Notes from the Field

Supply Interruptions of First- and Second-Line Oral Drugs to Treat Tuberculosis During the Previous 12 Months — California, January–March, 2023

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Tuberculosis (TB) drug supply disruptions are a recurring concern in the United States (*1*). Contributors to these disruptions include loss of manufacturers to the U.S. market, inefficient supply chains, and lack of active ingredients available for import.* The last severe U.S. TB drug shortage occurred in 2012, when isoniazid (INH) was temporarily unavailable for several months (*2*). INH and rifampin (RIF) are the cornerstones for treatment of drug-susceptible TB, and rifapentine (RPT), a long acting rifamycin, has been incorporated into shorter first-line regimens† to treat both latent TB infection (LTBI) (*3*) and TB disease§ (*4*). In recent years, the U.S. supply of several TB drugs has again been disrupted. The Food and Drug Administration has declared shortages of RPT (on March 25, 2020), RIF (on December 22, 2021), and INH (on May 17, 2023).¶ Approximately one fifth of all U.S. TB cases are reported from California (*5*). TB drug procurement is decentralized among the state's 61 local TB programs,** mirroring the decentralization among U.S. states and territories. The California Department of Public Health and the California TB Controllers Association assessed the impact of the shortage on California's TB programs.

Investigation and Outcomes

A web-based Research Electronic Data Capture (REDCap) survey (version 13.1.30; Vanderbilt University) was distributed to TB controllers and program managers of all 61 California TB programs†† to assess delays in availability§§ and unavailability of oral first- and second-line TB drugs during the preceding 12 months. On a priority scale of 1 (lowest) to 10 (highest), programs ranked the importance of addressing TB drug instability relative to other TB control priorities. Respondents were encouraged to confer with program, clinic, and pharmacy colleagues to obtain a single, comprehensive response for the TB program in each local health jurisdiction. Programs were categorized according to their average annual number of TB cases during 2016–2021 as high (15 or more cases) or low (fewer than 15 cases). This activity was reviewed by CDC and the California Department of Public Health, deemed not research, and conducted consistent with CDC policy.¶¶

Overall, 54 (89%) programs responded, including all categorized as high case-count programs. The mean priority level assigned to ensuring a stable supply of TB drugs was 8.6 (95% CI = 8.1–9.2) among all programs and 9.4 (95% CI = 8.8–9.9) among high case-count programs. Among the 50 programs in California reporting at least one TB case during 2016–2021, 32 (64%) experienced a delay in availability or unavailability of any oral first-line TB drug (Table). First-line oral TB drug supply interruptions led to delayed initiations or temporary pauses in treatment of TB disease or LTBI (37% for all programs and 55% for high case-count programs) and permanent changes in the choice of drugs to treat TB disease or LTBI and the duration of treatment (33% for all programs and 65% for high case-count programs). TB drug supply interruptions led to a negative patient outcome for 6% of all TB programs: two TB programs reported at least one case of prolonged treatment and a third program reported at least one adverse drug event.

Conclusions and Actions

Ensuring drug availability is a high priority for TB programs. This survey in California identified a high frequency of TB drug interruptions in 2022, which led to delayed treatment initiations and permanent regimen changes and restricted implementation of short-course regimens for both LTBI and TB disease. Programs also reported preventable negative patient outcomes

* https://www.hsgac.senate.gov/wp-content/uploads/2023-06-06-HSGAC-Majority-Draft-Drug-Shortages-Report.-FINAL-CORRECTED.pdf

† Oral first-line TB drugs include RIF, RPT, INH, rifabutin, pyrazinamide, and ethambutol. Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

§ These short course regimens include a 3-month regimen of weekly INH and RPT for LTBI treatment (3HP) and a 4-month regimen of INH, RPT, moxifloxacin, and pyrazinamide for drug-sensitive TB disease (4HPMZ).

¶ https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm (Accessed August 30, 2023).

** The 61 local TB programs in California have diverse infrastructures and TB incidences (average annual TB case counts during 2016–2021 ranged from zero to 508 cases).

†† The survey was available for completion from January 29 to March 17, 2023.

§§ TB drug delays were defined as short-lived interruptions in acquiring a drug, lasting a few weeks or less, and not broadly affecting programmatic or clinical practice. TB drug unavailability was defined as an interruption in the supply of a drug lasting more than a few weeks and potentially requiring a change in programmatic or clinical practice.

¶¶ 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

TABLE. Frequency and effects of the unavailability of oral first- and second-line tuberculosis drugs during the previous 12 months — California, January–March 2023

Effects on program	no./No. (%)	
	High case-count programs*	All programs
Delay†		
Rifampin	15/20 (75.0)	**25/50 (50.0)**
Rifapentine	16/20 (80.0)	**25/50 (50.0)**
Rifabutin	1/20 (5.0)	**5/50 (10.0)**
Isoniazid	5/20 (25.0)	**8/50 (16.0)**
Pyrazinamide	5/20 (25.0)	**8/50 (16.0)**
Ethambutol	3/20 (15.0)	**3/50 (5.0)**
Any second-line TB drug§	5/20 (25.0)	**8/50 (16.0)**
Unavailability†		
Rifampin	6/20 (30.0)	**11/50 (22.0)**
Rifapentine	14/20 (70.0)	**20/50 (40.0)**
Rifabutin	0/20 (—)	**2/50 (4.0)**
Isoniazid	4/20 (20.0)	**4/50 (8.0)**
Pyrazinamide	0/20 (—)	**2/50 (4.0)**
Ethambutol	3/20 (14.0)	**2/50 (4.0)**
Any second-line TB drug§	1/20 (5.0)	**2/50 (4.0)**
Delayed initiation or paused treatment	11/20 (55.0)	**20/54 (37.0)**
TB disease only	2/11 (18.2)	**5/20 (25.0)**
LTBI only	8/11 (72.7)	**11/20 (55.0)**
Both TB disease and LTBI	1/11 (9.1)	**4/20 (20.0)**
Permanently changed regimen	13/20 (65.0)	**18/54 (33.3)**
TB disease only	2/13 (15.4)	**2/18 (11.1)**
LTBI only	11/13 (84.6)	**15/18 (83.3)**
Both TB disease and LTBI	0/13 (—)	**1/18 (5.6)**
Recorded a negative patient outcome¶	2/20 (10.0)	**3/54 (5.6)**
Not using 3HP due to rifapentine unavailability**	11/12 (91.7)	**13/24 (54.2)**
Not using 4HPMZ due to rifapentine unavailability**	5/13 (38.5)	**5/31 (16.1)**

Abbreviations: LTBI = latent tuberculosis infection; TB = tuberculosis; 3HP = 3-month regimen of weekly isoniazid and rifapentine for LTBI treatment; 4HPMZ = 4-month regimen of isoniazid, rifapentine, moxifloxacin, and pyrazinamide for drug-sensitive TB disease.

* High case-count programs are those reporting 15 or more TB cases during 2016–2021.

† Denominator includes only those programs reporting one or more TB case during 2016–2021.

§ Oral second-line TB drugs included cycloserine, ethionamide, levofloxacin, linezolid, moxifloxacin, para-aminosalicylate, and pretomanid. Bedaquiline and clofazimine were not included in this survey because they have unique procurement processes.

¶ One program recorded a negative patient outcome for LTBI only, and two reported negative patient outcomes for both TB disease and LTBI (two programs reported at least one case with prolonged treatment and one program reported at least one adverse drug event).

** Denominator restricted to programs not using the stated regimen.

caused by drug delays or unavailability. Limitations of this analysis included a retrospective study design, possibility of recall bias, and variability in respondents' interpretation of the definitions of access delays and unavailability of TB drugs. To meet the standards of practice for TB disease and LTBI, and to continue progress toward TB elimination, California has established a centralized buffer supply of several TB drugs. Securing a more stable TB drug supply might avert some of the unfavorable clinical and programmatic effects of TB treatment interruptions.

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References

1. CDC. Interruptions in supplies of second-line antituberculosis drugs—United States, 2005–2012. MMWR Morb Mortal Wkly Rep 2013;62:23–6. PMID:23325352
2. CDC. Impact of a shortage of first-line antituberculosis medication on tuberculosis control—United States, 2012–2013. MMWR Morb Mortal Wkly Rep 2013;62:398–400. PMID:23698604
3. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep 2020;69(No. RR-1):1–11. PMID:32053584 https://doi.org/10.15585/mmwr.rr6901a1
4. Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim guidance: 4-month rifapentine moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis—United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:285–9. PMID:35202353 https://doi.org/10.15585/mmwr.mm7108a1
5. Schildknecht KR, Pratt RH, Feng PI, Price SF, Self JL. Tuberculosis—United States, 2022. MMWR Morb Mortal Wkly Rep 2023;72:297–303. PMID:36952282 https://doi.org/10.15585/mmwr.mm7212a1