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MAJOR ARTICLE

Latent Tuberculosis Infection Treatment Practices in Two Large Integrated Health Systems in California, 2009–2018

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Background. Treatment of latent tuberculosis infection (LTBI) is highly effective at preventing active tuberculosis (TB) disease. Understanding LTBI treatment practices in US health system settings is critical to identify opportunities to improve treatment prescription, initiation, and completion, and thus to prevent TB disease.

Methods. We assessed LTBI treatment practices among a cohort of adults after their first positive LTBI test (tuberculin skin test [TST] or interferon gamma release assay [IGRA]) between 2009 and 2018 at 2 large integrated health systems in California. We described the prescription, initiation, and completion of LTBI treatment (isoniazid [INH], rifampin, and rifamycin-INH short-course combinations) by demographic and clinical characteristics. We used multivariable robust Poisson regression to examine factors that were independently associated with treatment prescription and completion.

Results. Among 79 302 individuals with a positive LTBI test, 33.0% were prescribed LTBI treatment, 28.3% initiated treatment, and 18.5% completed treatment. Most individuals were prescribed INH (82.0%), but treatment completion was higher among those prescribed rifamycin-INH short-course combinations (69.6% for INH + rifapentine and 70.3% for INH + rifampin) compared with those prescribed INH (56.3%) or rifampin (56.6%). In adjusted analyses, treatment prescription and completion were associated with older age, female sex, more comorbidities, immunosuppression, not being born in a high–TB incidence country, and testing positive with IGRA vs TST.

Conclusions. LTBI treatment is underutilized, requiring tailored interventions to support treatment prescription and completion for patients with LTBI.

Keywords. adherence; latent tuberculosis; treatment; tuberculosis.

An estimated 13 million people in the United States are infected with *Mycobacterium tuberculosis*, most of whom are considered at risk of active tuberculosis (TB) disease from reactivation of latent tuberculosis infection (LTBI) [1, 2]. California has the highest incidence and largest number of TB cases in the contiguous United States; >2 million Californians are estimated to have LTBI, and 87% of active TB cases in 2021 were attributed to LTBI reactivation [3]. In 2019, the total medical and societal costs of TB in California exceeded $210 million [4]. If California achieves its targets for TB elimination by 2050, the state could avert 36 000 cases of TB and 3600 TB-related deaths, saving $2 billion in medical and societal costs [5]. However, barriers to TB elimination in California, including poor understanding and adoption of LTBI screening and treatment guidelines and poor adherence to treatment, may prevent the state from reaching this target.

Treatment is highly effective at preventing LTBI reactivation [6, 7]. Without appropriate treatment, patients with LTBI have a 5%–10% lifetime risk of developing active TB disease [8]. The mainstay of LTBI treatment has been daily isoniazid for 6–9 months, but treatment adherence has been low due to the long duration of treatment and the possibility of adverse effects such as hepatotoxicity [9, 10]. In 2020, the US Centers for Disease Control and Prevention (CDC) preferentially recommended shorter rifamycin-based treatment (weekly isoniazid [INH] plus rifapentine for 3 months, daily INH plus rifampin for 3 months, or daily rifampin for 4 months), with 6 or 9 months of isoniazid monotherapy as an alternative [11]. Shorter rifamycin-based treatments are efficacious and may have higher adherence and fewer adverse events compared with INH monotherapy [12–14].

To improve LTBI treatment rates and progress toward TB elimination, it is important for health systems to identify

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gaps in LTBI treatment practices and identify individuals who may require additional support to complete their treatment. Thus, we conducted a retrospective cohort study to investigate LTBI treatment patterns at 2 large integrated health systems in California among patients with LTBI between 2009 and 2018.

METHODS

Study Setting

The study was conducted at Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC), 2 distinct integrated health systems that provide health care coverage and services to >9.2 million members with diverse racial/ethnic and socioeconomic backgrounds generally representative of the California population [15, 16]. KPNC has 21 hospitals and 269 medical office buildings, while KPSC has 15 hospitals and 236 medical office buildings. Members of each of these health systems are enrolled through employer-provided, prepaid, or federally sponsored plans. Both KPNC and KPSC have comprehensive electronic health records (EHRs), which capture details of care received, including diagnoses, procedures, laboratory tests, and pharmacy records. Although members have incentive to seek care at facilities within the health systems, care received at outside facilities is generally captured as part of claims reimbursement and integrated into the EHR. The KPSC Institutional Review Board provided ethical approval (#12324), waiving the requirement for written informed consent, as this data-only study posed minimal risk to study participants.

Population

The cohort included adults aged ≥18 years with a positive LTBI test (tuberculin skin test [TST] or interferon gamma release assay [IGRA]) conducted at KPNC or KPSC between 2009 and 2018. Due to the high incidence of TB in California, an induration of ≥5 mm for immunosuppressed individuals and ≥10 mm for everyone else is considered standard for defining a positive TST [17]. The date of the first positive LTBI test was defined as the index date. Individuals were excluded if they had <2 years of enrollment following the index date or if they had active TB (defined as a positive culture or nucleic acid amplification test [Xpert MTB/RIF]) before the index date or during the study period to ensure equal opportunity for follow-up. In a sensitivity analysis, we included all individuals with LTBI, regardless of disenrollment or active TB during follow-up.

Measures

The outcomes of interest were LTBI treatment prescription, initiation, and completion. We defined treatment prescription as receiving an LTBI treatment prescription (INH, rifampin, or rifamycin-INH short-course combinations [INH + rifampin, or INH + rifapentine]) within the 12 months following the positive LTBI test. We defined treatment initiation based on pharmacy dispensing records of ≥1 prescription (ie, receipt of treatment by patient). We defined completion as dispensing of the required number of doses within the appropriate time interval, allowing a grace period for assessing completion (ie, for 6–9 months of daily INH, we allowed either 9 months for dispensing 180 doses or 12 months for dispensing 270 doses; for 4 months of daily rifampin, we allowed 6 months for dispensing 120 doses; for 3 months of daily INH + rifampin, we allowed 4 months for dispensing 90 doses; for 3 months of weekly INH + rifapentine [provided by directly observed therapy until 2018 when CDC recommendations included self-administered therapy [18]], we allowed 4 months for dispensing 12 doses). We categorized individuals who received >1 LTBI treatment during the study period as receiving "other" treatment regimens; these individuals were considered to have completed treatment if sufficient dosage of ≥1 treatment regimen was dispensed in the appropriate time interval for the given regimen.

Other Variables

Demographic and clinical characteristics identified a priori were collected from the EHR. These included age (18–35, 36–49, 50–64, 65–74, ≥75 years), sex (male, female), race/ethnicity (White, Asian, Black, Hispanic, Hawaiian/Pacific Islander, other/unknown), country of birth (high–TB incidence country as defined by the California Department of Public Health and California Tuberculosis Controllers Association Joint Guidelines [countries other than the United States, Canada, Australia, New Zealand, or a country in Western or Northern Europe] [17] or not born in high–TB incidence country), comorbidities in the year before the index date (Charlson comorbidity index score, diabetes, and immunosuppressed status based on HIV diagnosis, organ transplant, dialysis, and receipt of immunosuppressants, including high-dose corticosteroids [>20 mg prednisone equivalents per day for ≥30 days, tumor necrosis alpha inhibitors, chemotherapy and other immunomodulators]), number of outpatient visits in the year before the index date, and sites (KPNC and KPSC health systems). We also captured the type of LTBI test at index date (TST or IGRA; individuals who had an IGRA within ≤90 days of a TST were considered to have an IGRA) and year of index date.

Analyses

We described the LTBI treatment cascade, including the number and characteristics of individuals who tested positive for LTBI, those who were prescribed LTBI treatment, and those who completed treatment. We graphed the proportions of individuals who were prescribed treatment among those with a positive LTBI test and who completed treatment among those prescribed treatment, by year. We also examined the proportions of individuals who were prescribed treatment among

Table 1. Characteristics of Individuals With LTBI at Two California Health Systems, 2009–2018

Total	Tested Positive for LTBI n = 79 302 No. (%)	Prescribed LTBI Treatment n = 26 141 No. (%)	Completed Treatment n = 14 644 No. (%)
Age at index date, y			
18–35	24 997 (31.5)	7934 (30.4)	3818 (26.1)
36–49	26 989 (34.0)	8835 (33.8)	4886 (33.4)
50–64	18 251 (23.0)	6530 (25.0)	4090 (27.9)
65–74	5950 (7.5)	2114 (8.1)	1396 (9.5)
≥75	3115 (3.9)	728 (2.8)	454 (3.1)
Age at index date, median (IQR), y	43 (33–55)	43 (33–55)	45 (35–57)
Sex			
Male	47 288 (59.6)	14 971 (57.3)	8072 (55.1)
Female	32 014 (40.4)	11 170 (42.7)	6572 (44.9)
Race/ethnicity			
White	11 477 (14.5)	3718 (14.2)	2245 (15.3)
Asian	27 262 (34.4)	8592 (32.9)	5156 (35.2)
Black	6510 (8.2)	2030 (7.8)	1112 (7.6)
Hispanic	29 607 (37.3)	10 423 (39.9)	5394 (36.8)
Hawaiian/Pacific Islander	1423 (1.8)	445 (1.7)	243 (1.7)
Other/unknown	3023 (3.8)	933 (3.6)	494 (3.4)
Country of birth			
Not born in high–TB incidence country	14 061 (17.7)	4902 (18.8)	2824 (19.3)
Born in high–TB incidence country	29 009 (36.6)	9547 (36.5)	5396 (36.8)
Missing	36 232 (45.7)	11 692 (44.7)	6424 (43.9)
Weighted Charlson comorbidity score			
0	57 033 (71.9)	17 915 (68.5)	9495 (64.8)
1–3	18 280 (23.1)	6621 (25.3)	4042 (27.6)
≥4	3989 (5.0)	1605 (6.1)	1107 (7.6)
Immunosuppressed	4359 (5.5)	2453 (9.4)	1771 (12.1)
Diabetes	9655 (12.2)	3491 (13.4)	2239 (15.3)
No. of outpatient encounters in y prior			
0–5	35 905 (45.3)	11 102 (42.5)	5927 (40.5)
6–10	22 284 (28.1)	7364 (28.2)	4159 (28.4)
≥11	21 113 (26.6)	7675 (29.4)	4558 (31.1)
Type of positive test			
TST	59 048 (74.5)	16 798 (64.3)	8724 (59.6)
IGRA	20 254 (25.5)	9343 (35.7)	5920 (40.4)
Site			
Site 1	38 308 (48.3)	13 831 (52.9)	7998 (54.6)
Site 2	40 994 (51.7)	12 310 (47.1)	6646 (45.4)
Year of first positive test			
2009	6423 (8.1)	2126 (8.1)	1109 (7.6)
2010	6404 (8.1)	2142 (8.2)	1126 (7.7)
2011	6385 (8.1)	2122 (8.1)	1182 (8.1)
2012	6787 (8.6)	2211 (8.5)	1238 (8.5)
2013	7227 (9.1)	2480 (9.5)	1412 (9.6)
2014	8615 (10.9)	2992 (11.4)	1668 (11.4)
2015	8625 (10.9)	2691 (10.3)	1505 (10.3)
2016	9491 (12.0)	3012 (11.5)	1695 (11.6)
2017	9733 (12.3)	3169 (12.1)	1829 (12.5)
2018	9612 (12.1)	3196 (12.2)	1880 (12.8)
Treatment regimens			
Isoniazid		21 334 (81.6)	12 006 (82.0)
Rifampin		2210 (8.5)	1250 (8.5)
Isoniazid + rifampin		1268 (4.9)	891 (6.1)
Isoniazid + rifapentine		527 (2.0)	367 (2.5)
Other		802 (3.1)	130 (0.9)

Abbreviations: IGRA, interferon gamma release assay; IQR, interquartile range; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

those with a positive LTBI test and who completed treatment among those prescribed treatment, by demographic and clinical characteristics (described above). To assess whether demographic and clinical characteristics were independently associated with treatment prescription and completion, we used multivariable robust Poisson regression to estimate risk ratios (RRs) and 95% CIs for these outcomes comparing each characteristic and adjusting for all other characteristics [19].

RESULTS

Of 114 292 adults without a prior TB diagnosis who had a positive LTBI test from 2009 to 2018, 34 605 (30.3%) were excluded due to having <2 years of enrollment after the index date and 385 (0.34%) were excluded due to developing active TB. The study cohort included 79 302 individuals (38 308 from Site 1 and 40 994 from Site 2) with LTBI from 2009 to 2018 (Table 1). The median age at index date (interquartile range) was 43 (33–55) years, 59.6% were male, the majority were Asian (34.4%) or Hispanic (37.3%), and 36.6% were known to be born in a high–TB incidence country. Comorbidities in the year before the index date were uncommon; 71.9% of individuals had a weighted Charlson comorbidity index score of 0, 5.5% were immunosuppressed, 12.2% had diabetes, and 45.3% had ≤5 outpatient visits in the prior year. For 74.5% of individuals, the positive LTBI test was a TST.

As shown in Figure 1, 33.0% (n = 26 141) of individuals who tested positive for LTBI were prescribed treatment for LTBI in the 12 months after LTBI diagnosis. Of those who were prescribed treatment, 85.8% (n = 22 422) initiated treatment, and of those who initiated treatment, 65.3% (n = 14 644) completed treatment. Overall, treatment completion was 18.5% among those who tested positive for LTBI and 56.0% among those who were prescribed LTBI treatment. In the sensitivity analysis including all individuals with LTBI testing regardless of disenrollment within ≤2 years after the index date, the proportions

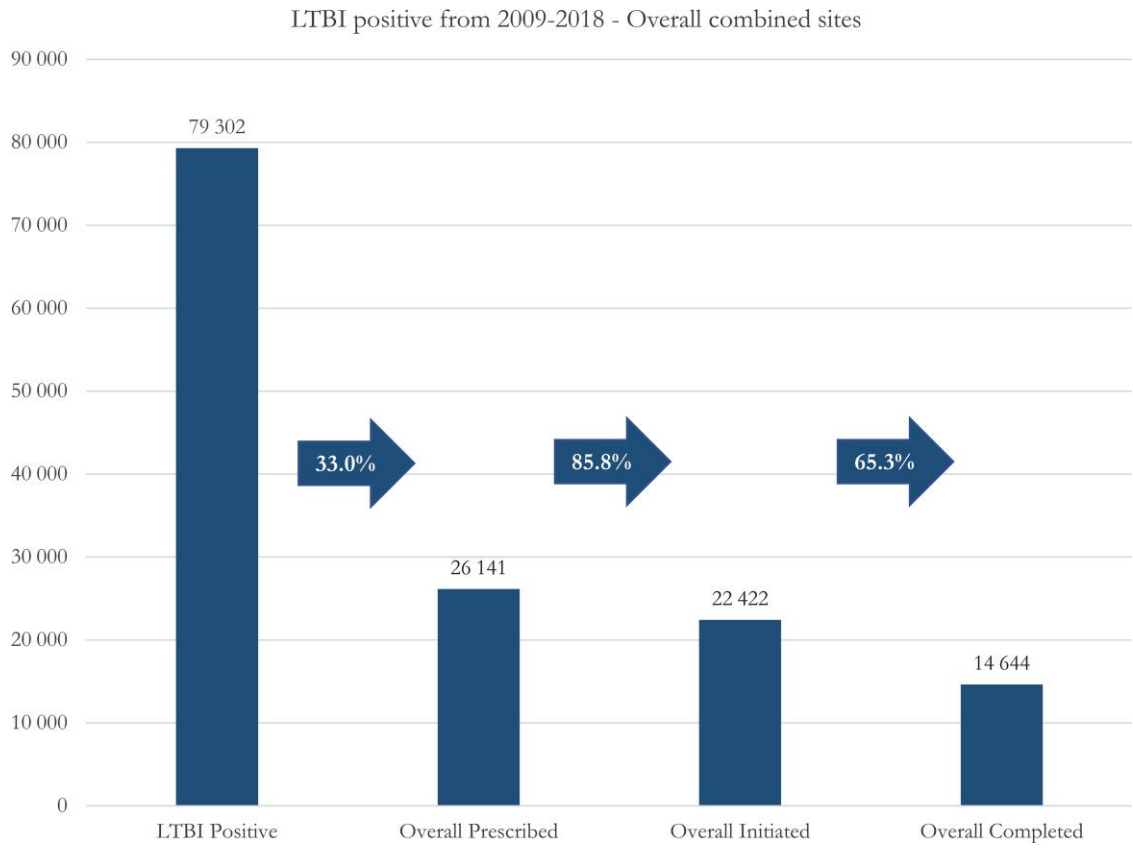

Figure 1. LTBI treatment cascade among individuals with a positive LTBI test during 2009–2018 at 2 California health systems. LTBI positive includes adults with LTBI based on the first positive tuberculin skin test or interferon gamma release assay among those with no prior tuberculosis diagnoses. Abbreviation: LTBI, talent tuberculosis infection.

across the treatment cascade were nearly identical (Supplementary Figure 1).

During the study period, the proportion of individuals with LTBI who were prescribed INH monotherapy decreased, accompanied by increases in prescription of rifampin or rifamycin-INH short-course combinations (Figure 2). Nonetheless, INH was the main treatment regimen in each year throughout the study period; of those prescribed treatment, 81.6% were prescribed INH, 8.5% rifampin, 6.9% rifamycin-INH short-course combinations, and 3.1% other regimens (Table 1). During the study period, IGRA were introduced, such that the proportion of individuals who had an IGRA vs TST as their positive LTBI test increased from 0% in 2009 to 47.1% in 2018 (Supplementary Figure 2).

The proportions of individuals who were prescribed treatment (of those with a positive LTBI test) and those who completed treatment (of those who were prescribed treatment) varied by demographic and clinical characteristics (Supplementary Table 1). For example, the proportions prescribed treatment and completing treatment were highest among those with immunosuppressed status (56.3% and 72.2%, respectively). The proportion prescribed treatment was lowest among those aged ≥75 years (23.4%), but the proportion completing treatment was lowest among those aged 18–35 years (48.1%). Treatment completion was also higher among those prescribed rifamycin-INH short-course combinations (69.6% for INH + rifapentine and 70.3% for INH + rifampin) compared with those prescribed INH (56.3%) or rifampin (56.6%).

In multivariable analyses examining factors associated with LTBI treatment prescription among those with LTBI (Figure 3), individuals aged 65–74 years and those ≥75 years, respectively, were less likely to be prescribed LTBI treatment compared with individuals aged 18–35 years (RR, 0.85; 95% CI, 0.81–0.88; RR, 0.54; 95% CI, 0.51–0.58). Treatment prescription was higher for females vs males (RR, 1.08; 95% CI, 1.06–1.10) and Hispanic individuals vs White individuals (RR, 1.17; 95% CI, 1.14–1.21). Treatment prescription was lower for individuals born in a high–TB incidence country vs those not born in a high–TB incidence country (RR, 0.92; 95% CI, 0.89–0.94). Individuals with comorbidities vs those without were generally more likely to be prescribed treatment, particularly those with vs without immunosuppression (RR, 1.42; 95% CI, 1.37–1.46) and those with 6–10 or ≥11 vs 0–5 outpatient

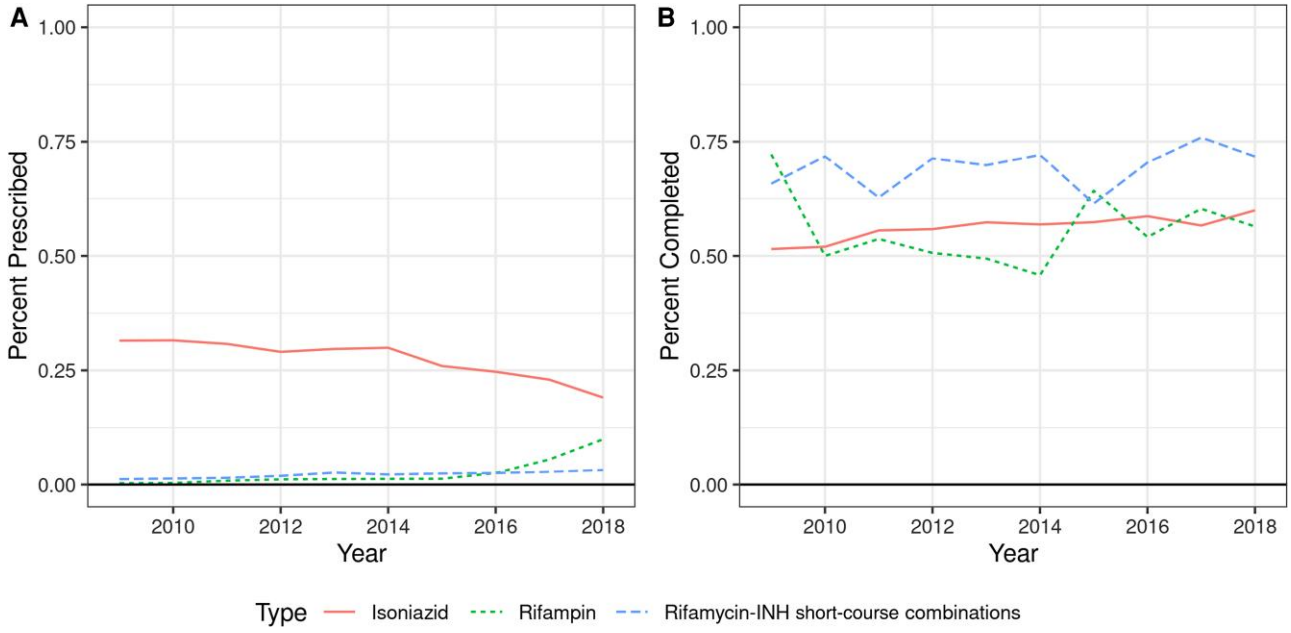

Figure 2. Changes in LTBI treatment regimens during 2009–2018 at 2 California health systems. *A*, The percentage prescribed LTBI treatment of those with a positive LTBI test. *B*, The percentage completing LTBI treatment of those prescribed LTBI treatment. Abbreviation: LTBI, talent tuberculosis infection.

encounters in the prior year (RR range, 1.08–1.13). However, diabetes was not associated with LTBI treatment prescription. Individuals who had an IGRA vs TST for their LTBI-positive test were more likely to be prescribed treatment (RR, 1.77; 95% CI, 1.73–1.81). In addition, there was variation between sites (RR, 0.76; 95% CI, 0.75–0.78; comparing Site 2 to Site 1) and year of positive test (eg, RR, 0.74; 95% CI, 0.70–0.77; comparing 2018 to 2009), possibly reflecting differences in demographics and treatment practices.

Similarly, in multivariable analyses examining factors associated with LTBI treatment completion among those prescribed treatment, females were more likely to complete treatment vs males (RR, 1.06; 95% CI, 1.04–1.08), and those born in a high–TB incidence country were less likely to complete treatment vs those not born in a high–TB incidence country (RR, 0.95; 95% CI, 0.91–0.98) (Figure 4). Older age groups vs those aged 18–35 years were more likely to complete treatment (RR range, 1.12–1.22), and Black and Hispanic vs White individuals were less likely to complete treatment (RR, 0.92; 95% CI, 0.88–0.96; RR, 0.90; 95% CI, 0.87–0.93). The associations of clinical risk factors with treatment completion were similar though not as strong as associations observed for treatment prescription. For example, individuals with vs without immunosuppression were more likely to complete treatment (RR, 1.18; 95% CI, 1.14–1.21), as were those with 6–10 vs 0–5 encounters in the prior year (RR, 1.03; 95% CI, 1.01–1.06). Individuals with an IGRA vs TST were more likely to complete LTBI treatment (RR, 1.19; 95% CI, 1.16–1.22). Compared with individuals prescribed INH, those prescribed rifampin were less likely to complete treatment (RR, 0.91; 95% CI, 0.87–0.95), as were those prescribed other regimens (RR, 0.28; 95% CI, 0.24–0.32), but those prescribed rifamycin-INH short-course combinations were more likely to complete treatment (RR range, 1.15–1.17).

DISCUSSION

In a large cohort of individuals with LTBI at 2 California health systems during 2009–2018, we observed substantial gaps across the LTBI treatment cascade. Less than one-third of individuals with a positive LTBI test were prescribed LTBI treatment, of whom only half completed treatment. These results indicate widespread underutilization of LTBI treatment, which may result in missed opportunities to prevent TB disease.

Our results add to a limited number of other studies on LTBI treatment practices. A meta-analysis of 58 global studies found that steps in the LTBI care cascade before treatment initiation accounted for more dropouts in care than adherence to treatment after initiation; [9] this is consistent with our study, in which the largest gap in care occurred between testing positive for LTBI and treatment prescription. In another study among 15 local health department TB clinics in 11 US states, 43% of patients diagnosed with LTBI in 2016–2018 initiated treatment, and 76% of those who initiated treatment completed treatment [20]. These findings are somewhat higher than results observed in our study (28% and 65%, respectively), potentially because of

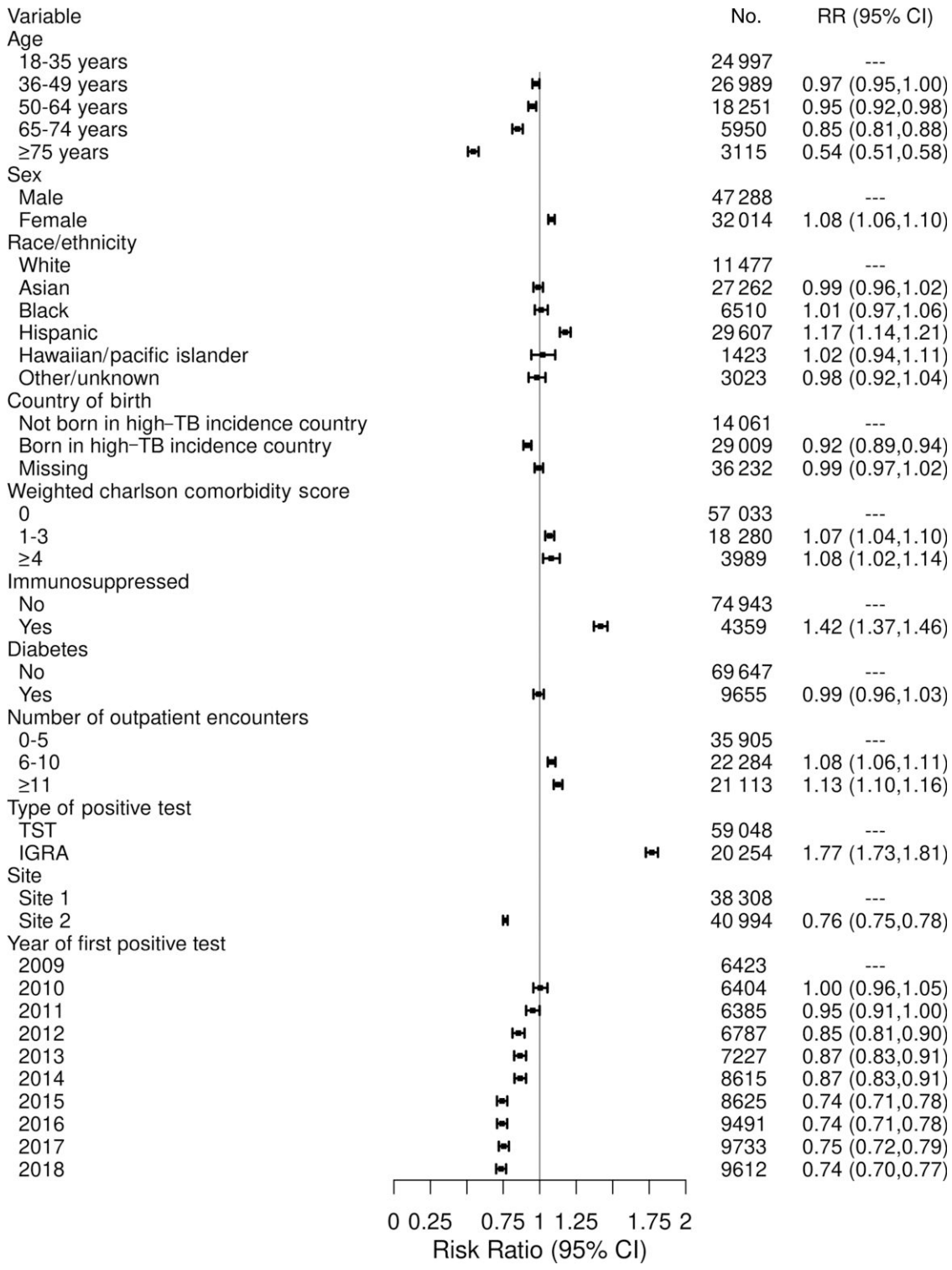

Figure 3. Factors associated with LTBI treatment prescription among individuals with a positive LTBI test. RRs are adjusted for all other variables in the model. Abbreviations: IGRA, interferon gamma release assay; IQR, interquartile range; LTBI, latent tuberculosis infection; RR, risk ratio; TB, tuberculosis; TST, tuberculin skin test.

differences in LTBI patient populations and more focused TB care provided by local health department TB clinics than KPNC/KPSC primary care settings.

The US Preventive Services Task Force (USPSTF) recommends LTBI screening in populations at increased risk (B recommendation) [21], including individuals who were born or

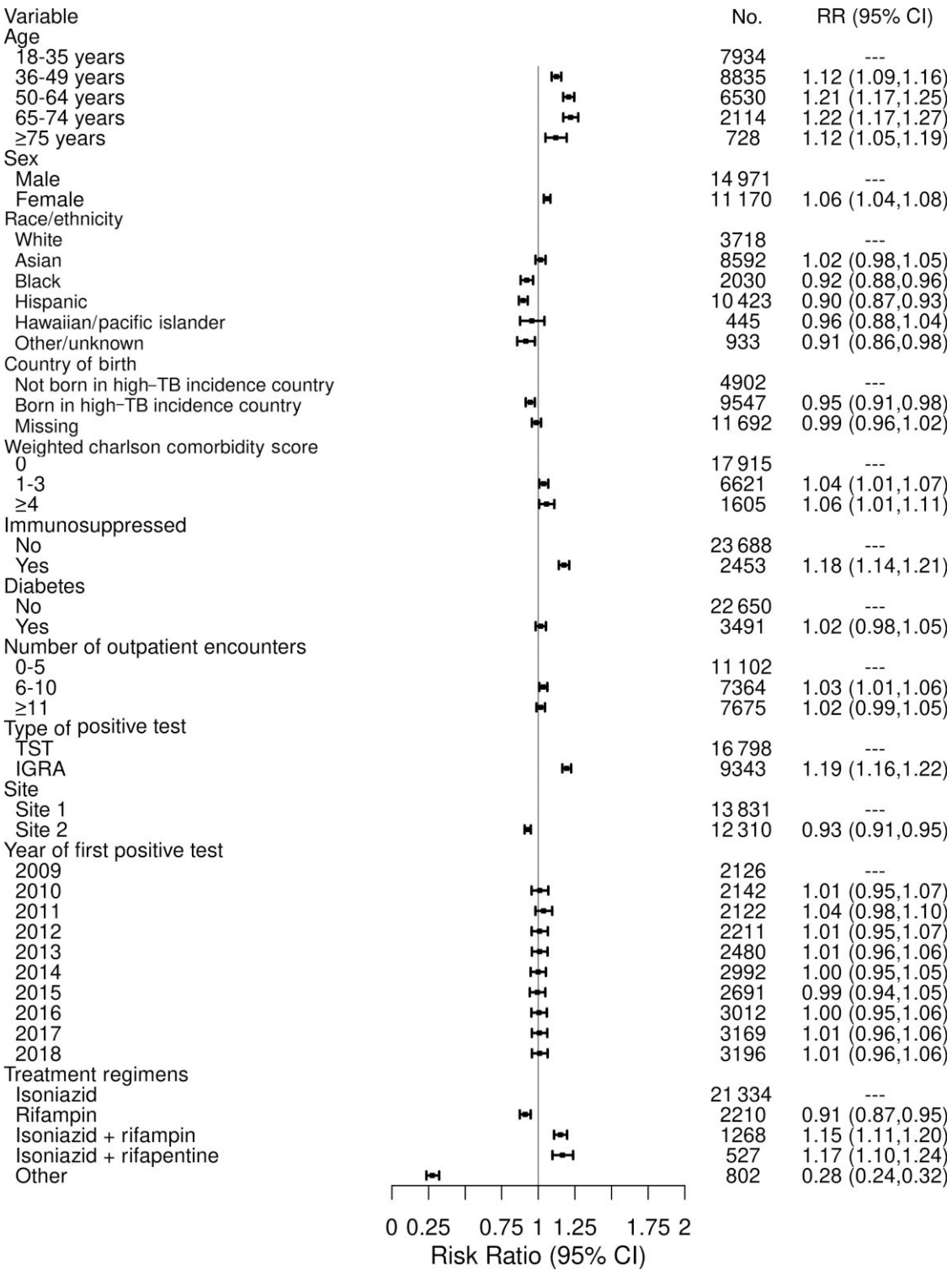

Figure 4. Factors associated with LTBI treatment completion among individuals prescribed treatment. RRs are adjusted for all other variables in the model. Abbreviations: IGRA, interferon gamma release assay; IQR, interquartile range; LTBI, latent tuberculosis infection; RR, risk ratio; TB, tuberculosis; TST, tuberculin skin test.

resided in a country with elevated TB risk, those with immunosuppression, and close contacts of individuals with active TB [22]. According to USPSTF, all individuals who have been screened and have a positive IGRA or TST should be treated. However, questions remain around implementation of USPSTF and California guidelines and ensuring that screening

practices optimally identify those with LTBI who are at high risk of reactivation [7]. Providers may be less likely to prescribe treatment for some groups of people if they do not perceive benefits to outweigh risk. For example, in our study, we found that in adjusted analyses older vs younger individuals were less likely to be prescribed LTBI treatment, perhaps because of concerns about hepatotoxicity and other side effects, or possibly because prior LTBI guidelines recommended treatment for individuals aged <35 years with a positive TST and no other risk factors [23]. In adjusted analyses, individuals born in a high–TB incidence country were also less likely to be prescribed treatment than those not born in a high–TB incidence country; however, the proportions prescribed treatment were similar (34.9% vs 32.9%). On the other hand, we found that individuals with immunosuppression or those with a positive IGRA were considerably more likely to be prescribed treatment, potentially due to greater perceived benefit.

Several other studies have reported higher completion rates with shorter treatment regimens compared with INH [10, 12, 24]. Although we did not find higher treatment completion among those prescribed rifampin, we found that those prescribed rifamycin-INH short-course combinations were 15%–17% more likely to complete treatment than those prescribed INH. This finding underscores the CDC recommendation favoring prescription of rifamycin-INH short-course combinations [12]. INH + rifapentine was delivered mostly via DOT, until CDC recommendations included SAT toward the end of our study period. Although it is possible that DOT increased treatment completion for those prescribed INH + rifapentine, treatment completion via SAT has previously been found to be noninferior to DOT [25]. In our study, those prescribed "other" treatment regimens had lower treatment completion; this group received multiple treatments or nonstandard treatment (eg, had switched LTBI treatments), and were thus inherently less likely to complete treatment. We also found in adjusted analyses that younger individuals, Black and Hispanic individuals, and those born in high–TB incidence countries were less likely to complete treatment; the latter group is particularly important due to their high risk of active TB and disparities in access to care [26]. Specific patient-centered interventions may be needed for health systems to engage these individuals in LTBI care and to address barriers to treatment completion.

Our study has several strengths and limitations. We used EHR data from a highly diverse population in 2 large health systems in California to examine the LTBI treatment cascade over the course of a decade. Although KPNC and KPSC EHR data are comprehensive, some variables such as birth in a country with high TB incidence are underreported [27]. We considered a range of comorbidities in our analyses, but we did not include smoking or body mass index, as these variables are not reliably captured in EHR data. Misclassification of steps along the treatment cascade could have occurred. For example, if the LTBI test was a false positive or if some patients had already completed treatment before joining KPNC or KPSC, some individuals may have been inappropriately included in the LTBI cohort; however, this is likely to be uncommon, as individuals who have previously completed treatment should not be tested [17, 28]. Misclassification may also have occurred if patients received treatment outside of the KPNC and KPSC health systems (eg, public health TB clinics); however, KPNC and KPSC members have financial incentive to receive care including pharmacy services within the health systems, and outside care is integrated into the EHRs with appropriate documentation. To ensure opportunity to complete treatment, we required ≥2 years of health system enrollment following the index date. Individuals who were excluded due to <2 years of enrollment after the index date may have differed from the study cohort; however, sensitivity analyses including all individuals with a positive LTBI test regardless of disenrollment found nearly identical results. In addition, treatment completion was based on dispensing records, but it is possible that patients were dispensed the full course of treatment but did not take all of the pills; this would overestimate treatment completion in our study. Last, the LTBI treatment cascade could vary in other settings with different populations, interventions, and patient retention; however, the consistency of our results with prior studies and the diversity of our population suggest high generalizability of our results to other US health systems.

CONCLUSIONS

TB is preventable, but LTBI treatment was vastly underutilized. To meet targets for TB elimination, it is critical for health systems to prioritize screening those at high risk of reactivation and to ensure that those with positive TST or IGRA are prescribed treatment, preferably rifamycin-INH short-course combinations. Patient-centered interventions are warranted to support treatment completion, particularly among individuals born in a country with elevated TB incidence.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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