bloodborne infections, the prevalence of chronic HBV in this population is outdated and poorly described.

Table 3. HBV prevalence data from several studies examining HIV and HCV patients^a

| Study | Years studied | Coinfection | Study population | N | HBV prevalence estimate |
|-----------------------|-----------------------------|-------------|---|---------|--------------------------|
| Kellerman et al. (63) | 1998–2001 | HIV | Unvaccinated HIV-infected patients from the Adult/Adolescent Spectrum of HIV Disease Project | 19,904 | 7.6% |
| Spradling et al. (64) | 1996–2007 | HIV | HIV-infected patients | 7,618 | 8.4% |
| Chun et al. (65) | 1986–2009 | HIV | Patients in the US Military HIV Natural History Study diagnosed during the specified time period | 2,352 | 3.0% |
| Chun et al. (66) | 1996–2012 | HIV | Patients in the US Military HIV Natural History study who initiated HAART during the specified time period | 2,536 | 6.0% |
| Belperio et al. (67) | January 2014–September 2016 | HCV | Veterans from the Department of Veteran's Affairs who received HCV DAA therapy during the specified time period | 62,920 | 0.7% |
| Tyson et al. (68) | 1997–2005 | HCV | HCV-positive patients in the National Veteran's Affairs HCV Clinical Case Registry | 102,971 | 1.4% |
| Bini et al. (69) | September 1998–July 2004 | HCV | Patients with chronic HCV from 2 medical centers in New York, NY | 1,257 | 5.8% (95% CI, 4.5%–7.1%) |

CI, confidence interval; DAA, direct-acting antiviral; HAART, highly active antiretroviral therapy; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
^aPrevalence data derived from HBsAg positivity.

- MSMs carry an increased risk of transmitting HBV through unprotected sexual behaviors, but national prevalence data specific to MSM in the US are not available.
- Prevalence estimates of HBV in PWID have a stronger evidence base in context of more extensive and systematic examination of communicable diseases in this population. Studies in PWID report HBV prevalence ranges between 4% and 12%.
- Chronic HBV prevalence estimates vary widely across both HCV (0.7%–5.8%) and HIV (3.0%–8.4%) cohorts.

HBV PREVALENCE IN OTHER SPECIAL POPULATIONS

Several other patient groups may be characterized as “special populations” in whom HBV prevalence has been defined and may influence approach to clinical evaluation and management (49).

Pregnant women

Perinatal or mother-to-child transmission remains one of the most common routes for HBV transmission in endemic regions (50). In the absence of an HBV vaccine and hepatitis B immune globulin, an estimated 90% of infants born to HBV-infected mothers will develop the infection (51), of whom 90% may progress to chronic HBV (45) and approximately 25% may experience HBV-related mortality because of liver cirrhosis and/or liver cancer (52). National guidelines across developed nations and low- and middle-income countries recommend universal screening of HBsAg in all pregnant women, regardless of vaccination status (52). However, there are limited data on HBV prevalence among pregnant women in the US. Din et al. examined 2006 data from 22 US states (2,359,912 births) and used imputation methods to calculate a total of 16,608 births to HBV-

infected women and an estimated chronic HBV prevalence of 0.7% among pregnant women. Foreign-born individuals (25.3% of mothers) accounted for 80.6% of births to HBV-infected mothers, particularly among those born in Southeast Asia (31.2%), East Asia (21.2%), or Africa (13.8%) (53). Another study examining US data from a nationally representative sample revealed a prevalence of maternal HBV infection of 85.8 cases per 100,000 deliveries (0.09%) during the period 1998–2011 and notably the rate of maternal HBV infection increased 5.5% annually during this period, suggesting that contemporary estimates may be higher (54), which is further supported by recent NHANES data from the 2003–2014 period which suggest a temporal decrease in detectable HBV immunity among pregnant women (52). These findings provide validation for existing US Preventative Service Task Force (USPSTF) recommendations for routine HBV screening of all pregnant women at the first prenatal visit (54).

Newborns

Infants born to HBV-infected mothers are at uniquely high risk for HBV infection. The US Perinatal Hepatitis B Prevention Program, a CDC-funded initiative, recommends postexposure prophylaxis to these at-risk infants, including administration of the first of a series of 3 hepatitis B vaccine shots plus hepatitis B immune globulin within 12 hours of birth, which has been demonstrated to be 85%–95% effective after just the first dose of vaccine. Despite an increase in the number of estimated births to HBsAg-positive women in the US during the period 2000–2009, perinatal HBV infection has remained stable likely attributable in large part to successful implementation of testing and prophylaxis: 796–876 (3.35%–4.07%) from 2000 to 2004, 799–836 (3.37%–3.40%) from 2005 to 2007, and 747–761 (3.01%–3.09%)

from 2008 to 2009; an updated HBV prevalence rate among infants born to HBsAg-positive mothers in 2009 was 3.84% (55).

Diabetics

Patients with diabetes mellitus have been observed to have a higher prevalence of chronic HBV infection compared with the general population. The CDC reported the results of a NHANES analysis of 1999–2010 data which revealed a 60% ($P < 0.001$) higher seroprevalence of positive anti-HBc among patients with diabetes compared to those without diabetes, with OR 1.7 (CI = 1.3–2.2) for persons aged 18 through 59 years, and 1.3 (CI = 1.0–1.6) for persons aged greater than or equal to 60 years (56). Furthermore, diabetes mellitus is associated with an increased incidence of hepatocellular carcinoma and all-cause mortality among patients with chronic HBV (57). Owing to the reports of 29 outbreaks of HBV in long-term care facilities from 1996 to 2011, the Hepatitis Vaccines Work Group of the Advisory Committee on Immunization Practices (ACIP) examined the risk for HBV infection among adult diabetic patients and concluded that HBV transmission was increased because of the reuse of insulin pens and glucose monitoring equipment, and inadequate sterilization of podiatry equipment (58,59). In this context, the CDC and ACIP currently recommends HBV vaccination in all diabetic patients (56).

Summary of HBV prevalence in other special populations

- Studies report that cases of HBV are increasing among pregnant women, indicating that routine HBV screening of all pregnant women at the first prenatal visit (per published recommendations) is necessary to avoid the high risk of transmission to newborns.
- Despite an increase in the number of estimated births to HBsAg-positive women in the US, perinatal HBV infection seems to have remained stable; this is likely attributable in large part to the successful implementation of HBV testing and prophylaxis in pregnant women.
- Although immunocompromised patients with inactive or resolved chronic HBV remain at lifelong risk for HBV reactivation, there are limitations to HBV prevalence data in these patients. The definition for reactivation is variable and existing studies consist of retrospective, single-center reports with small sample size, and largely restricted to selected patients undergoing TNF inhibiting therapies.
- Prevalence studies indicate a higher risk of HBV in diabetic patients. HBV vaccination is recommended in diabetic patients.
- The prevalence of chronic HBV among patients receiving hemodialysis in the US has not been reported perhaps because outbreaks in dialysis centers are now a rarity, given the standardized implementation of universal precautions and dialysis-specific infection control procedures.

UPDATED PREVALENCE OF HBV IN THE UNITED STATES

Recent epidemiologic surveys of US NHANES from 1988 to 2012, 2011–2014, and 1999–2016 have estimated a total prevalence of 0.35% (95% CI 0.28–0.45) or 0.84 million adults. However, because of the intrinsic methodologic limitations of the epidemiologic survey, including exclusion of institutionalized persons and under-sampling of high-risk populations, US NHANES is likely to underestimate the HBV prevalence. By contrast, imputation studies

such as those reported by Kowdley et al. using country-specific pooled HBV rates applied to US Census Bureau population data by country of birth have led to an estimated prevalence range of 1.62–2.21 million persons. However, these analyses may overestimate prevalence because of the reliance on country-specific prevalence studies enriched with high risk individuals who may not be representative of cohorts immigrating to the US and are of variable methodologic quality. In light of this disparity, the CLDF panel aimed to generate an updated prevalence estimate based on a literature review of HBV in US-born and foreign-born persons, and additional key populations at increased risk for HBV. However, the authors identified a significant paucity of quality evidence to support accurate nonsurvey prevalence estimates in key populations.

Applying the 2016 NHANES estimates by Le et al. to updated US Census Bureau population figures results in an estimated overall HBV prevalence in 2018 of 1.13 million persons (95% CI 904,837–1,454,202), including 416,622 US born (95% CI 277,748–666,595) and 581,222 foreign-born persons (431,376–785,558) (60), and an overall HBV prevalence in 2019 of 1.15 million persons (95% CI 923,678–1,484,483) (61). Given the limitations of NHANES, the authors proposed a new projected estimate which incorporates distinct subgroup estimates for US-born individuals (NHANES 2016), foreign-born individuals (NHANES and Kowdley et al.), and non-NHANES populations. Specifically, the number of US-born (196 million) and foreign-born (42 million) persons were derived from the NHANES 2016 data with appropriate sample weights. Prevalence data from NHANES 2016 analyses were applied to the race/ethnic categories of the denominator population with overall estimate of 303,237 persons (0.15%) (137,314–759,467 [0.07%–0.39%]). Prevalence data for HBsAg-positive individuals in Asian immigrants from Kowdley et al. was applied to the NHANES 2016 estimates of foreign-born non-Hispanic Asians, and NHANES 2016 estimates for non-Asian foreign-born individuals were applied, resulting in an overall estimate of 1,649,014 persons (0.69%) (1,212,383–2,380,727 [0.51%–1.00%]). Prevalence data for non-NHANES populations were derived from the available literature in homeless (44) and incarcerated populations and applied to the total noninstitutionalized civilian adult US population as of December 2016; because of the absence of adequate HBV prevalence data in military personnel and nursing home residents, NHANES average was applied for these subgroups (62). The overall estimated prevalence for chronic HBV infection in the US is 1.59 million persons (range 1.25–2.49 million), incorporating the NHANES point estimate for US-born persons, low-range estimate for the foreign-born NHANES, and middle estimate for non-NHANES populations (Table 4). It is likely that this range represents an underestimation of HBV prevalence because of the noted methodologic limitations. As such, the panel views its estimated US prevalence of chronic HBV to represent a conservative figure which will require modification as further evidence emerges.

CONCLUSIONS

Chronic HBV infection remains a US and global public health burden that is associated with significant morbidity and mortality. In light of articulated WHO and US Health and Human Services goals to achieve viral hepatitis elimination, a clearer understanding of current and evolving HBV prevalence in the overall US population and key high-risk populations is of high

Table 4. Estimated prevalence of chronic HBV in the United States^a

| US adult population | HBsAg % | | | # Infected | | | |
|---------------------|-------------|------|------|------------|-----------|-----------|-----------|
| | Estimate | Low | High | Estimate | Low | High | |
| NHANES | | | | | | | |
| US Born | | | | | | | |
| NHW | 147,987,653 | 0.08 | 0.03 | 0.22 | 118,390 | 44,396 | 325,573 |
| NHB | 24,218,518 | 0.52 | 0.32 | 0.85 | 125,936 | 77,499 | 205,857 |
| Mexican | 10,342,209 | 0.14 | 0.03 | 0.61 | 14,479 | 3,103 | 63,087 |
| Hispanic | 5,385,932 | 0.00 | 0.00 | 0.00 | — | — | — |
| Asian | 1,713,790 | 0.79 | 0.17 | 3.59 | 13,539 | 2,913 | 61,525 |
| Other | 6,715,866 | 0.46 | 0.14 | 1.54 | 30,893 | 9,402 | 103,424 |
| Total | 196,363,968 | 0.15 | 0.07 | 0.39 | 303,237 | 137,314 | 759,467 |
| Foreign born | | | | | | | |
| NHW | 5,973,450 | 1.82 | 1.31 | 2.32 | 108,681 | 78,463 | 138,440 |
| NHB | 3,241,836 | 6.26 | 4.05 | 8.47 | 202,886 | 131,153 | 274,552 |
| Latin American | 20,697,137 | 0.77 | 0.44 | 1.12 | 159,197 | 91,675 | 231,101 |
| Asian | 11,608,458 | 7.23 | 6.42 | 8.04 | 838,855 | 745,275 | 933,252 |
| Other | 1,049,022 | 3.45 | 2.72 | 4.19 | 36,156 | 28,503 | 43,914 |
| Total | 42,569,903 | 3.45 | 2.72 | 4.19 | 1,345,776 | 1,075,069 | 1,621,260 |
| NHANES total | 238,933,871 | 0.69 | 0.51 | 1.00 | 1,649,014 | 1,212,383 | 2,380,727 |
| Non-NHANES | | | | | | | |
| Incarcerated | 2,131,000 | 2.35 | 1.00 | 3.70 | 50,079 | 21,310 | 78,847 |
| Homeless | 160,600 | 2.00 | 0.99 | 3.00 | 3,204 | 1,590 | 4,818 |
| Military | 1,288,600 | 0.69 | 0.51 | 1.00 | 8,893 | 6,539 | 12,840 |
| Nursing home | 1,425,500 | 0.69 | 0.51 | 1.00 | 9,838 | 7,233 | 14,204 |
| Non-NHANES total | 5,005,700 | 1.44 | 0.73 | 2.21 | 72,013.96 | 36,671.66 | 110,708 |
| US total | 243,939,571 | 0.71 | 0.51 | 1.02 | 1,721,027 | 1,249,055 | 2,491,435 |
| Our estimate | | | | | 1,587,634 | | |

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NHB, non-Hispanic blacks; NHW, non-Hispanic whites.
^aPrevalence data derived from HBsAg positivity.

public health importance. This review summarizes key epidemiologic studies, addressing HBV prevalence. Based on epidemiologic surveys and imputation studies, the authors propose an overall estimated prevalence for chronic HBV infection in the US of 1.59 million persons (range of 1.25–2.49 million persons). Additional research to characterize HBV epidemiology in the US is needed to better inform public health strategies to improve screening/diagnosis, linkage to care, and both immunization and treatment of HBV infection.

CONFLICTS OF INTEREST

Guarantor of the article: Joseph K. Lim, MD.

Specific author contributions: J.K.L. led and participated in the panel that met to evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, facilitated and contributed to the development on the consensus statement regarding HBV prevalence rates in the US, and drafted the manuscript on the prevalence of HBV in the United States; J.K.L. has approved the final draft. M.H.N. participated in the panel that met to

evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, contributed to the development on the consensus statement regarding HBV prevalence rates in the United States, and drafted the manuscript on the prevalence of HBV in the United States; M.H.N. has approved the final draft. W.R.K. participated in the panel that met to evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, contributed to the development on the consensus statement regarding HBV prevalence rates in the United States, and drafted the manuscript on the prevalence of HBV in the United States; W.R.K. has approved the final draft; R.G. participated in the panel that met to evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, contributed to the development on the consensus statement regarding HBV prevalence rates in the United States, and drafted the manuscript on the prevalence of HBV in the United States; R.G. has approved the final draft; P.P. participated in the panel that met to evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, contributed to the development on the consensus statement regarding HBV

prevalence rates in the United States, and drafted the manuscript on the prevalence of HBV in the United States; P.P. has approved the final draft; I.M.J.: organized the panel consisting of the authors, participated in the panel that met to evaluate and summarize the most current and relevant peer-reviewed literature regarding the prevalence of HBV, contributed to the development on the consensus statement regarding HBV prevalence rates in the United States, and drafted the manuscript on the prevalence of HBV in the United States; I.M.G. has approved the final draft; and Rachel E. Bejarano, PharmD. provided medical writing assistance.

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