Title

Epidemiology and Treatment Outcomes of Tuberculosis With Chronic Hepatitis B Infection—California, 2016—2020

Journal

Clinical Infectious Diseases, 79(1)

ISSN

1058-4838

Authors

Bertumen, J Bradford
Pascopella, Lisa
Han, Emily
et al.

Publication Date

2024-07-19

DOI

10.1093/cid/ciae169

Note: The snapshot PDF is a proof copy of the corrections marked in EditGenie, the layout will be different from a typeset PDF and the view of the article in EditGenie.

Author Queries & Comments:

AQ1 : Since there is no financial support, can this section be deleted here?

Response: Don't we still have to say no funding source for transparency? Similar to how we still need to explicitly say no conflicts of interest if we do not have any?

AQ2 : Please ensure that any color that should appear in the Figure art is reproduced correctly on the proof.

Response: Resolved

AQ3 : Please check the spelling and accuracy of all author names and affiliations, particularly for any co-authors. Also check that author surnames are correctly highlighted. This is to ensure that forenames and surnames are tagged correctly for online indexing. Incorrect names and affiliations may lead to an author not being credited for their work by funders, institutions, or other third parties. Make any changes directly in the text.Note that changes to your authorship list (adding or removing authors, changing designation of corresponding author) require additional approvals. Email jnls.author.support@oup.com if this is required.

Response: Resolved

AQ4 : Please provide department for affiliations 1-6, as applicable, directly in the text.

Response: Resolved

AQ5 : Please provide the department for the corresponding author “J. B. Bertumen” directly in the text.

Response: Resolved

AQ6 : Please provide the manufacturer’s name for all proprietary products mentioned in text, directly in the text, if not already done.

Response: Resolved

AQ7 : Note that the trademark symbol was deleted per style.

Response: How we denote a trademarked product like SAS if we cannot use the trademark symbol?

AQ8 : Because in-text footnotes are not allowed the footnote here was set as parenthetical text. Please check. Note also that legal citations are usually set as numbered references. If possible, please set each of these citations as a separate reference and renumber subsequent references and citations in text accordingly.

Response: Resolved

AQ9 : If your manuscript has figures or text from other sources, please ensure you have permission from the copyright holder. Also ensure that the copyright owner is properly credited, for instance in the figure legends. Make any changes directly in the text. For any questions about permissions, contact jnls.author.support@oup.com.

Response: Resolved

AQ10 : Please check this section as set/edited and amend if needed directly in the text.

Response: Resolved

AQ11 : Please ensure all “conflicts of interest” (or “disclosures”) have been included for you and your co-authors, and that this section is correct. Edit the text directly if changes are required.

Response: Resolved

AQ12 : Missing details have been imported to the references from PubMed/CrossRef. Please check and, if necessary, edit the references directly.

Response: Resolved

AQ13 : Please provide the publisher's location for reference [21] directly in the reference.

Response: Resolved

AQ14 : References 27, 33: Can more specific URLs be provided? If so, please provide directly in the reference.

Response: Resolved

AQ15 : Reference 31: Please add page range.

Response: There is no page range because it appears to be an internet journal. I cited the journal exactly as Pubmed recommended. I added the DOI in place of pages.

AQ16 : Please provide the page range for reference [31] directly in the reference.

Response: Resolved

AQ17 : Please note there is a charge per figure for colour reproduction (pricing information can be found on the journal website [**https://academic.oup.com/cid/pages/General_Instructions**]). Please confirm you accept this charge or confirm which figures should be published in black and white for no charge. If you have a pre-agreed discount, it will be applied to the charge in the licensing and payments portal.

Response: I accept the color charge for figure 3. All other figures and tables should be in black and white. Also, I noticed that the top of the tables is in orange. Is that just for this proof? It will not be printed orange, correct? I want tables to be just black and white.

AQ18 : Because there was no asterisk callout (*) in Figure 2 art, this was deleted in the figure legend. Please check.

Response: Resolved

AQ19 : Can "jiggered" be reworded in the figure legend to avoid jargon?

Response: Resolved

AQ20 : To match journal style, part tables are not allowed. We have renumbered Table [Table 1a and Table 1b] as Tables [1] and [2] and subsequent tables have been renumbered. Check and correct if necessary, directly in the text.

Response: Resolved

AQ21 : Please check placement of "37 386" as set in the stub column.

Response: Resolved

AQ22 : Please check the table footnotes as set/edited to better correspond to style.

Response: Resolved

AQ23 : Add "**2016–2020**" after "California" in the table title wanted?

Response: Resolved

AQ24 : Please add definition of N/A directly in the text.

Response: Resolved

AQ25 : We have received the following files for publication as supplementary material.• Supplemental Figures_Tables_CID_Bertumen_v2These will be published in the format provided, without edits. If any files need to be removed from this list, specify by responding to this query, stating the filename. If any files need to be added, upload them directly or email them with your proof corrections. If any files need to be updated, upload them directly or email them, without altering the filename. We will seek editor approval for any changes to supplementary material, which may delay publication of your article.

Response: Resolved

AQ26 : The caption for Figure 3 currently contains reference to colour used within the figure. For accessibility purposes reference to colour should be avoided. If possible, please update the wording for the figure caption to remove reference to colour.

Response: Resolved

CM1 (AUTHOR) : If this is going to be spelled out, it should be "Chronic Hepatitis B Virus Infection

Epidemiology and Treatment Outcomes of Tuberculosis With Chronic Hepatitis B Infection—California, 2016–2020

J Bradford Bertumen[1,2], Lisa Pascopella[2], Emily Han[2], Rosie Glenn-Finer[2], Robert J. Wong[3], Amit Chitnis[4], Devan Jaganath[5], Mirna Jewell[6], Prabhu Gounder[6], Sara McElroy[2], Lauren Stockman[2], Pennan Barry[2] [AQ3]

1 Centers for Disease Control and Prevention, Epidemic Intelligence Service, Atlanta, Georgia, USA [AQ4]

2 California Department of Public Health, Division of Communicable Disease Control, Richmond, California, USA

3 Stanford University School of Medicine, Department of Medicine/Gastroenterology and Hepatology Palo Alto, California, USA

4 Alameda County Public Health Department, Tuberculosis Section/Division of Communicable Disease Control and Prevention, San Leandro, California, USA

~~Tubercul~~

~~San Leandro, California, USA~~

5 University of California, San Francisco School of Medicine, Center for Tuberculosis San Francisco, California, USA

6 Los Angeles County Public Health Department, Communicable Disease Control and Prevention Division, Los Angeles, California, USA

Correspondence: J~~.~~ Bradford~~.~~ Bertumen, Centers for Disease Control and Prevention, Epidemic Intelligence Service 1600 Clifton Rd, Atlanta, GA 30022 (jbertumen@cdc.gov~~rhz5@cdc.gov~~). [AQ5]

ciae169_Supplementary_Data

History : received : 2023-12-312024-03-20

Background

Improved epidemiologic and treatment data for active tuberculosis (TB) with chronic hepatitis B virus (cHBV) infection might inform and encourage screening and vaccination programs focused on persons at risk of having both conditions.

Methods

We matched the California Department of Public Health TB registry during 2016–2020 to the cHBV registry using probabilistic matching algorithms. We used chi-square analysis to compare the characteristics of persons with TB and cHBV with those with TB only. We compared TB treatment outcomes between these groups using modified Poisson regression models. We calculated the time between reporting of TB and cHBV diagnoses for those with both conditions.

Results

We identified 8435 persons with TB, including 316 (3.7%) with cHBV. Among persons with TB and cHBV, 256 (81.0%) were non–US-born Asian versus 4186 (51.6%) with TB only ($P < .0001$). End-stage renal disease (26 [8.2%] vs 322 [4.0%]; $P < .001$) and HIV (21 [6.7%] vs 247 [3.0%]; $P = .02$) were more frequent among those with TB and cHBV compared with those with TB only. Among those with both conditions, 35 (11.1%) had TB diagnosed >60 days before cHBV (median, 363 days) and 220 (69.6%) had TB diagnosed >60 days after cHBV (median, 3411 days).

Conclusions

Persons with TB and cHBV were found more frequently in certain groups compared with TB only, and infrequently had their conditions diagnosed together. This highlights an opportunity to improve screening and treatment of TB and cHBV in those at high risk for coinfection.

Summary

Persons with tuberculosis and chronic hepatitis B are more likely to be non–US-born Asian people and have chronic medical conditions. Their 2 conditions were diagnosed with 60 days of each other only 19% of the time.

KEYWORDS

- tuberculosis
- hepatitis B
- diagnostic timing
- treatment outcomes
- epidemiology

Active tuberculosis (TB) disease and chronic hepatitis B virus (cHBV) infection are 2 conditions that lead to substantial morbidity and mortality. In 2022, TB caused an estimated 1.6 million deaths and cHBV caused 820 000 deaths worldwide [1, 2]. California has the third highest TB incidence rate in the United States (4.7 cases/100 000 population) and reports the most TB cases of any state [3]. Similarly, California has among the highest reported cHBV incidence rates (24.8 reports per 100 000 population) in the United States [4]. Tuberculosis is preventable through testing and treatment of latent TB infection (LTBI); cHBV is prevented by HBV vaccination. However, the cascade of care for both infections remains suboptimal, and only a limited percentage of those at risk for these infections are screened and linked to care [5–9].

The 2 infectious diseases share multiple risk factors, including human immunodeficiency virus (HIV) coinfection, substance use, history of incarceration, and birth in countries with a high reported prevalence of TB and cHBV [5, 10, 11]. Despite these shared risk factors, limited US data regarding persons with both TB and cHBV are available. This is mainly because national and state surveillance systems for TB and HBV have not routinely collected coinfection data, although a variable to collect viral hepatitis coinfection was recently added to the national TB disease case report form [5, 12]. Prior literature suggests a high prevalence of TB and cHBV coinfection outside of the United States [13, 14]. To date, data in the United States have been restricted to LTBI and cHBV coinfection and smaller studies that might not be generalizable to the California population [6, 15, 16].

Given the severity of both conditions individually, TB with cHBV infection could increase the risk for poor treatment outcomes, compared with TB only. Much of the literature regarding TB treatment outcomes among those with cHBV infection focuses on hepatotoxicity secondary to TB medications, with only a limited number of studies analyzing mortality during TB treatment and TB treatment completion [15, 17–20]. Data regarding the timing of TB and cHBV diagnoses have been limited to LTBI and cHBV coinfection, and improved data might elucidate how well providers screen for 1 condition in the presence of the other [16].

Current US guidelines recommend TB screening of populations with risk factors and universal HBV screening of all adults, but do not recommend routine screening for TB in those with cHBV and vice versa [10, 11]. Characterizing the epidemiology of TB with cHBV might inform and encourage screening and vaccination programs focused on communities with persons at risk of having both conditions. Additionally, a better understanding of the timeliness of detection and of treatment outcomes might lead to improvements in prevention and care for both conditions.

California has the largest non–US-born population of any state in the United States, with many of California's residents reporting their births in countries with a high prevalence of TB or cHBV [21–23]. This, plus California's high burden of both conditions, raises concern that there might be many persons with TB and cHBV. We sought to characterize the epidemiology of TB with cHBV and describe TB treatment outcomes among persons with both conditions.

METHODS

Data Sources

We analyzed data among California residents aged 15 years and older from the California Department of Public Health TB and cHBV registries, which include surveillance data collected from all 61 local health jurisdictions in California. Persons who received a diagnosis of TB during 1 January 2016–31 December 2020 were included in this analysis. We identified persons reported to the cHBV registry during 1989–2020 who were born before 1 January 2006 (ie, would be ≥15 years during the study period).

Tuberculosis and Chronic Hepatitis B Virus Definitions

We defined TB disease as a report of TB with microbiologic confirmation (ie, positive acid-fast smear, positive culture, or nucleic acid amplification test for *Mycobacterium tuberculosis).* In the TB treatment outcomes analysis, we included those who were alive at the time of TB diagnosis, had either TB with cHBV infection or TB only, and had a recorded TB treatment start date. We defined cHBV using the Council of State Territorial Epidemiologists (CSTE) case definition for confirmed or probable cHBV infection [24].

Analysis

We applied a probabilistic matching algorithm using Match*[AQ6]Pro v2.0.6 software (Information Management Services, Inc., Rockville, Maryland) for the persons identified in the TB and cHBV registries for the study period to identify persons with both conditions in California. The matching algorithm used first name, last name, date of birth, sex, and postal code of residence (or local jurisdiction of residence if postal code was missing) at the time of first report of TB or cHBV. Potential matches between persons in the registries were required to match exactly on first name, last name, or date of birth and meet a threshold score for the person to be considered to have both conditions.

We chose 3 TB treatment outcomes for this analysis: treatment completion, all-cause mortality during treatment, and treatment duration. Tuberculosis treatment completion and mortality were based on the treatment outcome variable in the TB registry, which categorizes a person with TB as having died during treatment, completed treatment in 365 days or less or more than 365 days, as lost to follow-up, or refused treatment. For mortality analysis, all those who were not listed as having died during treatment were treated as having lived through treatment. For treatment completion analysis, those who were not listed as having completed treatment, including those who died, were treated as not having completed treatment. We calculated TB treatment duration as the total time between recorded treatment start and stop dates, inclusive of treatment interruptions. We assessed duration by creating 3 possible dichotomous outcomes—more than 6 months, more than 9 months, and more than 12 months—versus shorter duration—, which represent the most common TB treatment durations. Treatment duration was intended to indirectly evaluate treatment failure, treatment interruption, or drug intolerance, because these events are not captured in the registry data but all necessitate a longer treatment duration.

We performed modified Poisson regression models with robust variance to calculate adjusted relative risk (aRR) of TB treatment outcomes among those with TB and cHBV and those with TB only. We created a directed acyclic graph to find confounders for adjustment in the model, including race and ethnicity, age, HIV infection, non-HIV immunosuppressive conditions, substance use, and sex (Supplementary Figure 1).

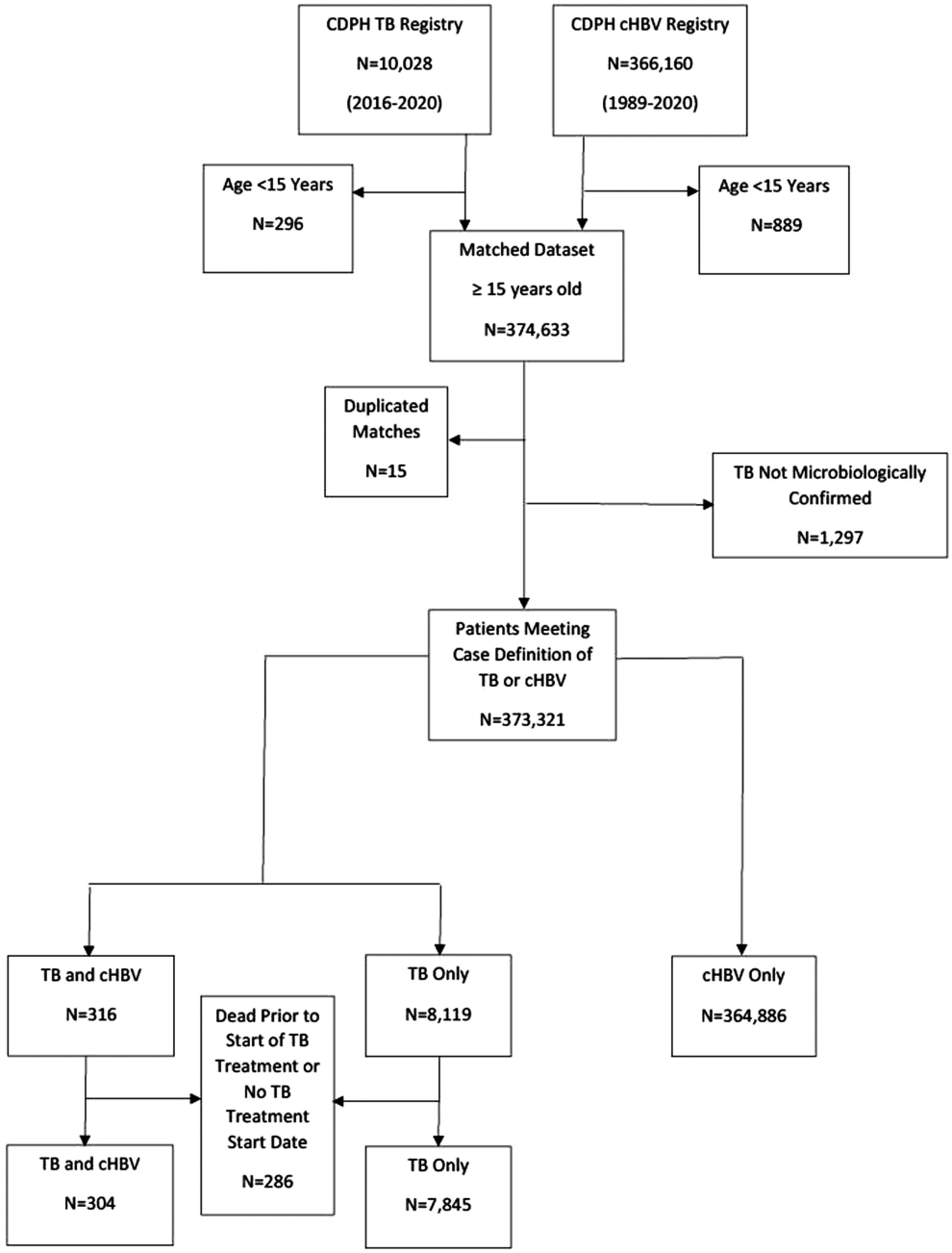
We used chi-square analysis to compare the proportion of persons with TB and cHBV with the proportions of those with TB only for multiple demographic characteristics, risk factors, and clinical characteristics. We calculated the time elapsed between TB and cHBV diagnoses using the dates of first report to the TB and cHBV registries. We categorized persons with both diagnoses into 3 groups: TB before cHBV (TB reported >60 days before cHBV report), simultaneous (TB reported ≤60 days either before or after cHBV report), and TB after cHBV (TB reported >60 days after cHBV report). We chose a 60-day interval to account for the time needed to complete diagnostic workup for TB. We used SAS ve[AQ7]rsion 9.4 (SAS Institute, Inc, Cary, North Carolina) to perform all analyses. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy [see, e.g., 45 C.F.R. pa[AQ8]rt 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq].

RESULTS

During 2016–2020, 10 028 reports of TB were submitted to the California TB registry. California's cHBV registry showed a total of 366 160 persons with confirmed or probable cHBV during 1989–2020. After 2497 persons were excluded because of duplicate reports, or did not meet age or microbiologic confirmation criteria, data for 373 321 persons were included in this analysis (Figure 1 [AQ9]). In total, 8435 persons were reported with TB disease. Of those, 316 (3.7%) had TB and cHBV and 8119 persons had TB only. There were 364 886 persons with cHBV only (Figure 1).

Figure 1.

Patient selection flowchart—California, 2016–2020. The persons identified from the CDPH TB registry were reported during 1 January 2016–31 December 2020. All persons in the CDPH cHBV registry were reported during 1989–2020[AQ17]. Abbreviations: CDPH, California Department of Public Health; cHBV, chronic hepatitis B virus; TB, tuberculosis.

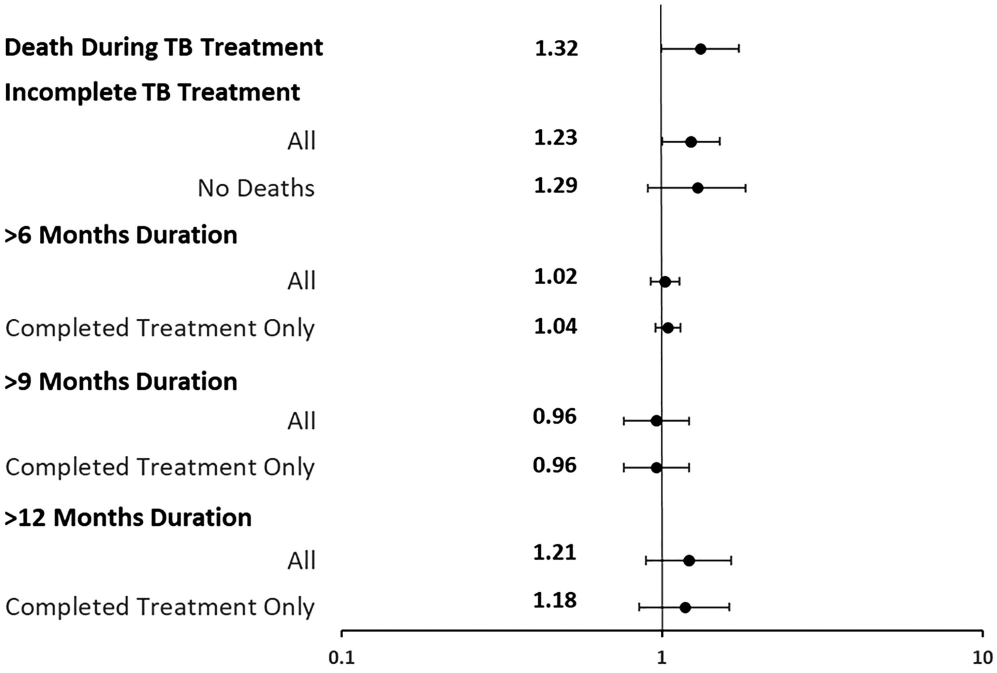


Tuberculosis Treatment Outcome Statistical Analysis

In total, 304 persons with TB and cHBV and 7845 with TB only were included in the TB treatment outcome analysis (Figure 1). The aRR for incomplete TB treatment among those with TB and cHBV, compared with those with TB only, was 1.23 (95% confidence interval [CI]: 1.00, 1.51). Of the 1539 persons who did not complete TB treatment, 826 (53.7%) died during treatment. When the analysis was restricted to only persons who did not die during treatment, the aRR for incomplete TB treatment was 1.29 (95% CI: .90, 1.82). The aRR for all-cause mortality during treatment was 1.32 (95% CI: .99, 1.74) (Figure 2).

Figure 2.

Adjusted relative risk with 95% CIs for TB treatment outcomes for TB and cHBV cases versus TB-only cases—California, 2016–2020. Mo**[AQ18]**del adjusted for age, gender, race and ethnicity, substance use, HIV infection, and other non-HIV immunosuppressive conditions. Abbreviations: cHBV, chronic hepatitis B virus; CI, confidence interval; HIV, human immunodeficiency virus; TB, tuberculosis.



The median TB treatment duration for persons with TB and cHBV was 250 days (range: 3–937 days) compared with 254 days (range: 0–3417 days) for those with TB only. The aRRs for treatment durations of more than 6 months and more than 9 months were 1.02 (95% CI: .92, 1.13) and .96 (95% CI: .76, 1.21), respectively. The more-than-12-month treatment duration aRR was 1.21 (95% CI: .89, 1.64) (Figure 2). No statistically significant differences were observed for all 3 durations for the unadjusted analysis (Supplementary Figure 2) and for subanalysis that was restricted to those who completed therapy (Figure 2).

Descriptive Analysis

The descriptive analysis showed that 259 (82.0%) persons with TB and cHBV were aged 45 years or older, compared with 5520 (68.0%) persons with TB only ($P < .001$) (Table 1). Analysis of race, ethnicity, and place of birth showed that 256 (81.0%) cases of TB and cHBV occurred among non–US-born Asian persons, compared with 4186 (51.6%) persons with TB only ($P < .0001$) (Table 1). Of those with TB and cHBV, 233 (74.0%) were born in China or Southeast Asia, compared with 3312 (40.9%) persons with TB only ($P < .0001$). More persons with TB and cHBV (212; 67.1%) resided in either the San Francisco Bay Area or Los Angeles County at the time of their TB report (Figure 3), compared with those with TB only (4,318, 53.1%; $P < .0001$) (Table 1).

Figure 3.

Geographic distribution of active TB and cHBV and TB-only cases in California (2016–2020) over overall local jurisdiction cHBV reported prevalence (1989–2020). Plotted points for TB and cHBV and TB-only cases are randomly relocated ("jittered") by 3 kilometers ~~jiggered~~[AQ19] for confidentiality purposes. For case status, persons with TB and cHBV are represented by the[AQ2] ~~red~~ triangles and persons with TB only are represented by the ~~yellow~~ circles. The~~For~~ cHBV prevalences (per 100 000), ~~the 4 shades of green (~~from lightest to darkest,~~)~~ represent 0.0 to 224.0, 224.1 to 320.0, 320.1 to 533.0, and >533.0~~, respectively~~. Abbreviations: cHBV, chronic hepatitis B virus; TB, tuberculosis.[AQ26]

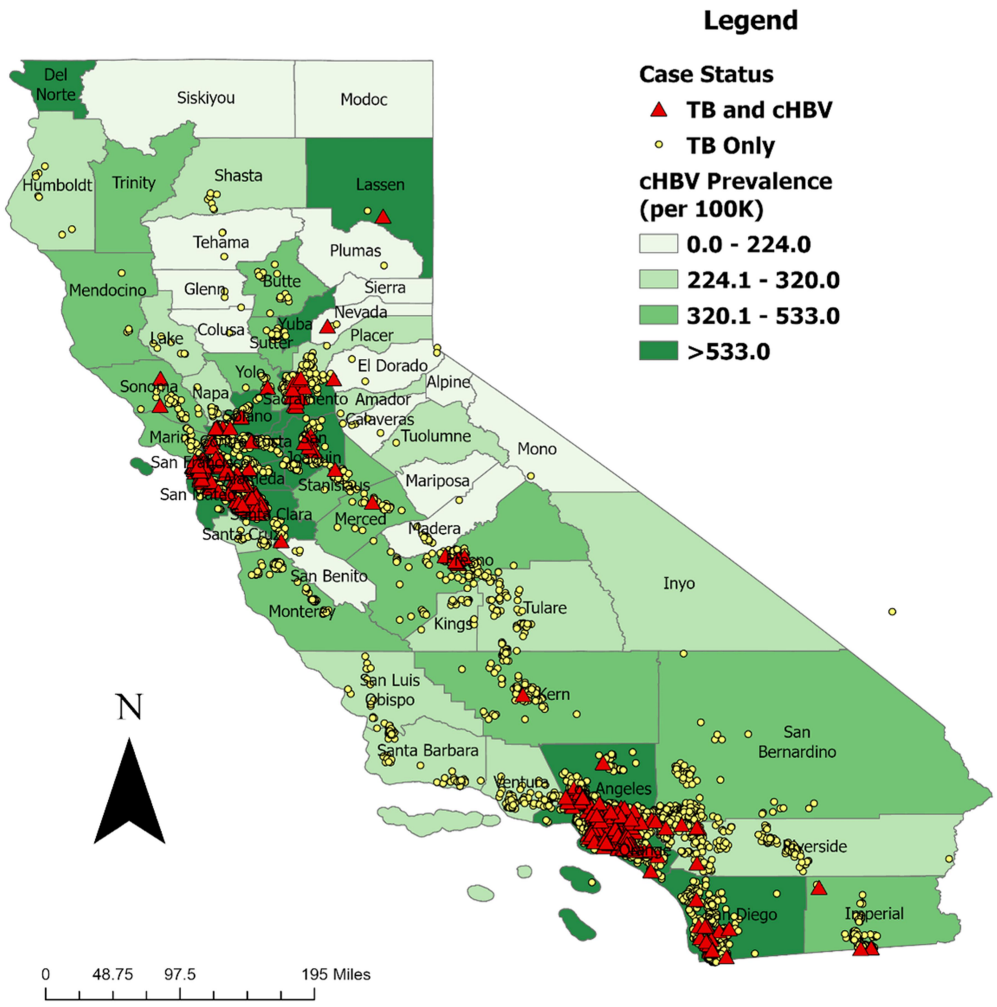


Table 1.

Demographic Characteristics of Persons With Active Tuberculosis Disease (TB) and Chronic Hepatitis B Virus Infection (cHBV), TB Only, and cHBV Only—California, 2016–2020[AQ20]

	TB and cHBV, n (%)	TB Only, n (%)	cHBV Only, n (%)	*P* (TB and cHBV vs TB Only)
Total	316	8119	364 886	
Sex				.38
Male	204 (64.6)	5042 (62.1)	189 024 (51.8)	
Female	112 (35.2)	3077 (37.9)	171 131 (46.9)	
Other	0	0	28 (0.01)	
Unknown	0	0	4703 (1.3)	
Age				<.001
15–24 y	4 (1.3)	666 (8.2)	31 586 (9.0)	
25–44 y	53 (16.8)	1933 (23.8)	162 838 (46.5)	
45–64 y	132 (41.8)	2523 (31.1)	115 575 (33.0)	
≥65 y	127 (40.2)	2997 (36.9)	39 862 (11.4)	
Missing	0	0	20 196[a]	

Race				<.0001
American Indian or Alaska Native	0	7 (0.1)	544 (0.3)	
Asian (non-Hispanic)	259 (82.0)	4336 (53.4)	25 375 (75.8)	
US birth	3 (1.0)	144 (1.8)	1567 (4.7)	
Non–US birth	256 (81.0)	4186 (51.6)	23 808 (71.1)	
Black (non-Hispanic)	18 (5.7)	355 (4.4)	1534 (4.6)	
US birth	9 (2.9)	204 (2.5)	1050 (3.1)	
Non–US birth	9(2.9)	150 (1.9)	484 (1.5)	
Hispanic	27 (8.5)	2854 (35.1)	2286 (6.8)	
US birth	6 (1.9)	582 (7.2)	633 (1.9)	
Non–US birth	21 (6.7)	2260 (27.8)	1653 (4.9)	
Multirace or other (non-Hispanic)	0	17 (0.2)	78 (0.2)	
US birth	0	8 (0.1)	17 (0.1)	
Non–US birth	0	9 (0.1)	61 (0.2)	
Native Hawaiian or Pacific Islander (non-Hispanic)[b]	3 (1.0)	51 (0.6)	…	
US birth	1 (0.3)	31 (0.4)	…	
Non–US birth	2 (0.6)	20 (0.3)	…	
White (non-Hispanic)	9 (2.9)	498 (6.1)	2166 (6.5)	
US birth	5 (1.6)	287 (3.5)	1397 (4.2)	
Non–US birth	4 (1.3)	208 (2.6)	769 (2.3)	
Unknown	0	1 (0.01)	674 (2.0)	
Missing[c]	0	0	331 419	
Places of birth ~~(n = 37 386~~[AQ21]~~)~~			n= 37 386	<.0001
Africa	8 (2.5)	138 (1.7)	745 (2.0)	
Australia	0	1 (0.01)	4 (0.01)	
Canada	0	2 (0.02)	22 (0.06)	
China	49 (15.5)	542 (6.7)	10 976 (29.4)	
Europe	1 (0.3)	61 (0.8)	359 (1.0)	
India	4 (1.3)	498 (6.2)	359 (1.0)	
Mexico	16 (5.1)	1793 (22.2)	1185 (3.2)	

Other Asia (except Southeast)	22 (7.0)	551 (6.8)	5400 (14.4)	
Other Southeast Asia	33 (10.4)	347 (4.3)	2186 (5.8)	
Other Latin America	5 (1.6)	473 (5.8)	486 (1.3)	
Other Pacific Islands	3 (1.0)	31 (0.4)	320 (0.9)	
Philippines	60 (19.0)	1595 (19.7)	2559 (6.8)	
United States	23 (7.3)	1234 (15.3)	5293 (14.2)	
Vietnam	91 (29.1)	828 (10.2)	7492 (20.0)	
Missing[d]	0	25	327 500	
California region[e]				<.0001
San Francisco Bay Area	117 (37.0)	2252 (27.7)	117 097 (32.1)	
Mexican Border	23 (7.3)	1150 (14.2)	22 529 (6.2)	
Central	26 (8.2)	917 (11.3)	34 030 (9.3)	
Los Angeles County	95 (30.1)	2066 (25.4)	120 836 (33.1)	
Northern	2 (0.6)	54 (0.7)	3247 (0.9)	
Southern (except Los Angeles County)	53 (16.7)	1680 (20.7)	65 824 (18.4)	
Missing	0	0	1323	

Persons with TB and cHBV and TB only were reported during 2016–2020. Those with cHBV only were reported during 1989–2020. Unknown = entered by local jurisdiction as information on variable is not known; data included in percentages. Missing = variable not completed for patient, data not included in percentages. ~~Border: San Diego and Imperial; Central: Alpine, Amador, Calavera, El Dorado, Fresno, Inyo, Kings, Madera, Merced, Mariposa, Mono, Placer, Sacramento, San Joaquin, Stanislaus, Sutter, Yuba, Tulare, Tuolumne, and Yolo; Northern: Butte, Colusa, Del Norte, Glenn, Humboldt, Lake, Lassen, Mendocino, Modoc, Nevada, Plumas, Shasta, Sierra, Siskiyou, Tehama, and Trinity; Southern: Kern, Orange, Riverside, San Bernardino, San Luis Obispo, Santa Barbara, Ventura, Long Beach City, and Pasadena City. Unknown = entered by local jurisdiction as information on variable is not known; data included in percentages. Missing = variable not completed for patient, data not included in percentages.~~

a 5.5% of age data are missing for cHBV-only cases.

b The cHBV registry does not have a separate Native Hawaiian or Pacific Islander category for the race and ethnicity variable.

c 9.2% of cHBV cases have both race and birth country values available.

d 10.2% of cHBV cases have birth country values available.

e Bay Area: Alameda, Contra Costa, Marin, Monterey, Napa, San Benito, San Francisco, San Mateo, Santa Clara, Santa Cruz, Solano, Sonoma, and Berkeley; Border: San Diego and Imperial; Central: Alpine, Amador, Calavera, El Dorado, Fresno, Inyo, Kings, Madera, Merced, Mariposa, Mono, Placer, Sacramento, San Joaquin, Stanislaus, Sutter, Yuba, Tulare, Tuolumne, and Yolo; Northern: Butte, Colusa, Del Norte, Glenn, Humboldt, Lake, Lassen, Mendocino, Modoc, Nevada, Plumas, Shasta, Sierra, Siskiyou, Tehama, and Trinity; Southern: Kern, Orange, Riverside, San Bernardino, San Luis Obispo, Santa Barbara, Ventura, Long Beach City, and Pasadena City. ~~Unknown = entered by local jurisdiction as information on variable is not known; data included in percentages. Missing = variable not completed for patient, data not included in percentages.~~

Analysis revealed that 26 (8.2%) persons with TB and cHBV had end-stage renal disease at the time of reporting, compared with 332 (4.0%) persons with TB only ($P < .001$). Additionally, 21 (6.7%) persons with TB and cHBV were HIV positive, compared with 247 persons (3.0%) with TB only ($P = .03$); 32 persons (11.4%) with TB and cHBV had non-HIV immunosuppressive conditions, compared with 637 persons (7.9%) with TB only ($P = .01$) (Table 2).

Table 2.

Risk Factor and Clinical Characteristics of Persons With Active Tuberculosis Disease (TB) and Chronic Hepatitis B Virus Infection (cHBV), TB Only, and cHBV Only—California, 2016 – 2020

	TB and cHBV, n (%)	TB Only, n (%)	cHBV Only, n (%)	*P* (TB and cHBV vs TB only)
Total	316	8119	364 886	
Risk factors				
Incarceration at date classified or diagnosis received				
Yes	4 (1.3)	185 (2.3)	3809 (1.0)	.43
No	312 (98.7)	7925 (97.6)	360 358 (99.0)	
Unknown	0 (0)	7 (0.1)	0 (0)	
Missing	0	2	719	
Homelessness				.20
Yes	11 (3.5)	441 (5.4)	N/A	
No	305 (96.5)	7652 (94.3)	N/A	
Unknown	0 (0)	24 (0.3)	N/A	
Missing	0	2	N/A	
HIV status				.02
Positive	21 (6.7)	247 (3.0)	N/A	
Negative	265 (83.9)	6981 (86.1)	N/A	
Not offered	21 (6.7)	639 (7.9)	N/A	
Test done, results unknown	0 (0)	9 (0.1)	N/A	
Procedure refused	3 (1.0)	78 (1.0)	N/A	
Unknown	6 (1.9)	165 (1.9)	N/A	
Diabetes				.71
Yes	97 (30.7)	2414 (29.7)	N/A	
No	219 (69.3)	5705 (70.3)	N/A	
End-stage renal disease				<.001
Yes	26 (8.2)	322 (4.0)	N/A	
No	290 (91.8)	7797 (96.0)	N/A	
Substance use				.03
Yes	23 (7.3)	907 (11.2)	N/A	
No	293 (92.7)	7212 (88.8)	N/A	

Other non-HIV immunosuppression[a]				.02
Yes	32 (11.4)	637 (7.9)	N/A	
No	280 (88.6)	7482 (92.2)	N/A	
Clinical characteristics				
Dead at diagnosis				
Yes	10 (3.2)	202 (2.5)	1925 (0.5)	.45
No	306 (96.8)	7916 (97.5)	362 961 (99.5)	
Unknown	0 (0)	1 (<0.0001)	0 (0)	
Completed TB treatment				.04
Yes	233 (76.6)	6377 (81.3)	N/A	
No	71 (23.4)	1468 (18.7)	N/A	
Died during TB treatment				.05
Yes	42 (13.5)	785 (10.0)	N/A	
No	263 (86.5)	7060 (90.0)	N/A	

Persons with TB and cHBV and TB only were reported during 2016–2020. Those with cHBV only were reported during 1989–2020. Unknown = entered by local jurisdiction as information on variable is not known; data included in percentages. Missing = variable not completed for patient, data not included in percentages.

Abbreviations: HIV, human immunodeficiency virus; N/A, not applicable~~XXX~~ **[AQ24]**.

a Conditions include organ transplantation, tumor necrosis factor-α inhibitor use, and other nonspecified immunosuppressive conditions.

Diagnostic Timing

Among persons with TB and cHBV, 255 (80.7%) had their diagnoses reported more than 60 days apart. This included 35 (11.1%) persons in the TB-Before-cHBV group (median: 363 days; range: 67–1554 days) and 220 (69.6%) in the TB-After-cHBV group (median: 3411 days; range: 62–10 338 days). Among 61 (19.3%) persons in the Simultaneous group, the median time between report dates was 3 days (range: 56 before–58 days after cHBV report) (Table 3).

Table 3.

Time Between Report Dates of Active Tuberculosis Disease (TB) and Chronic Hepatitis B Virus Infection (cHBV)—California, 2016–2020

	TB Before cHBV	Simultaneous	TB After cHBV
Total: 316, n (%)	35 (11.1%)	61 (19.3%)	220 (69.6%)
Median time between report dates, d	363	3	3411
Range between report dates, d	67 to 1554	From 56 before to 58 after cHBV reporting	62 to 10 338

TB Before cHBV = TB reported >60 days before cHBV reporting; Simultaneous = TB reported within 60 days before or after cHBV reporting; TB After cHBV = TB reported >60 days after cHBV reporting.

DISCUSSION

Our estimated prevalence of cHBV among California's population with TB of approximately 4% is consistent with prior estimates of cHBV prevalence among persons with TB in the United States [5, 15]. The higher prevalence of cHBV among non–US-born Asian persons with TB is consistent with the literature showing a 15-fold higher incidence rate of TB among non–US-born persons relative to US-born persons, and a 35-fold higher rate among Asian persons compared with White persons [5, 6]. It is also consistent with the nearly 50-fold higher prevalence of cHBV among non–US-born Asian persons compared with US-born White

persons [5, 6, 16, 23, 25]. The proportion of TB and cHBV cases reported in the San Francisco Bay Area and Los Angeles County, compared with those with TB only, might be explained partially by patterns of Asian immigration in these regions [21]. Additionally, robust screening programs such as Hep B Free (a program that provides hepatitis B education, screening, and prevention in the San Francisco Bay Area) are available in larger population centers [26].

Tuberculosis disease affects older persons because, with advanced age, there is a higher likelihood for LTBI and progression to active TB [13, 16, 27]. The substantial proportion of persons aged greater than 45 years with both conditions might reflect the ability of LTBI and cHBV to persist into older age. The higher proportion of chronic medical conditions in persons with both conditions is likely because of shared risk factors and potential interactions between immunological status and infections. For example, HIV is a common risk factor for both TB and cHBV [5, 13]. End-stage renal disease is a risk factor for TB and a potential complication of cHBV [28, 29]. Persons with immunosuppressive conditions such as solid-organ transplant and tumor necrosis factor α (TNF-α) inhibitor use are at increased risk, including progression of LTBI to TB disease, and worsening manifestations of cHBV infection [30–32].

Our analysis showed an increased risk for all-cause mortality of TB with cHBV compared with TB only. Although the increased aRR for death during TB treatment was not statistically significant, the results are concerning and consistent with prior studies that have shown increased mortality among those with TB and cHBV, compared with those with TB only [15, 17–19]. However, no similar studies have been reported at the state level using adjusted multivariable analysis. One potential reason for the increased risk for all-cause mortality is that persons with uncontrolled cHBV infection are more likely to have liver dysfunction [33]. This might make survival and recovery in those with TB disease less likely. Moreover, studies have reported that persons with uncontrolled cHBV are at increased risk for hepatotoxicity from TB medications, including liver failure exacerbation and death, potentially leading to longer TB treatment regimens or complications [15, 17–19].

Our analysis also showed an increased risk for incomplete TB treatment among those with cHBV, compared with those with TB only. However, over half of those who did not complete treatment because they died during treatment, and the aRR lost its statistical significance when those persons were removed from the analysis. Hepatotoxicity and other medical adverse effects also increase the risk for TB treatment interruption or discontinuation [20].

An unexpected result was the lack of difference in TB treatment duration. We had hypothesized that patients with cHBV might experience more hepatotoxicity or be treated with alternate liver-sparing regimens that would necessitate longer duration, thus making treatment duration a proxy for hepatotoxicity or concern for hepatotoxicity [34]. While this study was not specifically powered to detect a difference, 1 potential reason for a lack of difference might be that some patients may have received effective treatment of cHBV, which has been shown to improve tolerance of these medications and reduce complications [35].

The finding that approximately 81% of persons with both conditions had their diagnoses reported more than 60 days apart was concerning because this might mean that those persons had previously undiagnosed LTBI or cHBV, possibly for many years. The median time of approximately 1 year between reporting among those in the TB-Before-cHBV group showed that many had completed their TB treatment before cHBV screening was complete. The median time of 10 years between reporting for those in the TB-After-cHBV group showed that those with cHBV might not have been routinely screened for LTBI. This supports prior findings that only a limited percentage of those at risk for TB or HBV are being screened for both infections despite sharing risk factors [5–9]. Undiagnosed LTBI or cHBV potentially can lead to increased morbidity and mortality.

The major strength of this analysis was the use of statewide TB and cHBV data to develop a comprehensive assessment in California's large, diverse population. Additionally, the adjusted multivariable analysis combined with the evaluation of diagnostic timing are unique, compared with prior studies. Limitations include the frequency of missing variables in the cHBV registry, which prevented certain comparisons between persons with TB and cHBV and those with cHBV only. Additionally, the US TB surveillance system only includes treatment completion, death, loss to follow-up, and patient refusal as possible treatment outcomes [12]. As a result, occurrence of TB treatment failure could not be fully evaluated. Treatment duration was analyzed instead because it is a proxy of treatment success, as treatment is continued until one of those outcomes is attained. Additionally, we could not detect hepatotoxicity nor resulting treatment regimen changes because neither laboratory parameters of liver dysfunction nor TB treatment regimen changes after 2 weeks of the initial treatment were available in either registry. This information could have revealed mechanisms for potentially poorer outcomes in patients with both TB and cHBV. Third, actual dates of diagnosis were not available to calculate the diagnostic timing of TB and cHBV. Therefore, the first public health report dates were the best approximation of diagnosis for both conditions. Last, it was assumed that many of the persons with TB and cHBV who were not diagnosed simultaneously had undiagnosed LTBI or cHBV when their other condition was reported, given the chronicity and general underdiagnosis of both infections, and therefore represent missed opportunities to prevent TB disease and uncontrolled cHBV [7, 36]. However, this cannot be proven with the current data.

Conclusions

Our estimate of cHBV infection among patients with TB in California of approximately 4% was similar to prior estimates of prevalence of TB with cHBV in the United States. Most persons with TB and cHBV were born in Asia, particularly in Southeast Asia and China. Treatment analysis was concerning for worse TB treatment outcomes among those with cHBV, compared with TB only. Our analysis also showed opportunities for the prevention and treatment of these infections, with more than 80% of those with both conditions having their diagnoses first reported more than 2 months apart. Analysis of LTBI among persons with cHBV could reveal further opportunities to prevent TB and reduce disparities in those at risk for coinfection.

The results of this study can serve as baseline estimates as California begins to track viral hepatitis in persons with TB with the updated TB surveillance report form [12]. California TB and cHBV programs can collaborate to ensure that persons with TB or cHBV in communities at high risk for both conditions will be tested for the other. Concomitant LTBI or untreated cHBV could potentially be identified and treated, therefore preventing worse outcomes, and vaccination could be offered to HBV-negative persons.

Supplementary Data[AQ25]

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. B. B. was primarily responsible for developing the concept and analysis plan[AQ10], performing the analyses, and writing the ~~initial~~ manuscript. P. B. is the senior author who supervised the first author. L. P. assisted in the concept and analysis plan development. E. H. performed the match of the 2 registries. L. S. and R. G.-F. provided much of the hepatitis B intellectual content. R. J. W., A. C., and D. J. provided much of the TB intellectual content, including coinfection with HBV. M. J. and P. G. helped interpret the data from Los Angeles County, which had ~~a lot of~~ missing data. S. M. helped develop the figures for this manuscript. All authors reviewed the manuscript and provided revisions to the first author.

Acknowledgments. The authors acknowledge Bruce Gutelius of the Centers for Disease Control and Prevention and Shua J. Chai, MD, of the California Department of Public Health and Centers for Disease Control and Prevention for their assistance in reviewing this manuscript.

Disclaimer. The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, California Department of Public Health, or the California Health and Human Services Agency.

***Financial support*[AQ1].** There is no source of funding for this project.

***Potential conflicts of interest*[AQ11].** R. J. W. discloses research grants from Gilead Sciences, Exact Sciences, and Thera Technologies, and a consulting/advisory role for Gilead, all of which are unrelated to this project. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References[AQ12]

1 Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Available at: Global Tuberculosis Report 2022 (who.int). Accessed June 10, 2023.

2 **World Health Organization**. Hepatitis B. 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed 10 June 2023.

3 **Schildknecht KR, Pratt RH, Feng P-JI, Price SF, Self JL**. Tuberculosis—United States, 2022. *MMWR Morb Mortal Wkly Rep* 2023; 72:297–303.

4 **California Department of Public Health**. Chronic Hepatitis B in California: 2016 Executive Summary. 2016. Available at: www.cdph.ca.gov. Accessed 21 May 2023.

5 **Chitnis AS, Cheung R, Gish RG, Wong RJ**. Epidemiology and Prevention of Tuberculosis and Chronic Hepatitis B Virus Infection in the United States. *J Immigr Minor Health* **2021**; 23:1267–79.

6 **Chen J, Hubbard A, Bagley L, Shiau R, Wong RJ, Chitnis AS**. Prevalence of Latent Tuberculosis Infection Among Persons with Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis. *Dig Dis Sci* **2022**; 67:2646–54.

7 **Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D**. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; 16:1269–78.

8 **Harris AM, Osinubi A, Nelson NP, Thompson WW**. The hepatitis B care cascade using administrative claims data, 2016. *Am J Manag Care* 2020; 26:331–8.

9 **Le S, Martin B, Chitnis AS, Wong RJ**. Screening Practices for Latent Tuberculosis Infection in Clinical Trials Evaluating Treatments for Chronic Hepatitis B Virus Infection. *J Immigr Minor Health* **2022**; 24:1594–8.

10 **Conners EE, Panagiotakopoulos L, Hofmeister MG,** et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations—United States, 2023. *MMWR Recomm Rep* **2023**; 72:1–25.

11 **Lewinsohn DM, Leonard MK, LoBue PA,** et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis* **2017**; 64:e1–33.

12 **Centers for Disease Control and Prevention**. 2020 Report of Verified Case of Tuberculosis (RVCT) instruction manual. August 2021. Available at: https://www.cdc.gov/tb/programs/rvct/instructionmanual.pdf. Accessed 17 May 2023.

13 **Blal CA, Passos SRL, Horn C**, et al. High prevalence of hepatitis B virus infection among tuberculosis patients with and without HIV in Rio de Janeiro, Brazil. *Eur J Clin Microbiol Infect Dis* 2005; 24:41–3.

14 **Nooredinvand HA, Connell DW, Asgheddi M**, et al. Viral hepatitis prevalence in patients with active and latent tuberculosis. *World J Gastroenterol* 2015; 21:8920–6.

15 **Bushnell G, Stennis NL, Drobnik AM**, et al. Characteristics and TB treatment outcomes in TB patients with viral hepatitis, New York City, 2000–2010. *Epidemiol Infect* 2015; 143:1972–81.

16 **Wong RJ, Kaufman HW, Niles JK, Meyer WAIII, Chitnis AS**. Prevalence of Hepatitis B Virus and Latent Tuberculosis Coinfection in the United States. *J Public Health Manag Pract* **2022**; 28:452–62.

17 **Khan AF, Sajjad A, Mian DA,** et al. Co-infection with Hepatitis B in Tuberculosis Patients on Anti-tuberculosis Treatment and the Final Outcome. *Cureus* **2021**; 13:e14433.

18 **Chen L, Bao D, Gu L**, et al. Co-infection with hepatitis B virus among tuberculosis patients is associated with poor outcomes during anti-tuberculosis treatment. *BMC Infect Dis* 2018; 18:295.

19 **Chou C, Veracruz N, Chitnis AS, Wong RJ**. Risk of drug-induced liver injury in chronic hepatitis B and tuberculosis co-infection: a systematic review and meta-analysis. *J Viral Hepat* 2022; 29:1107–14.

20 **Chua AP, Lim LK, Gan SH, Chee CB, Wang YT**. The role of chronic viral hepatitis on tuberculosis treatment interruption. *Int J Tuberc Lung Dis* 2018; 22:1486–94.

21 **Mejia MC, Perez CA, Johnson H**. Immigrants in California: Fact Sheet-January 2023. Public Policy Institute of California: 2023. Immigrants in California - Public Policy Institute of California (ppic.org). Accessed June 10, 2023.**[AQ13]**

22 **Cohen A, Mathiasen VD, Schön T, Wejse C**. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2019; 54:1900655.

23 **Wong RJ, Brosgart CL, Welch S,** et al. An Updated Assessment of Chronic Hepatitis B Prevalence Among Foreign-Born Persons Living in the United States. *Hepatology* **2021**; 74:607–26.

24 **Council of State and Territorial Epidemiologists**. Public health reporting and national notification for chronic hepatitis B, 11-ID-04. 2011. Available at: https://cdn.ymaws.com/www.cste.org/resource/resmgr/PS/11-ID-04.pdf. Accessed 17 May 2023.

25 **Le MH, Yeo YH, Cheung R, Henry L, Lok AS, Nguyen MH**. Chronic Hepatitis B Prevalence Among Foreign-Born and U.S.-Born Adults in the United States, 1999–2016. *Hepatology* **2020**; 71:431–43.

26 Hep B Free San Francisco Bay Area. Home page. Available at: https://www.sfhepbfree.org/. Accessed 11 June 2023.

27 **Centers for Disease Control and Prevention**. Tuberculosis TB: deciding when to treat latent TB infection. 2023. Available at: Treatment for Latent TB Infection and TB Disease | TB | CDC. Accessed 17 May 2023.**[AQ14]**

28 **Okada RC, Barry PM, Skarbinski J, Chitnis AS**. Epidemiology, detection, and management of tuberculosis among end-stage renal disease patients. *Infect Control Hosp Epidemiol* 2018; 39:1367–74.

29 **Fabrizi F, Cerutti R, Ridruejo E**. Hepatitis B virus infection as a risk factor for chronic kidney disease. *Expert Rev Clin Pharmacol* 2019; 12:867–74.

30 **Abad CLR, Razonable RR**. Mycobacterium tuberculosis after solid organ transplantation: a review of more than 2000 cases. *Clin Transplant* 2018; 32:e13259.

31 **Dobler CC**. Biologic agents and tuberculosis. *Microbiol Spectr* **2016**; 4(6). 10.1128/microbiolspec.TNMI7-0026-2016. PMID: 28084208.**[AQ15][AQ16]**

32 **Loomba R, Liang TJ**. Hepatitis B Reactivation Associated with Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* **2017**; 152:1297–309.

33 **Centers for Disease Control and Prevention**. Viral Hepatitis: Hepatitis B Information. 2023. Available at: Hepatitis B - FAQs, Statistics, Data, & Guidelines | CDC. Accessed 17 May 2023.

34 **Saukkonen JJ, Cohn DL, Jasmer RM**, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006; 174:935–52.

35 **Lui GCY, Wong N-S, Wong RYK,** et al. Antiviral Therapy for Hepatitis B Prevents Liver Injury in Patients with Tuberculosis and Hepatitis B Coinfection. *Clin Infect Dis* **2020**; 70:660–6.

36 **Roberts H, Ly KN, Yin S, Hughes E, Teshale E, Jiles R**. Prevalence of HBV Infection, Vaccine-Induced Immunity, and Susceptibility Among At-Risk Populations: US Households, 2013–2018. *Hepatology* **2021**; 74:2353–65.