

Trends in Diagnosed Chronic Hepatitis B in a US Health System Population, 2006–2015

Mei Lu,¹ Yueren Zhou,¹ Scott D. Holmberg,³ Anne C. Moorman,³ Philip R. Spradling,³ Eyasu H. Teshale,³ Joseph A. Boscarino,⁴ Yihe G. Daida,⁵ Mark A. Schmidt,⁶ Jia Li,¹ Loralee B. Rupp,² Sheri Trudeau,¹ and Stuart C. Gordon⁷, for the Chronic Hepatitis Cohort Study Investigators

¹Department of Public Health Sciences, ²Center for Health Policy and Health Services Research, and ⁷Division of Gastroenterology and Hepatology, Henry Ford Health System, and Wayne State University School of Medicine, Detroit, Michigan, ³Division of Viral Hepatitis, National Center for HIV, Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta Georgia, ⁴Department of Epidemiology and Health Services Research, Geisinger Clinic, Danville, Pennsylvania, ⁵Center for Health Research, Kaiser Permanente Hawaii, Honolulu, Hawai'i and ⁶Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

Background: Trends in the epidemiology of chronic hepatitis B (CHB) among routine clinical care patients in the United States are not well documented. We used data from the Chronic Hepatitis Cohort Study to investigate changes in prevalence and newly recorded cases of CHB from 2006 to 2015.

Methods: Annual percentage changes (APCs) were estimated using join point Poisson regression. Analyses were adjusted by study site; when an interaction with the trend was observed, APCs were estimated by subgroups. Differences in rates based on race, age, and sex were calculated with rate ratios.

Results: We identified 5492 patients with CHB within select health systems with total populations that ranged from 1.9 to 2.4 million persons. From 2006 to 2014, the prevalence of diagnosed CHB increased from 181.3 to 253.0 per 100 000 persons in the health system population; from 2014 to 2015, it declined to 237.0 per 100 000 persons. APC was +3.7%/y through 131 December 2014 ($P < .001$) and $-15.0\%/y$ ($P < .001$) thereafter. The rate of newly reported cases of CHB did not change significantly across the study period (APC, $-1.1\%/y$; $P = .07$). The rates of newly reported cases were 20.5 times higher among patients in the Asian American/American Indian/Pacific Islander (ASINPI) category, compared with white patients, and 2.8 times higher among African American patients. The ratio of male to female patients was roughly 3:2.

Conclusions: The prevalence of diagnosed CHB in this US patient population increased from 2006 to 2014, after which it decreased significantly. Rates declined most rapidly among patients ≤ 40 or 61–70 years old, as well as among ASINPI patients. The rate of newly reported cases remained steady over the study period.

Key words: cirrhosis prevalence; decompensated cirrhosis; hepatocellular carcinoma (HCC); join point modeling; liver transplant.

Understanding the epidemiology of chronic hepatitis B (CHB) infection in the United States may improve identification and management strategies, prevent serious sequelae, and inform immunization strategies to eliminate new infections [1]. A better understanding of how existing and new case diagnoses of CHB have changed in the last decade, particularly among patient subgroups, is an important step in determining how to best leverage care.

A number of studies have sought to estimate the burden of CHB prevalence and incidence in the United States. A 2015 Centers for Disease Control and Prevention (CDC) surveillance

report reported an overall rate of new CHB cases of 7.6 per 100 000 population [2]; this report also found differences by age, race, and sex; a 2016 CDC surveillance summary reported that the 4-year new case rate was 23.3 per 100 000 from 2013 to 2016 (a mean of 5.8 per 100 000 annually) [3]. The National Health and Nutrition Examination Survey (NHANES), which used serological testing to identify CHB (eg, with positive hepatitis B surface antigen [HBsAg] results), found a period prevalence of CHB ranging from 270.0 to 470.0 per 100 000 persons living in the United States from 1999 to 2006 [4–6]; this estimate was revised to 300.0–500.0 per 100 000 in 2009 [7]. A study of Medicaid enrollees reported similar period prevalence of 290.0 per 100 000 persons for the period of 2000–2007 [8]. A recent comparative meta-analysis [9] estimated US prevalence of CHB at 270.0 per 100 000, but these findings were criticized for not including groups at particular risk of CHB, such as migrants from endemic areas, or high-risk groups, such as the homeless or incarcerated [10].

Despite the number of reports describing point or period prevalence of CHB, there are few analyses seeking to investigate changes in CHB prevalence and rates of newly reported

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Correspondence: Mei Lu, PhD, Department of Public Health Sciences, Henry Ford Health System, 1 Ford Pl, 3E, Detroit MI 48202 (mlu1@hfhs.org).

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cases over time. A 2016 study using NHANES data suggested that the prevalence of CHB has been roughly steady at 300.0 per 100 000 from 1988 through 2012 [7], but there are no recent formal statistical trend analyses of CHB epidemiology among patients under routine clinical care in the United States. In addition, there are no recent analyses of trend differences by age, race, and sex, despite a recent study that showed considerable disparities by race (2740 per 100 000 among Asian Americans and 640 per 100 000 among African Americans) using NHANES data (2011–2012; n = 81 CHB cases) [11]. Based on a sample of patients with CHB drawn from the Chronic Hepatitis Cohort Study (CHeCS)—a racially diverse longitudinal study of 4 geographically distinct US health systems serving >2 million patients—we investigated temporal trends in newly reported cases and prevalence of CHB from 2006 to 2015 in the CHeCS health systems and also looked at whether those trends differed by patient demographic characteristics.

METHODS

CHeCS includes patients ≥ 18 years old who received health-care services on or after 1 January 2006 at 1 of 4 healthcare systems—Henry Ford Health System, Detroit, Michigan; Geisinger Health System, Danville, Pennsylvania; Kaiser Permanente Northwest, Portland, Oregon; and Kaiser Permanente, Hawai'i, Honolulu, Hawai'i. The study follows all US Department of Health and Human Services guidelines regarding the protection of human subjects; the CHeCS protocol was approved and is renewed annually by the institutional review boards at all 4 sites. Owing to the de-identified nature of this observational study, requirements for written informed consent were waived.

CHeCS methods have been described elsewhere [12, 13]. Briefly, CHeCS uses a comprehensive case identification and data collection system based on electronic health records. For the present study, CHB cases were identified electronically using a validated Classification and Regression Tree model, which has excellent predictive accuracy (area under the receiver operating characteristic curve, 0.97) [13], using a combination of laboratory results and diagnosis codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, and *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*. Specifically, patients were identified as having CHB if they met ≥ 1 of the following 3 criteria (in hierarchical order): (1) a laboratory record of HBsAg or detectable hepatitis B virus (HBV) DNA and the presence of ≥ 1 ICD-9-CM or ICD-10-CM diagnosis code associated with viral hepatitis B (070.20–070.23, 070.30–070.33, B18.0, B18.1, B16.0, B16.1, B16.2, B16.9, B17.0, B19.10, or B19.11) or chronic liver disease (571.5, 456.0, 456.1, 789.59, 155.0, v42.7, v42.70, v49.83, I85.00, I85.01, K74.0, k74.60, K74.69, C22.0, C22.7, C22.8, R18.8, or Z94.4); (2) ≥ 2 positive laboratory results for HBsAg, hepatitis B e antigen, or

HBV DNA, in any combination, occurring ≥ 6 months apart; and (3) positive laboratory results for total hepatitis B core antibody and HBsAg. Medical chart abstraction was used to confirm CHB among patients identified by the third criterion—positive laboratory results for total hepatitis B core antibody and HBsAg in the absence of other criteria—to exclude patients with acute HBV infection.

Data Collection and Analysis

Data were collected for the period spanning 1 January 2006 through 31 December 2015. The *index date* was defined as the earliest date of either (1) CHB diagnosis, based on ICD-9-CM or ICD-10-CM codes, or (2) first positive CHB-related laboratory test result (eg, HBsAg, HBV DNA, or hepatitis B e antigen) in the electronic health record during the study period [12]. Patients with CHB diagnosed before 2006 were captured in CHeCS prevalence estimates for later years if they remained in a CHeCS health system. Patient demographic data—age category at index date (≤ 40 , 41–50, 51–60, 61–70, or >70 years) and race (black/African American, Asian American/American Indian/Pacific Islander [ASINPI], white, or other/unknown)—were collected for both patients with CHB and the overall health system populations (HSPs).

For prevalence, the numerator for a given year included all living adult CHB cases with an index date on or between 1 January 2006 and 31 December of that given year and who continued to receive healthcare within the health system. For example, the prevalence numerator for 2010 would be defined as all patients with index dates between 1 January 2006 and 31 December 2010 and whose last encounter was in 2010 or later. The numerator for newly reported cases for a given year was defined as the number of adults with CHB whose index date fell into that particular calendar year. Adult patients in the HSP were included in the denominator for all years in which they had an encounter with a CHeCS health system, as well as any years between their first and last encounters. In other words, a patient whose first encounter was in 2007 and last encounter was in 2010 would be included in the HSP (denominator) for years 2007, 2008, 2009, and 2010. We also performed an ad hoc analysis to estimate the rate of new CHB cases in 2015 in the 4 CHeCS health systems using the CDC surveillance case definition, and we compared our results with the CDC-reported rate of new cases in 2015.

Join point modeling was used to study the dynamics of longitudinal trends in prevalence and rates of newly reported cases. We adapted and extended a 2-step join point Poisson regression modeling approach [14] by fitting a series of straight lines on a log scale to the trend; each join point represents a statistically significant ($P < .05$) change in trend (ie, slope of the line segment). For example, a single join point splits the trend line into 2 line segments, and zero join points indicates that the best fit to the trend consists of only a single line segment.

In the first step, we identified the optimal joinpoints using a nonlinear modeling approach. Next, multivariable analyses were performed based on the selected joinpoints, as well as potential stratification variables. Interactions were tested only for individual variables that were significant. Variables were retained in the adjusted analyses if they had either a significant individual effect on the trend or demonstrated a variable-by-trend interaction ($P < .05$). We also evaluated whether the annual percentage change (APC) of each line segment differed from no change (APC, 0).

Unadjusted APCs were reported for overall trends. Adjusted APCs (aAPCs) were reported for trends by patient subgroup if there was a significant trend-by-variable interaction. Adjusted

rate ratios (RRs) were estimated for rate differences within variable categories if there was no interaction between trend and the variable. SAS software (version 9.4; SAS Institute) was used for all analyses. The study site was included in all analyses as a stratification variable.

RESULTS

Study Population

From 2006 to 2015, we identified a total of 5492 unique patients with CHB. During that period, the total adult HSP for the 4 health systems that participate in CHcCS increased from 1.9 million to 2.5 million (Table 1). The majority of patients

Table 1. Unadjusted Prevalence and Incidence of Chronic Hepatitis B Among Patients in the 4 Chronic Hepatitis Cohort Study Health Systems (per 100 000 Adult Health System Population)

Prevalence and Newly-reported cases of CHB	Year (HSP in Millions)									
	2006 (1.91)	2007 (1.95)	2008 (1.99)	2009 (2.03)	2010 (2.05)	2011 (2.07)	2012 (2.07)	2013 (2.09)	2014 (2.16)	2015 (2.47)
Prevalence per 100 000 persons ^a										
Overall	181.1	193.1	203.6	211.1	221.9	231.0	237.0	249.2	253.9	236.9
Race										
African American	271.9	271.2	277.2	268.6	281.7	275.0	290.3	308.1	328.9	323.5
ASINPI	1412.3	1472.7	1401.7	1408.2	1431.1	1397.2	1350.6	1364.8	1383.9	1263.3
White	70.4	71.8	73.0	73.1	75.3	77.0	79.0	80.5	73.5	63.6
Unknown	60.9	71.5	85.8	99.0	120.3	128.1	132.3	138.2	148.7	134.6
Sex										
Female	162.5	173.6	184.0	193.4	203.8	213.8	222.6	237.2	246.5	237.8
Male	205.6	219.0	230.0	235.7	247.0	255.1	258.2	268.3	267.5	239.8
Age, y										
≤40	160.9	169.8	173.9	177.2	182.3	189.1	187.6	187.7	181.5	160.1
41–50	256.9	262.7	276.8	282.6	298.6	305.8	317.2	341.2	365.4	348.7
51–60	221.4	250.5	265.0	279.7	299.6	305.2	314.2	331.7	333.2	323.4
61–70	152.5	161.7	180.2	193.1	210.6	232.9	250.6	276.9	287.7	265.4
>70	72.0	82.1	97.1	108.4	109.9	121.7	128.2	139.7	152.8	149.4
M:F ratio	1.3	1.3	1.2	1.2	1.2	1.2	1.2	1.1	1.1	1.0
Newly recorded cases per 100 000 persons ^a										
Overall	18.5	18.0	19.2	17.3	19.8	17.5	17.6	19.4	18.4	18.4
Race										
African American	56.8	21.9	34.3	18.0	26.6	16.0	33.3	33.8	39.6	48.6
ASINPI	156.7	164.7	95.7	148.3	137.0	112.3	107.4	117.7	100.8	99.5
White	7.5	5.8	5.4	5.6	6.9	5.6	7.1	5.8	4.5	5.4
Unknown	9.7	12.6	19.3	16.2	25.8	10.4	10.8	11.1	18.5	10.6
Sex										
Female	15.1	14.1	17.0	14.8	16.5	14.1	15.0	17.4	15.7	15.4
Male	22.5	22.8	22.2	20.4	23.9	21.7	20.9	22.4	21.7	21.9
Age, y										
≤40	19.7	20.4	23.7	19.1	22.8	21.6	20.8	20.6	18.3	17.8
41–50	25.8	20.1	18.4	19.0	24.1	20.2	19.8	28.1	29.3	27.0
51–60	20.3	20.6	18.4	20.0	22.3	16.5	20.2	21.6	17.9	21.1
61–70	12.2	11.9	15.9	14.7	14.0	11.8	14.8	13.9	15.6	15.6
>70	2.9	7.9	9.2	5.9	4.7	6.8	2.9	5.9	7.4	7.2
M:F ratio	1.5	1.6	1.3	1.4	1.4	1.5	1.4	1.3	1.4	1.4

Abbreviations: ASINPI: Asian American/American Indian/Pacific Islander; CHB, chronic hepatitis B; HSP health system population.

^aFor prevalence, the numerator is all living adult patients with CHB with an index date on or before 31 December of the given year. For newly recorded cases, the numerator is the number of adult patients with CHB whose index date fell within a given year. For both, the denominator is adult patients in the HSP for all years in which they had an encounter with a Chronic Hepatitis Cohort Study health system, as well as any years between their first and last encounter.

in the HSP were white (64%–70%), female (55%–56%), and ≤ 40 years of age (34%–39%). Among patients with CHB, however, ASINPI patients were overrepresented. Despite making up $< 10\%$ of the HSP, they represented $> 50\%$ of patients with CHB. Likewise, CHB was disproportionately more prevalent among male patients, with a 3:2 male-female ratio among patients with CHB. Overall, the prevalence of CHB was highest among patients 41–50 or 51–60 years old, averaging roughly 300 cases per 100 000 HSP over the study period for both groups.

Trends in CHB Prevalence

From 2006 through 2015, the number of prevalent CHB cases per year ranged from 3098 to 3924. Table 1 presents observed annual CHB prevalence rates in the CHeCS HSP from 2006 to 2015, overall and by race, sex, and age categories. Over the study period, CHB prevalence increased steadily from 181.1 to 253.9 per 100 000 HSP from 2006 to 2014, after which it declined to 236.9 per 100 000 in 2015. Similar patterns and timing were observed by sex. The prevalence of CHB among female patients increased from 162.5 to 246.4 per 100 000 HSP in 2014, then declined to 237.8 in 2015; the prevalence among male patients increased from 205.6 to 267.5 per 100 000 HSP, then declined to 239.8. Patterns were similar for all race and age categories, although the timing varied for some groups. For example, prevalence peaked in 2011 among patients aged ≤ 40 years, before slowly declining.

Join point analyses demonstrated trends in 2 segments: (1) 1 January 2006 through 31 December 2014 and (2) 1 January through 31 December 2015 (Figure 1). Overall, the APC in prevalence for the first segment was $+3.7\%/y$ (95% confidence interval [CI], $+3.3$ to $+4.2$; $P < .001$), indicating a significant

increase (Table 2). For the second segment, APC was $-15.0\%/y$ (95% CI, -18.1 to -11.8 ; $P < .001$), indicating a significant decline. Prevalence was consistently 1.5 times higher in male patients compared with female patients across the study period (RR, 1.5; 95% CI, 1.4–1.5; $P < .001$), indicating no change in the relative prevalence by sex during 2006–2015 (Figure 2A).

Interactions were observed between time and age and between time and race, indicating that there were different trends within age, and race subgroups. Although the joinpoint remained at 2014, trends in prevalence varied by age category. In stratified analyses, aAPCs for the first segment (2006–2014) indicated increasing prevalence among all age groups, except patients aged ≤ 40 years, for whom no significant trend was detected ($P = .06$). APCs for this period were highest among patients aged 61–70 or > 70 years (aAPC, $+9.9\%/y$ [95% CI, $+8.4$ to $+11.3$] and $+9.1\%/y$ [$+7.0$ to $+11.2$], respectively), indicating rapidly increasing prevalence among these patients. From 2014 to 2015, aAPCs decreased rapidly among all groups except patients > 70 years old, reflecting the decrease in prevalence observed in the overall results. Declines were most rapid among the youngest patients (≤ 40 years) (aAPC, $-17.6\%/y$; 95% CI, -24.1 to -10.6) and those aged 61–70 years ($-22.1\%/y$; -29.5 to -13.9).

Trends in prevalence also differed by race. For the first segment (2006–2014), CHB prevalence increased in all groups. However, aAPCs differed significantly between race groups; prevalence increased most rapidly in ASINPI patients (aAPC, $+11.5\%/y$; 95% CI, $+9.6$ to $+13.4$), followed by African American ($+6.8\%/y$; $+5.4$ to $+8.2$) and white ($+2.3\%/y$; $+1.4$ to $+3.1$) patients. After the 2014 join point, prevalence declined among ASINPI (aAPC, $-27.5\%/y$; 95% CI, -37.4 to -16.1)

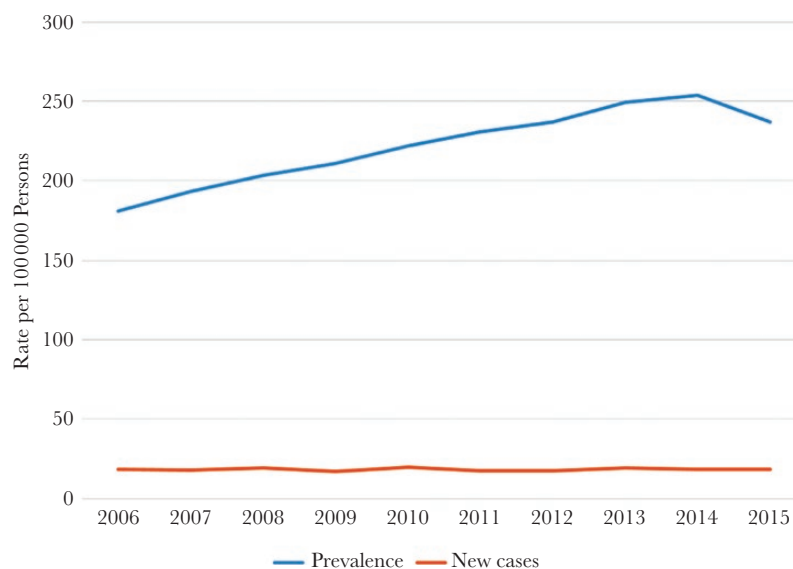


Figure 1. Overall prevalence and newly reported cases of chronic hepatitis B in participating Chronic Hepatitis Cohort Study health systems, 2006–2015. A join point (significant decrease in prevalence) was identified at the end of 2014.

Table 2. Annual Percentage Change in Prevalence of Chronic Hepatitis B Among Patients in the Chronic Hepatitis Cohort Study Health Systems, 2006–2015

Prevalence	First Segment (1 January 2006 to 31 December 2014)		Second Segment (1 January to 31 December 2015)	
	APC (95% CI)	PValue	APC (95% CI)	PValue
Overall	+3.7% (3.3–4.2)	<.001	–15.0% (–18.1 to –11.8)	<.001
Adjusted analysis				
Stratified by age				
≤40 y	+0.9% (–.0 to 1.7)	.06	–17.6% (–24.1 to –10.6)	<.001
41–50 y	+3.6% (2.6–4.6)	<.001	–10.9% (–18.1 to –3.1)	.001
51–60 y	+4.7% (3.7–5.7)	<.001	–15.1% (–21.8 to –7.7)	<.001
61–70 y	+9.9% (8.4–11.3)	<.001	–22.1% (–29.5 to –13.9)	<.001
>70 y	+9.1% (7.0–11.2)	<.001	–13.3% (–25.5 to 1.0)	.07
Stratified by race				
ASINPI/other	+11.5% (9.6–13.4)	<.001	–27.5% (–37.4 to –16.1)	<.001
African American	+6.8% (5.4–8.2)	<.001	–13.5% (–22.0 to –4.1)	.006
White	+2.3% (1.4–3.1)	<.001	–1.9% (–7.3 to 3.8)	.50

Abbreviations: APC, annual percentage change; ASINPI, Asian American/American Indian/Pacific Islander; CI, confidence interval.

and African American (–13.5%/y; –22.0 to –4.1) patients but remained steady among white patients (–1.9%/y; –7.3 to +3.8).

Trends in Newly Reported CHB Cases

Over the study period, the number of newly identified cases ranged from 288 to 358 per year. Table 1 presents observed yearly rates of newly reported cases of CHB, overall and by age, sex, and race. The overall rates of new cases ranged from 17.3 to 19.8 per 100 000 HSP across the study period, but these variations were not significant. Observed rates of newly recognized cases were highest among ASINPI patients but declined from 156.7 per 100 000 HSP in 2006 to 99.5 in 2015; rates were generally steady among African Americans (averaging 32.9 per 100 000 HSP across the study period) and whites (averaging 6.0 per 100 000 HSP). Consistent with observed prevalence, the rates of newly reported cases among male patients were roughly 1.5 times those among female patients. In 2006, the rate of new cases was highest among patients aged 41–50 years, followed closely by those aged ≤40 or 51–60 years; by 2015, the rate of new cases had declined somewhat among the youngest patients (≤40 years). Across the study period, the rate of newly reported cases remained lower and generally steady among all patients aged ≥61 years.

In join-point analyses, there was no detectable trend in the rate of newly reported cases across the study period ($P = .07$; Table 3 and Figures 1 and 2B). There was no interaction between time and sex, race, or age categories, indicating a flat trend of newly reported cases in all subgroups. The RRs for sex were consistent across the study period (RR for male vs female patients, 1.6; 95% CI, 1.5–1.8). Likewise, rates of new cases were significantly higher among ASINPI and African American patients than among white patients (RR, 20.5 [95% CI, 18.5–22.8] and 2.8 [2.5–3.2], respectively) across the study period. Rates of newly reported cases were consistently lowest in the oldest age group (>71 years) across the study period.

DISCUSSION

In a diverse, “real world” cohort of >5000 patients with CHB from 4 large US health systems with a combined patient population of >2 million, we observed that the prevalence of diagnosed CHB cases increased from 1 January 2006 through 31 December 2014, after which it decreased (through the 2015 calendar year). Adjusted analyses showed that prevalence increased most rapidly among the oldest patients in our cohort (those >60 years old) from 2006 to 2014 but remained flat thereafter. Rates of newly reported CHB cases, on the other hand, were flat across the study period. Such findings—increasing prevalence in combination with a steady rate of new cases—generally indicate longer disease duration. Given that recent advances in antiviral treatment options and uptake are credited with reducing CHB-related liver transplantation [15] and mortality [16] rates, our results suggest that persons with CHB are living longer. It is possible that the decline in prevalence we observe after 2014 is the result of death from multiple causes among elderly patients with CHB as the cohort ages. It is also possible that this trend will not be sustained in future years.

Prevalence was highest among ASINPI patients but declined substantially over the study period. The drivers of this dramatic shift among these patients are not clear, but given that a large proportion of ASINPI patients with CHB in the United States have emigrated from endemic countries [17], it is possible that changes in immigration patterns and/or rates of CHB vaccination or CHB prevalence in those countries may have influenced these rates.

Newly reported cases of CHB were steady across the study period. There were no differences in trends of new cases within race, sex, or age groups; that is, the RRs remained consistent across time within these groups. However, owing to the structure of our data set, we were unable to further refine our age categories. As a result, the youngest patients in our sample were

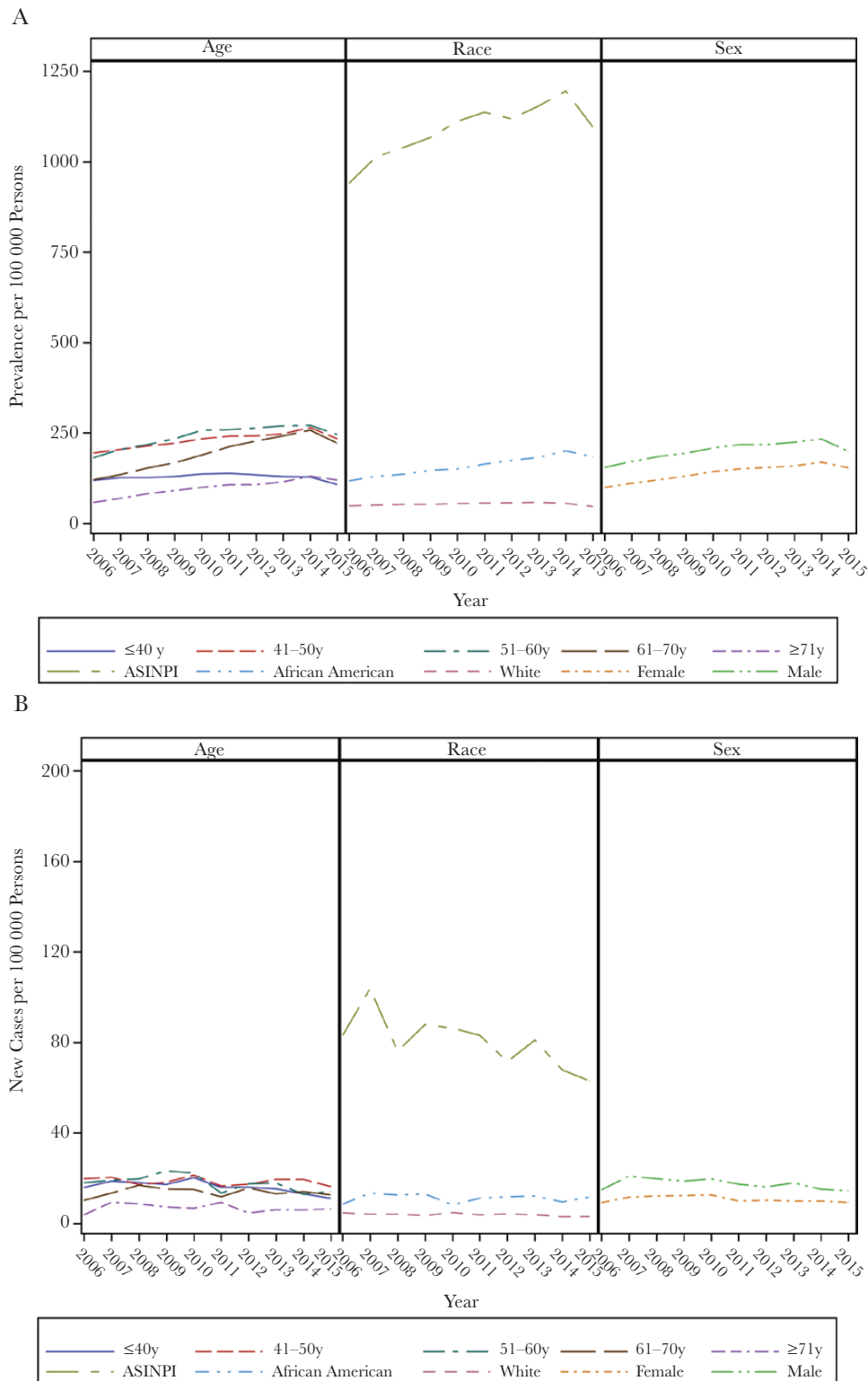


Figure 2. Prevalence of chronic hepatitis B (A) and rate of newly reported cases (B) by age, race, and sex in participating Chronic Hepatitis Cohort Study health systems from 2006 to 2015. Abbreviation: ASINPI, Asian American/American Indian/Pacific Islander.

categorized into a single age category of ≤ 40 years, making it difficult to draw conclusions regarding the impact of universal vaccination campaigns initiated in the 1990s, as well as the

proportion of new diagnoses found among women of child-bearing age who undergo prenatal testing for CHB. Previous studies have suggested that new infections in the United States

Table 3. Annual Percentage Change in Newly Reported Cases of Chronic Hepatitis B Among Patients in the Chronic Hepatitis Cohort Study Health Systems, 2006–2015

Newly Reported Cases	APC or RR (95% CI)	P Value
Overall APC	-1.1 (-2.3 to .1)	.07
Adjusted RR		
Prevalence		
Male vs female	1.5 (1.4–1.5)	<.001
Newly reported cases		
Male vs female	1.6 (1.5–1.8)	<.001
ASINPI vs white	20.5 (18.5–22.8)	<.001
African American vs white	2.8 (2.5–3.2)	<.001
ASINPI vs African American		
Age ≤40 vs >70 y	2.8 (2.3–3.3)	<.001
Age 41–50 vs >70 y	2.6 (2.2–3.2)	<.001
Age 51–60 vs >70 y	2.1 (1.7–2.5)	<.001
Age 61–70 vs >70 y	2.4 (2.0–2.8)	<.001

Abbreviations: APC, annual percentage change; ASINPI, Asian American/American Indian/Pacific Islander; CI, confidence interval; RR, rate ratio.

are declining among many groups of US-born persons but that newly diagnosed cases (rather than recently acquired infections), especially among immigrants from endemic regions, contribute to slower observed declines [17]. Constraints of our observational health system data also limit our ability to stratify patients by country of birth; such data are not routinely collected at all CHeCS sites and were missing for 77% of our sample.

There are few recent longitudinal studies regarding trends in prevalence of CHB in the United States. Period prevalence has been estimated using survey data from NHANES; for 1999–2006, estimates ranged from 270 to 470 per 100 000 persons [15]; this estimate was revised to 300 to 500 per 100 000 in 2009 based on multiple sources [6]. A more recent study using NHANES data suggested that the prevalence of CHB has been roughly steady, at 300 per 100 000, from 1988 through 2012 [7]. A recent comparative meta-analysis reported the US prevalence of CHB at 270.0 per 100 000 persons, based on studies published from 1965 to 2013 [10]. Likewise, a cross-sectional study of Medicaid patients from 5 states (California, Florida, New York, Ohio, and Pennsylvania) estimated CHB as 290.0 per 100 000 persons (2000–2007). The trends in prevalence that we observed from 2006 to 2013 (181 to 249 per 100 000) are consistent with these estimates, if a bit lower. Variation in results may be due to difference in sample populations and social determinants of health (such as access to care). We also note that CHeCS sites do not conduct universal testing for hepatitis B. As a result, the clinical care setting of our sample may underestimate prevalence compared with prospective samples, given that persons whose CHB has not been diagnosed would not be included in our medical record-based sample [1, 11].

For our main analysis, we identified CHB cases using previously validated criteria that included both diagnosis codes and

laboratory test results. Based on this definition, the rate of newly reported CHB cases was 18.3 per 100 000 HSP in 2015. For our ad hoc analysis, we applied the more conservative CDC surveillance case definition [1] to CHeCS data. Using this definition, the rate of newly reported CHB cases was 8.3 per 100 000 HSP in 2015; this is roughly consistent with the rate reported by the CDC (7.6 per 100 000) using surveillance data from 40 states for that year.

The inclusion of patients under routine care in US health-care systems is both a limitation and a strength of our analysis. Although our health system-based sample does not include some groups considered to be at particularly high risk for CHB (including homeless and incarcerated populations) [18, 19], our geographically diverse study spans the continental United States and Hawai'i, representing a broad cross section of the United States, and includes large proportions of African Americans and immigrants from China and Southeast Asia, among whom rates of CHB are generally recognized to be higher than in the overall US population [20]; this may limit its generalizability. A further limitation of this data, however, is that data regarding country of origin is not regularly collected at all CHeCS sites, making it impossible to draw conclusions regarding the proportion of US-born and foreign-born patients in our sample. In addition, American Indians are included in our category for Asian Americans and Pacific Islanders, although they may demonstrate distinct risk factors and rates of CHB. However, <1% of patients in our ASINPI category are identified as American Indian, so their inclusion in this group is not likely to have biased our results.

CHeCS uses an electronic health record-based data collection system, which permits us to stratify our sample by a number of patient characteristics to identify trends distinguishing groups, but by definition our cohort is limited to persons with at least some contact with the CHeCS health systems, so we cannot address trends among individuals who do not access healthcare services. We also note that our study focused on trends in CHB prevalence and newly reported cases rather than risk factors associated with hepatitis B screening and prevalence. Of course, screening rates will affect disease detection and therefore prevalence. Our group has previously analyzed a sample of >850 000 persons without previous hepatitis B; of them, 18.8% were tested for HBV infection, of whom 1.4% tested positive [21]. We are unable to perform an updated analysis to study risk factors related to screening and treatment patterns owing to limited system-wide data collection.

Given the importance of understanding the role of antiviral treatment in patients with CHB, we are undertaking a number of analyses related to treatment and long-term outcomes. Because these analyses are complicated by within-patient variation in CHB treatment indication and uptake across time, recent changes in treatment guidelines, as well as by disparities

in access to liver transplantation, such studies are outside the scope of the current article.

Across most of the study period, we observed that prevalence increased most rapidly among patients aged 61–70 years. In 2006, CHB prevalence was lower in these patients than among those aged 51–60 years; over time, prevalence increased in the former but remained flat in the latter group. The results is that by 2015, prevalence among the 2 age groups was similar. However, over the entire study period, the rate of newly reported CHB cases was constant in all age groups. This suggests that by 2015, all patients (but particularly those aged 61–70 years) were living longer than in 2006. The lack of a concomitant rise in newly reported cases of CHB in our health system cohort gives reason for optimism about the long-term success of hepatitis B prevention and treatment efforts in the United States.

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Author contributions. Design and conduct of the study: M. L., L. B. R., and S. C. G. Collection, management, analysis, and interpretation of the data: M. L., Y. Z., J. A. B., Y. G. D., M. A. S., J. L., L. B. R., ST and S. C. G. Preparation, review, or approval of the manuscript: M. L., Y. Z., S. D. H., A. C. M., P. R. S., E. H. T., J. A. B., Y. G. D., M. A. S., J. L., L. B. R., ST and S. C. G. Full access to all data in the study and responsibility for the integrity of the data and the accuracy of the data analysis: M. L.

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