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Using the Food and Drug Administration's Sentinel System for surveillance of TB infection

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Abstract

BACKGROUND: We examined patterns in care for individuals treated for latent TB infection (LTBI) in the US Food and Drug Administration's Sentinel System.

METHODS: Using administrative claims data, we identified patients who filled standard LTBI treatment prescriptions during 2008–2019. In these cohorts, we assessed LTBI testing, clinical management, and treatment duration.

RESULTS: Among 113,338 patients who filled LTBI prescriptions, 80% (90,377) received isoniazid (INH) only, 19% (21,235) rifampin (RIF) only, and 2% (1,726) INH+rifapentine (RPT). By regimen, the proportion of patients with documented prior testing for TBI was 79%, 54%, and 91%, respectively. Median therapy duration was 84 days (IQR 35–84) for the 3-month once-weekly INH+RPTregimen, 60 days (IQR 30–100) for the 6- to 9-month INH regimen, and 30 days (IQR 2–60) for the 4-month RIF regimen.

CONCLUSIONS: Among the cohorts, INH-only was the most commonly prescribed LTBI treatment. Most persons who filled a prescription for LTBI treatment did not have evidence of completing recommended treatment duration. These data further support preferential use of shorter-course regimens such as INH+RPT.

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RÉSUMÉ

Nous avons examiné les tendances en matière de soins des individus traités pour infection tuberculeuse latente (LTBI) dans le cadre du Système Sentinelle de la Food and Drug Administration desÉtats-Unis.

En utilisant les donneés des réclamations administratives, nous avons identifié les patients ayant reçu une ordonnance pour traitement standard de la LTBI pendant la période 2008–2019. Dans ces cohortes, nous avons évalué le dépistage de la LTBI, la prise en charge clinique et la dureé du traitement.

Parmi 113 338 patients ayant reçu une ordonnance pour LTBI, 80% (90 377) recevaient uniquement de l'isoniazide (INH), 19% (21 235) uniquement de la rifampine (RIF) et 2% (1 726) l'INH + rifapentine (RPT). Par schéma thérapeutique, la proportion de patients avec documentation de dépistage antérieur de la TBI était de 79%, 54% et 91%, respectivement. La dureé médiane du traitement etait de 84 jours (IQR 35–84) pour le schéma de 3 moiś INH + RPT avec une prise hebdomadaire, de 60 jours (IQR 30–100) pour le schéma INH de 6 à 9 mois et de 30 jours (IQR 2–60) pour le schéma RIF de 4 mois.

Parmi les cohortes, l'INH seul était le traitement de la LTBI le plus prescrit. La plupart des personnes ayant reçu une ordonnance pour traitement de la LTBI ne disposaient d'aucun document justifiant la bonne observance de la dureé recommandée du traitement. Ces donneés étayent donc l'utilisation privilégiée de schémas plus courts, tels que l'INH+RPT.

Keywords

administrative claims data; treatment completion; prescription-based cohort; LTBI

Identifying and treating persons with latent TB infection (LTBI) is critical to reaching the goal of TB elimination.[1,2] LTBI is a condition that occurs when a person is infected with *Mycobacterium tuberculosis* without signs and symptoms or radiographic or bacteriologic evidence of TB disease. Without treatment, 5% to 10% of infected persons will develop TB disease during their lifetime.[3] Recommendations for LTBI treatment were first issued in 2000 and updated in 2011, 2018, and 2020.[3–6] In general, these recommendations increasingly favor the use of short-course rifamycin-based regimens for LTBI therapy over longer isoniazid (INH) only regimens.

The Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) have estimated that 9–13 million persons in the United States are living with LTBI.[7,8] Direct estimates of LTBI prevalence based on nationwide surveillance data are unavailable because, unlike TB disease, LTBI is not a nationally notifiable condition. In 2020, CDC began accepting voluntary reports that meet the Council of State and Territorial Epidemiologists case definition for LTBI.[9] Given the limitations of data sources, efforts to identify additional sources of population-level LTBI surveillance data continue.[7,8]

One potential source of complementary surveillance data is the US Food and Drug Administration's (FDA; Washington DC, USA) Sentinel System. Sentinel is a nationwide postmarket surveillance system used to monitor the safety of FDA-regulated medical

products.[10–12] With longitudinal administrative claims data from Medicare fee-for-service, national commercial insurers, and regional integrated delivery systems, Sentinel is one of the largest repositories of curated electronic health data. As of August 2020, more than 228 million patients were included in this distributed database.[13]

We assessed the demographic and health-related characteristics of patients receiving treatment for LTBI and examined patterns in care including the LTBI treatment regimens used and duration of therapy for these patients. More broadly we sought to understand how Sentinel might be used for LTBI surveillance.

METHODS

Study populations

Using Sentinel's Cohort Identification and Descriptive Analysis module v9.0.1, we identified three cohorts of health plan members from 2008 to 2018 who filled outpatient prescriptions consistent with standard LTBI treatment between January 1, 2008, and December 31, 2019. These standard LTBI treatment regimens included INH-only, rifampin (RIF) only, or the combined INH + rifapentine (RPT) regimen, which was first recommended as a treatment regimen for LTBI in 2011.[3–6]

For all cohorts, health plan members had to be enrolled with medical and prescription drug coverage for ≥365 continuous days before the first medication in one of the three LTBI treatment regimens was dispensed and could show no evidence of LTBI treatment during those 365 preceding days. Only the first qualifying filled outpatient prescription for each member was included. For example, an incident INH-only user had to meet all eligibility criteria, including no use of RIF or INH + RPT in the prior 365 days. Each of the three cohorts was created separately. Individuals could be counted in multiple cohorts if they met all criteria during the study period. To exclude persons prescribed RIF for conditions other than LTBI, we required a minimum treatment duration of 20 days and excluded anyone who had an International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnostic code for another condition sometimes treated with RIF (e.g., endocarditis, Lyme disease, cellulitis, pneumonia, osteomyelitis) during the past 365 days.

Treatment episodes

We created LTBI treatment episodes by combining the data for dispensings of the same product and the number of days supplied for each dispensing. Treatment episode length was based on the days' supply of dispensings (i.e., the number of days the dispensed medication is to be used for). For example, if a patient was dispensed a 30-day supply of medication with three dispensings and all dispensings occurred exactly as prescribed, then the treatment episode was 90 days. If any dispensings (i.e., refills) occurred after the end of the prior dispensing, the treatment episode was censored (e.g., if the third refill was dispensed at least 1 day after the second refill supply ended, the treatment episode length would be censored after the second refill and the third was not counted). Treatment episode length was compared to recommended INH-only regimens prescribed for 6-to 9- months with

daily dosing (i.e., 180–270 days of therapy) and RIF-only for 4-months with daily dosing (i.e., 120 days of therapy). The recommended 3-month once-weekly INH + RPT regimen was considered 84 days treatment episode length (i.e., 12 doses × 7-day dosing interval). We required the days' supply of the INH dispensing to overlap the days' supply of the RPT dispensing. We censored treatment episodes at initiation of one of the other LTBI treatments, gap in treatment (described above), evidence of death, data availability end date, or disenrollment from the health plan. In addition, the INH + RPT regimen was censored when INH and RPT dispensings stopped overlapping.

Diagnostic testing for TB and LTBI

We characterized the most recent TB diagnostic test that members had in the 365 days before treatment, estimated time from diagnosis to treatment, and examined selected risk factors for progression to TB disease before and after treatment. The TB evaluation tests of interest included the tuberculin skin test (TST), interferon-gamma release assays (IGRAs), sputum culture or sputum smear microscopy, chest radiograph, and thoracic computed tomography scans. These procedures were identified by ICD-9-CM and ICD-10-CM; Procedural Coding System; Healthcare Common Procedure Coding System; and Current Procedural Terminology, Second, Third, and Fourth Editions codes.

Risk factors for TB infection and progression to TB disease

Similar to TB evaluation testing, diagnosis of LTBI, HIV, and diabetes, HIV testing, and tumor necrosis factor-α inhibitor use were assessed in the 365 days before and after initiating treatment. LTBI diagnosis was identified for each member using the first qualifying (index) ICD-9-CM or ICD-10-CM diagnosis code in any care setting. Additional details, including diagnosis and procedure codes used in the analysis are publicly available at https://www.sentinelinitiative.org/sites/default/files/Methods/Report_cder_mpl1p_wp039.pdf.

Institutional review

This FDA Sentinel System project is a public health surveillance activity conducted under the authority of the US Food and Drug Administration and is accordingly not subject to Institutional Review Board oversight or further review.[14] This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.

RESULTS

Of 113,338 patients who filled prescriptions consistent with LTBI treatment, most were ≥45 years old (62%) (Table 1). Of the 60% of the cohort with known race, 29% were White, 17% Asian; and 12% Black. Of the 50% of the cohort with known ethnicity, 11% of patients were identified as Hispanic. The South and West regions of the United States accounted for the largest proportions of patients (26% and 47%, respectively).

During 2008–2019, the INH-only regimen was the most common LTBI treatment prescribed, followed by RIF-only, and then INH + RPT (80%, 19%, and 2%, respectively). INH-only and INH + RPT were prescribed more frequently in the West than other regions

(50% and 57%, respectively). From 2013 to 2018, the yearly number of dispensings remained relatively stable (range 9,161–12,935); however, the proportion of RIF dispensings rose from 17% to 33% (96% increase) and INH + RIF dispensings rose from 2% to 3% (54% increase) while INH-only dispensings fell from 81% to 64% (21% decline). Of those receiving any LTBI treatment, only 44% of patients had an LTBI diagnostic code recorded before starting treatment.

The proportion of patients with documentation of HIV testing before or after LTBI treatment start was 15% and 10%, respectively; 3% had documented HIV infection (Table 2). Approximately one quarter of patients (24%) had a documented diagnosis of diabetes mellitus. Most patients (74%) had a documented test for TBI (TST or IGRA) before starting treatment; the proportion of patients with a documented TST (65%) was higher than those with a documented IGRA (32%). More patients had a documented TST or IGRA in the INH + RPT cohort (91%) than the INH-only cohort (79%) or RIF-only cohort (54%). Some patients had documentation of both a TST and IGRA (24% in the INH-only cohort, 19% in the RIF-only cohort, and 37% in the INH + RPT cohort). Most patients overall (80%), and within each treatment cohort, had documentation of a chest radiograph before treatment start. Overall, 88% of patients had at least one element of a TB diagnostic evaluation documented before starting treatment.

Those receiving INH + RPT had a higher median treatment episode duration at 84 days (interquartile range [IQR] 35–84) compared with 60 days (IQR 30–100) for INH-only and 30 days (IQR 2–60) for RIF-only (Table 3). The time from LTBI diagnosis to LTBI treatment initiation was a median of 10 days (IQR 2–36) for INH-only, 31 days (IQR 8–98) for RIF-only and 22 days (IQR 8–64) for INH + RPT.

DISCUSSION

Using administrative claims data from a population of more than 115 million federally and privately insured persons, we identified more than 113,000 patients who filled prescriptions consistent with LTBI therapy during 2008–2019. Our study had several interesting findings. First, despite a decrease in INH-only dispensings, this 180–270-day regimen was the most widely used regimen during the 12-year analysis period. From 2013 to 2018, we noted an increasing shift towards dispensing shorter-course rifamycin-based regimens while total yearly dispensings remained relatively stable. In contrast, patients treated at local public health clinics in 2016–2017 in one study more often received 4-month RIF-only (57%) and 3-month INH + RPT (21%) than 6- or 9-month of INH-only therapy (15%).[15] These findings offer important insight into prescribing behavior. Despite recommendations first issued in 2000 and updated in 2011, 2018, and 2020 that support use of shorter-course rifamycin-based regimens, INH use predominates (although declining) in our known insured population.[3–6] Local health department clinics may have greater uptake of newer prescribing recommendations for LTBI therapy than healthcare providers for an insured population. Second, based on prescription drug claims, median duration of therapy was only 60 days for the INH-only regimen and 30 days for the RIF-only regimen, well short of the recommended treatment durations of 180–270 and 120 days, respectively. These findings are consistent with other studies showing suboptimal LTBI treatment completion, highlighting the need

for additional interventions to support patients' completion of LTBI therapy.[15–18] Notably, the median duration of therapy for the INH + RPT regimen was 84 days, corresponding exactly to the recommended once weekly dosing for 12 weeks.[4–6] This finding may reflect the dispensing practices for the shorter INH+RPT regimen, which may be dispensed in its entirety rather than requiring refills and therefore fewer opportunities for censoring due to late refills. In addition, initial recommendations for the INH+RPT regimen included administration via directly observed therapy which potentially affects therapy duration. Moreover, patients receiving this combination regimen had higher rates of diagnostic testing with TST or IGRA (91% vs. 79% with INH-only or 54% with RIF-only) and higher rates of HIV testing (21% vs. 16% or 14%, respectively), possibly indicating greater familiarity with LTBI recommendations among providers prescribing this regimen and regionally in the West. However, in this analysis a higher proportion of patients in the INH-only regimen were tested using TST (70%) or IGRA (33%) vs. 41% and 20% of patients in a separate study of administrative claims data from 2011 to 2014.[18] The finding of only approximately half of patients in the RIF cohort having documentation of diagnostic testing with TST or IGRA may be due to misclassification in this cohort. Third, across all three regimens, 88% of patients receiving LTBI therapy had at least some evidence of prior TB diagnostic evaluation. Interestingly, a proportion of patients in all three cohorts had documentation of both a TST and IGRA; using both tests for diagnostic purposes is not currently recommended. Fourth, the time from LTBI medical evaluation to a filled prescription for LTBI treatment was relatively short, suggesting there did not appear to be delays between evaluation and treatment.

Limitations

Our analysis also had several important limitations, some of which are common to administrative claims-based data sources. Because we did not have access to LTBI test results, our treatment-based cohorts might include people without LTBI, particularly among the RIF-only group. This differential misclassification is most likely to have occurred with the RIF-only cohort because RIF is indicated for a range of infectious conditions. In addition, we assessed the occurrence of a test via procedure codes for TST and IGRA tests; however, if reimbursement was not tied to appropriate coding of these tests, undercoding might have occurred. Also, among those who filled a prescription for one of the LTBI treatment regimens, a low proportion had an LTBI diagnosis code recorded. It is unclear whether this is because our treatment-defined cohorts include people without LTBI or a diagnosis of LTBI is not consistently captured by providers. Importantly, a recent systematic review reported that in high-income countries like the United States, only 64% of individuals diagnosed with LTBI initiate treatment; thus, our cohorts probably underrepresent the true prevalence of LTBI in the study population.[17] In addition, claims data capture whether a prescription was filled and do not guarantee that the patient actually initiated treatment. Furthermore, the time between test or diagnosis and the filling of a prescription is dependent upon both clinician and patient behaviors, which make these findings more difficult to interpret. Although our analysis attempted to examine race and ethnicity, the high level of missing race and ethnicity data in Sentinel, and medical and prescription claims data in general, complicated our ability to fully describe the demographics of persons who filled prescriptions consistent with LTBI treatment. LTBI treatment guidance since 2000

has changed, with progressively more emphasis on the use of short-course LTBI therapy. Although our analysis encompasses the timeframe and regimen changes, a more detailed temporal analysis would be beneficial and should be considered for future studies. Finally, because the study population is limited to those federally and privately insured, we do not expect our findings will be generalizable to all patients with LTBI, but rather represent a subset of this population; many LTBI patients are diagnosed and treated in public health clinics or community health clinics and might not have health insurance.[19]

Because of these limitations, Sentinel cannot presently serve as a source of data for general, population-level LTBI surveillance in the United States. Nonetheless, these administrative claims data hold promise as a complementary source of data for other LTBI-related public health surveillance activities and could be useful to address other important public health questions. For example, these data could be used to identify severe adverse events (e.g., liver toxicity, systemic drug reactions, hypotension) among patients receiving treatment for LTBI and to examine demographic and medical characteristics that might be associated with these events. These data could also be valuable to assess trends in LTBI treatment prescribing practices by following the proportions of patients receiving certain treatment regimens over time and by geographic region. Additionally, these data can be used to characterize the prevalence of concomitant use of rifamycin-based regimens with other medications that might increase the risk for drug-drug interactions (e.g., warfarin, oral contraceptives, antiretroviral therapies). In future studies, validation of our treatment-based LTBI identification through patient chart reviews could be conducted to improve confidence in the accuracy of identifying LTBI cohorts with this approach.

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Table 1

Characteristics of persons who filled prescriptions consistent with treatment of LTBI, United States, 2008–2019

Characteristic	Isoniazid-only (*n* = 90,377) *n* (%)	Rifampin-only* (*n* = 21,235) *n* (%)	Isoniazid + rifapentine (*n* = 1,726) *n* (%)	Total† (*N* = 1 13,338) *N* (%)
Age, years				
<5	967 (1)	190 (1)	__‡	__‡
5–14	3,772 (4)	453 (2)	__‡	__‡
15–24	9,430 (10)	1,136 (5)	175 (10)	10,741 (10)
25–44	22,464 (25)	3,846 (18)	489 (28)	26,799 (24)
45–64	27,524 (31)	6,506 (31)	546 (32)	34,576 (31)
≥65	26,220 (29)	9,104 (43)	487 (28)	35,811 (32)
Sex				
Female	47,374 (52)	11,744 (55)	858 (50)	59,976 (53)
Male	43,003 (48)	9,491 (45)	868 (50)	53,362 (47)
Race/ethnicity				
American Indian or Alaska Native	702 (1)	148 (1)	57 (3)	907 (1)
Asian	16,515 (18)	2,355 (1 1)	264 (15)	19,134 (17)
Black or African American	11,476 (13)	1,768 (8)	244 (14)	13,488 (12)
Native Hawaiian or Other Pacific Islander	1,079 (1)	91 (0)	25 (1)	1,195 (1)
White	24,008 (27)	8,588 (40)	571 (33)	33,167 (29)
Unknown race	36,597 (41)	8,285 (39)	565 (33)	45,447 (40)
Hispanic	11,536 (13)	1,209 (6)	181 (11)	12,926 (11)
Non-Hispanic	32,943 (37)	10,043 (47)	597 (35)	43,583 (39)
Unknown ethnicity	45,898 (51)	9,983 (47)	948 (55)	56,829 (50)
Region§				
Northeast	12,948 (14)	3,275 (15)	133 (8)	16,356 (14)
Midwest	9,955 (11)	3,213 (15)	203 (12)	13,371 (12)
South	22,163 (25)	7,078 (33)	409 (24)	29,650 (26)
West	45,094 (50)	7,587 (36)	978 (57)	53,659 (47)
Other	60 (0)	25 (0)	__‡	__‡

Characteristic	Isoniazid-only (*n* = 90,377) *n* (%)	Rifampin-only* (*n* = 21,235) *n* (%)	Isoniazid + rifapentine (*n* = 1,726) *n* (%)	Total† (*N* = 1 13,338) *N* (%)
Invalid or missing	157 (0)	57 (0)	_‡	_‡

*Rifampin cohort is among those meeting 20-day minimum supply and has certain exclusions (see Appendix D of the full report for specific codes; https://www.sentinelinitiative.org/sites/default/files/Methods/Report_cder_mpl1p_wp039.pdf).

†The same patient might appear in more than one treatment cohort if the patient switches treatment regimens and also meets the incidence criteria of having filled no other prescription for a regimen used to treat LTBI in the prior 365 days.

‡Cell counts are too small to report.

§US Census Bureau Regions: Northeast Region includes Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; Midwest Region includes Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; South Region includes Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia; West Region includes Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming; Other includes American Samoa, Guam, Republic of the Marshall Islands, Federated States of Micronesia, Commonwealth of the Northern Mariana Islands, Republic of Palau, Puerto Rico, and US Virgin Islands.

LTBI = latent TB infection.

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Table 2

Diagnoses, risk factors, and diagnostic evaluations for persons who filled prescriptions consistent with treatment of LTBI, United States, 2008–2019

	Isoniazid-only (*n* = 90,377) *n* (%)	**Rifampin-only[*] (*n* = 21,235) *n* (%)**	**Isoniazid + rifapentine *n* = 1,726) *n* (%)**	**Total[†] (*N* = 113,338) *N* (%)**
Diagnoses of LTBI and selected risk factors for progression to TB disease				
HIV test				
0–365 days before prescription filled	14,160 (16)	3,025 (14)	360 (21)	17,545 (15)
1–365 days after prescription filled	9,254 (10)	1,733 (8)	138 (8)	11,125 (10)
HIV diagnosis				
0–365 days before prescription filled	3,380 (4)	212 (1)	21 (1)	3,613 (3)
1–365 days after prescription filled	3,398 (4)	213 (1)	21 (1)	3,632 (3)
Diabetes				
0–365 days before prescription filled	21,972 (24)	4,869 (23)	386 (22)	27,227 (24)
1–365 days after prescription filled	22,265 (25)	4,964 (23)	387 (22)	27,616 (24)
Tumor necrosis factor-α inhibitor use				
0–365 days before prescription filled	2,778 (3)	516(2)	60 (4)	3,354 (3)
1–365 days after prescription filled	4,423 (5)	677 (3)	105 (6)	5,205 (5)
Diagnostic evaluation during 365 days before prescription filled				
Encounter screening for LTBI	24,681 (27)	3,606 (17)	585 (34)	28,872 (26)
TST	62,919 (70)	9,754 (46)	1,428 (83)	74,101 (65)
IGRA test	30,042 (33)	5,786 (27)	791 (46)	36,619 (32)
Patients with either TST or IGRA	71,207 (79)	11,496 (54)	1,574(91)	84,277 (74)
Patients with both TST and IGRA	21,754 (24)	4,044 (19)	645 (37)	26,443 (23)
Patients with neither TST nor IGRA	19,170 (21)	9,739 (46)	152 (9)	29,061 (26)
CXR	75,793 (84)	13,722 (65)	1,411 (82)	90,926 (80)
Thoracic CT scan	14,923 (17)	6,159 (29)	167 (10)	21,249 (19)
CXR or thoracic CT scan	77,174 (85)	14,535 (68)	1,434 (83)	93,143 (82)
Sputum culture	7,564 (8)	4,989 (24)	82 (5)	12,635 (11)
Sputum smear microscopy	150 (0)	70 (0)	__≠	__≠
TB testing in relation to LTBI treatment initiation				
Any testing (−365 to −1 days before prescription filled)	81,502 (90)	16,062 (76)	1,615 (94)	99,179 (88)

	Isoniazid-only (*n* = 90,377) *n* (%)	Rifampin-only* (*n* = 21,235) *n* (%)	Isoniazid + rifapentine *n* = 1,726) *n* (%)	Total† (*N* = 113,338) *N* (%)
Any testing (0 to 365 days after prescription filled)	66,588 (74)	14,570 (69)	1,243 (72)	82,401 (73)

*Rifampin cohort is among those meeting 20-day minimum supply and has certain exclusions (see Appendix D of the full report for specific codes; https://www.sentinelinitiative.org/sites/default/files/Methods/Report_cder_mpl1p_wp039.pdf).

†The same patient might appear in more than one treatment cohort if the patient switches treatment regimens and also meets the incidence criteria of having filled no other prescription for a regimen used to treat LTBI in the previous 365 days.

‡Cell counts are too small to report.

LTBI = latent TB infection; TST = tuberculin skin test; IGRA = interferon-gamma release assay; CXR = chest X-ray; CT = computed tomography.

Table 3

Characteristics of treatment regimens consistent with treatment of LTBI, United States, 2008–2019

Characteristic	Isoniazid-only* (*n* = 90,377)	Rifampin-only*† (*n* = 21,235)	Isoniazid + rifapentine* (*n* = 1,726)
Days supplied per patient, mean‡	93.1	41.6	67.7
Dispensings per patient, mean§	2.1	1.4	1.0
Days supplied per dispensing, mean¶	44.4	29.1	67.7
Treatment episode length, days# Minimum	1	1	1
Q1	30	2	35
Median	60	30	84
Q3	100	60	84
Maximum	2,234	2,600	196

*The same patient might appear in more than one treatment cohort if the patient switches treatment regimens and also meets the incidence criteria of having filled no other prescription for a regimen used to treat latent tuberculosis infection in the prior 365 days.

†Rifampin cohort is among those meeting 20-day minimum supply and has certain exclusions (see Appendix D of the full report for specific codes; https://www.sentinelinitiative.org/sites/default/files/Methods/Report_cder_mpl1p_wp039.pdf).

‡Number of days supplied for all dispensings in qualifying treatment episodes. Expected days supplied for isoniazid-only was 180–270 daily doses, rifampin-only 120 daily doses with a 20-day minimum for inclusion, and isoniazid + rifapentine 84 days (12 doses at a 7-day dosing interval).

§Number of consecutive dispensings (i.e., without a gap in refills).

¶Number of doses of medication supplied in a single dispensing.

#Based on number of days ofmedication supplied per dispensing and the number of consecutive dispensingswithout a gap.

LTBI = latent TB infection.