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# Estimated Population-Level Impact of Using a Six-Week Regimen of Daily Rifapentine to Treat Latent Tuberculosis Infection in the United States

**Sourya Shrestha, Ph.D.**[*,‡],
Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland

**Andrea Parriott, Ph.D.**[*],
University of California San Francisco San Francisco, California

**Nicolas A. Menzies, Ph.D.**,
Harvard T.H. Chan School of Public Health Boston, Massachusetts

**Priya B. Shete, M.D.**,
University of California San Francisco San Francisco, California

**Andrew N. Hill, M.Sc., Ph.D.**,
Centers for Disease Control and Prevention Atlanta, Georgia

**Suzanne M. Marks, M.P.H., M.A.**,
Centers for Disease Control and Prevention Atlanta, Georgia

**David W. Dowdy, M.D., Ph.D.**
Johns Hopkins Bloomberg School of Public Health Baltimore, Maryland

To the Editor:

The Centers for Disease Control and Prevention attributes only 13% of incident tuberculosis (TB) disease in the United States to recent (≤2 yr) transmission; nearly all of the remaining incident cases of TB disease are believed to occur via reactivation of latent TB infection (LTBI) acquired by individuals earlier in their lives (1). It is estimated that up to 13 million people would test positive on the tuberculin skin test, and 9 (6–15) million people have untreated LTBI in the United States (2, 3). As such, treatment of LTBI is central to the current U.S. TB elimination strategy (4). Treatment regimens such as 3 months of isoniazid and rifapentine (3HP), 4 months of rifampin (4R), and 6–9 months of isoniazid are efficacious in preventing TB disease (5–8), but effectiveness of any LTBI regimen in general populations may be limited by suboptimal levels of treatment initiation and completion (8, 9) and by discontinuation because of adverse effects (AEs) (7, 9). Novel regimens with shorter duration of therapy, such as 6 weeks of daily 600-mg doses of rifapentine (6wP), which is currently being evaluated in a phase III clinical trial, may have important benefits,

[‡]Corresponding author (sourya@jhu.edu).
[*]These authors equally contributed to this work.

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particularly if determined to be noninferior to 3HP and 9 months of isoniazid with lower discontinuation rates (10).

We evaluated the epidemiological impact of implementing 6wP as a replacement for currently used regimens to treat LTBI in the United States using six models of TB transmission and epidemiology (11–13) as a part of the Centers for Disease Control and Prevention's National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Epidemiologic and Economic Modeling Agreement (http://www.cdc.gov/nchhstp/neema/index.html). These models included Harvard University model for the United State (HVD-US) (11), University of California, San Francisco model of California (UCSF-CA) (12), and Johns Hopkins School of Public Health models for California (JHSPH-CA), Florida (JHSPH-FL), New York (JHSPH-NY), and Texas (JHSPH-TX) (13). We projected the number of TB cases that would occur during the 16-year period from 2020 to 2035 under the assumption that 6wP is used to treat LTBI compared with an assumed standard-of-care baseline, with 72% initiation, 78% completion, and 93% efficacy rates (Table 1).

We evaluated the models under scenarios representing different efficacy rates of 6wP, discontinuation rates of 6wP because of AEs, and discontinuation rates of 6wP because of other causes (e.g., nonadherence). Because data on the rates of efficacy and discontinuation of 6wP are not currently available, we generated potential ranges for these parameters based on corresponding data from other LTBI regimens (4, 6, 14). With shorter treatment length and expectations of lower AE risk, 6wP could result in higher treatment initiation and increased population coverage (i.e., percentage of population with LTBI receiving treatment). We therefore also considered additional scenarios with higher initiation rates and increased population coverage using 6wP. Modeled scenarios, including rates of efficacy, initiation, and discontinuation, are detailed in Table 1.

Under the baseline (Scenario A, Table 1), all models projected declines in TB incidence rates, with some flattening in this decline over time. The projected annual percentage declines, averaged across the models, were 3.0% between 2015 and 2020 and 2.6% between 2020 and 2035 (Figure 1A). Substituting 6wP for existing regimens without increasing initiation rates or population coverage (Scenarios B–G, Table 1) was projected to have relatively little impact on further reducing TB incidence, with the total number of cases between 2020 and 2035, on average, within 3% of the baseline (Figure 1B). By contrast, 6wP scenarios that assumed an increase in initiation, treatment completion, and population coverage as well as more favorable AE profile resulted in appreciable population-level impact. Assuming 92.5% initiation and 95% completion (Scenario H, High Initiation and Completion), we projected an average reduction of 4.8% in cumulative incidence of TB. In addition, increasing population coverage 3.5-fold over baseline (Scenario I, Increased LTBI Screening) resulted in an average reduction of 26.7% in the number of TB cases, which was equivalent to 33,357 TB cases averted between 2020 and 2035 in the United States (HVD-US), 7,846 (JHSPH-CA) cases in California, 2,025 in Florida (JHSPH-FL), 1,830 in New York (JHSPH-NY), and 3,914 in Texas (JHSPH-TX).

The individual models used for this analysis differed in conceptualization and primary aim, in modeled jurisdictions, and in assumptions about TB epidemiology (15). Nevertheless,

their projections all agreed on the magnitude of the relative impact of 6wP under various scenarios. The models also consistently indicated the value of increases in population coverage, treatment initiation, and treatment completion over baseline testing and treatment to maximize epidemiological impact. Some results, particularly long-term baseline projections, are likely to be sensitive to modeling assumptions about future immigration patterns, LTBI prevalence, and the effect of preventive therapy on LTBI. Importantly, this analysis takes a population-level perspective of the impact of 6wP on progress toward TB elimination. If 6wP has a more favorable safety profile than other LTBI treatment options, patients at the individual level will greatly benefit regardless of the magnitude of projected population-level effects.

In summary, these modeling results suggest that replacing current LTBI regimens with a shorter regimen such as 6wP can substantially reduce TB incidence if doing so enables TB programs to achieve greater population coverage, higher treatment initiation, and better completion. However, without these improvements, the population-level impact of 6wP may be muted. This underscores the need to develop effective implementation strategies for 6wP (or any novel LTBI treatment regimen) that can increase population coverage and uptake and reduce discontinuation. With generically produced rifapentine available internationally and likely to enter the U.S market soon, drug costs for the daily 6wP regimen might be within $10 of those for weekly 3HP (16). Furthermore, individuals might benefit from 6wP use because of greater uptake, a halved regimen duration, and the potential for fewer AEs. These benefits might result in lower societal costs for 6wP compared with those for other regimens. However, we caution that these analyses should not be considered a substitute for ongoing clinical trials of 6wP (and in fact depend on those data showing noninferiority) (10). While awaiting specific trial results, this analysis can be helpful to both clinicians and public health officials in developing implementation strategies to optimize the potential impact of 6wP and other short course regimens in the future.

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## References

1. Centers for Disease Control and Prevention (CDC). Reported tuberculosis in the United States, 2018. Atlanta, GA: US Department of Health and Human Services, CDC; 2019 [accessed 2020 Jan 29]. Available from: https://www.cdc.gov/tb/statistics/reports/2018/Exec_Commentary.html.
2. Haddad MB, Raz KM, Lash TL, Hill AN, Kammerer JS, Winston CA, et al. Simple estimates for local prevalence of latent tuberculosis infection, United States, 2011–2015. Emerg Infect Dis 2018;24: 1930–1933. [PubMed: 30226174]
3. Miramontes R, Hill AN, Yelk Woodruff RS, Lambert LA, Navin TR, Castro KG, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. PLoS One 2015; 10:e0140881. [PubMed: 26536035]

4. Centers for Disease Control and Prevention (CDC). Division of tuberculosis elimination strategic plan 2016–2020. Atlanta, GA: CDC; 2018 [accessed 2020 Jan 29]. Available from: https://www.cdc.gov/tb/about/strategicplan.htm.

5. Ferebee SH. Controlled chemoprophylaxis trial in tuberculosis: a general review. Adv Tuberc Res 1970;17:28–106.

6. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. Bull World Health Organ 1982;60:555–564. [PubMed: 6754120]

7. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al.; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365:2155–2166. [PubMed: 22150035]

8. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, 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: 1–11.

9. Horsburgh CR Jr, Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al.; Tuberculosis Epidemiologic Studies Consortium. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest 2010;137:401–409. [PubMed: 19793865]

10. NIH. Assessment of the safety, tolerability, and effectiveness of rifapentine given daily for LTBI (ASTERoiD). Bethesda, MD: NIH–National Library of Medicine; 2018 [accessed 2020 Jan 29]. Available from: https://clinicaltrials.gov/ct2/show/NCT03474029?term=ASTERoiD&cond=Latent1Tuberculosis&draw=2&rank=1.

11. Menzies NA, Cohen T, Hill AN, Yaesoubi R, Galer K, Wolf E, et al. Prospects for tuberculosis elimination in the United States: results of a transmission dynamic model. Am J Epidemiol 2018;187:2011–2020. [PubMed: 29762657]

12. Goodell AJ, Shete PB, Vreman R, McCabe D, Porco TC, Barry PM, et al. Outlook for tuberculosis elimination in California: an individual-based stochastic model. PLoS One 2019;14:e0214532. [PubMed: 30964878]

13. Shrestha S, Cherng S, Hill AN, Reynolds S, Flood J, Barry PM, et al. Impact and effectiveness of state-level tuberculosis interventions in California, Florida, New York, and Texas: a model-based analysis. Am J Epidemiol 2019;188:1733–1741. [PubMed: 31251797]

14. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med 2018;379:440–453. [PubMed: 30067931]

15. Menzies NA, Parriott A, Shrestha S, Dowdy DW, Cohen T, Salomon JA, et al. Comparative modeling of tuberculosis epidemiology and policy outcomes in California. Am J Respir Crit Care Med 2020;201:356–365. [PubMed: 31626560]

16. Shepardson D, Marks SM, Chesson H, Kerrigan A, Holland DP, Scott N, et al. Cost-effectiveness of a 12-dose regimen for treating latent tuberculous infection in the United States. Int J Tuberc Lung Dis 2013;17:1531–1537. [PubMed: 24200264]

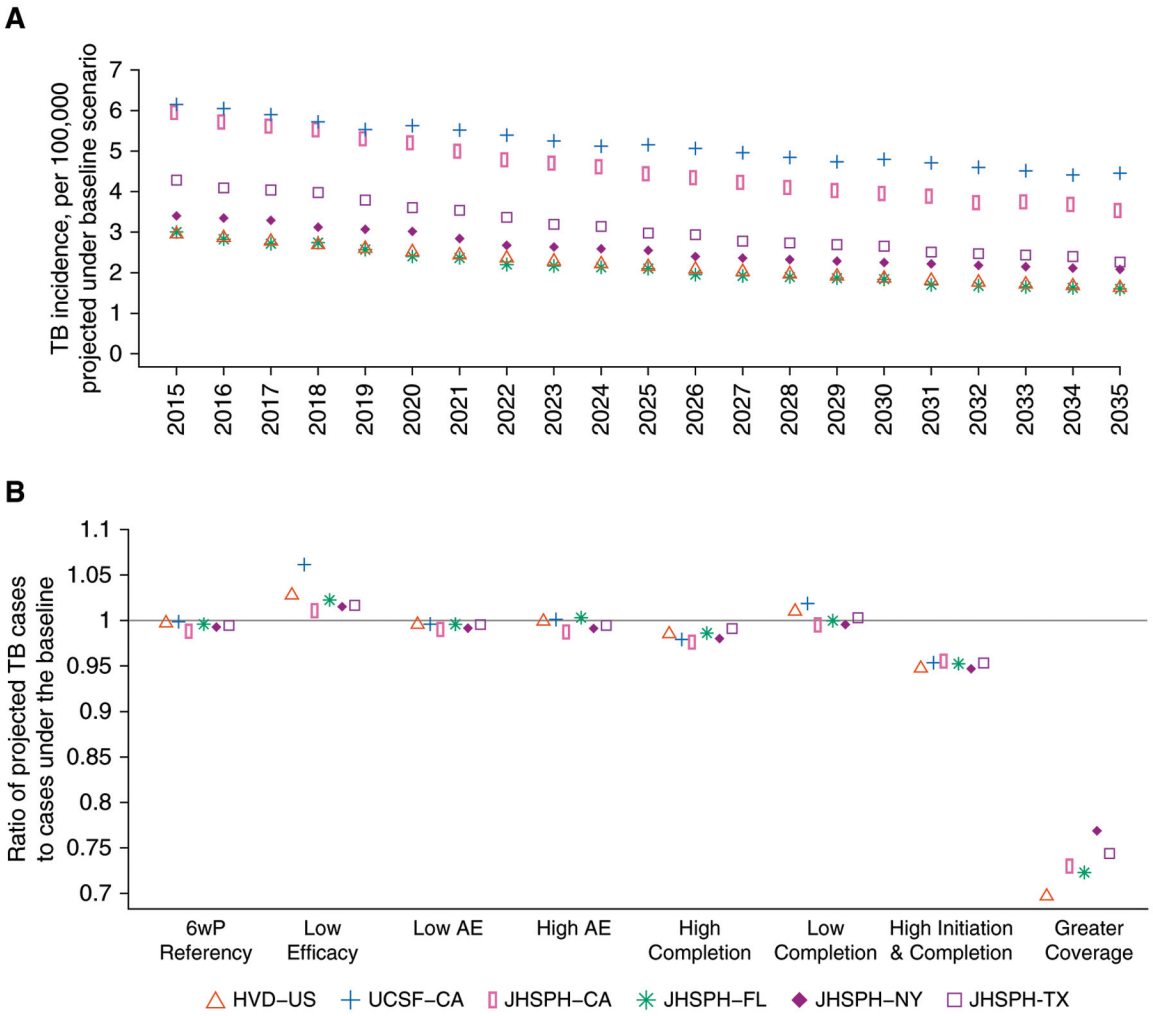


**Figure 1.**

Projected population-level impact of a 6-week daily regimen of rifapentine to treat latent tuberculosis (TB) infection in the United States. (*A*) Point estimates of TB incidence per 100,000 between 2015 and 2035, projected across various jurisdictions in the United States using six different models under the baseline scenario (Scenario A, Table 1). This scenario assumed continuation of standard of care. (*B*) Point estimates of the total number of projected TB cases between 2020 and 2035, as a proportion of the number of projected cases assuming use of existing regimens, for the eight scenarios (Scenario B–I) described in Table 1. UCSF-CA model projections were not available for Scenario I. 6wP = 6-week daily regimen of rifapentine; AE = adverse effect; HVD-US = Harvard University Model for United States; JHSPH-CA = Johns Hopkins School of Public Health Model for California; JHSPH-FL = Johns Hopkins School of Public Health Model for Florida; JHSPH-NY = Johns Hopkins School of Public Health Model for New York; JHSPH-TX = Johns Hopkins School of Public Health Model for Texas; UCSF-CA = University of California, San Francisco Model for California.

**Table 1.**

Scenarios used to estimate the impact of a 6wP for treatment of latent tuberculosis infection in the United States

| Scenarios | Efficacy | Initiation Rate | Discontinuation due to AEs | Discontinuation due to Other Reasons | Overall Completion Rate | Population Coverage |
|---|---|---|---|---|---|---|
| (A) Baseline* | 93% | 72% | — | — | 78% | Baseline |
| (B) 6wP reference | 93%† | 72% | 3.6%‡ | 16.4%§ | 80% | Baseline |
| (C) Low efficacy | 69%† | 72% | 3.6% | 16.4% | 80% | Baseline |
| (D) Low AE | 93% | 72% | 2.2%‡ | 16.4% | 81.4% | Baseline |
| (E) High AE | 93% | 72% | 4.9%‡ | 16.4% | 78.7% | Baseline |
| (F) High completion | 93% | 72% | 3.6% | 6.4%§ | 90% | Baseline |
| (G) Low completion | 93% | 72% | 3.6% | 26.4%§ | 70% | Baseline |
| (H) High initiation and completion‖ | 93% | 92.5% | — | — | 95% | Baseline |
| (I) Greater population coverage with high initiation and completion¶ | 93% | 92.5% | — | — | 95% | 3.5 × baseline |

*Definition of abbreviations:* 6wP = 6-week daily regimen of rifapentine; AE = adverse effect.

*Baseline scenario modeled an assumed existing standard of care, which consisted of a mixture of three regimens: 4 months of daily rifampin (4R) at 50%, 12 wk of weekly isoniazid and rifapentine (3HP) at 35%, and 9 months of daily isoniazid (9H) at 15%. We assumed completion rates of 79% for 4R (14), 81% for 3HP (7), and 69% for 9H (7), resulting in a weighted average of 78% overall completion rate. Baseline population coverage of latent tuberculosis infection treatment varied between 2% and 3% across the models (11–13).

†Assumptions are based on the noninferior efficacy levels of 6 months of daily isoniazid and 9H (4, 6); low value corresponds to efficacy of 6 months of daily isoniazid, and high value corresponds to efficacy of 9H.

‡Assumptions are based on AE-related discontinuations for 4R and 3HP (6, 14); low value corresponds to 4R, high value corresponds to 3HP, and medium value corresponds to the mean of the two.

§Assumptions are based on 3HP regimen (6); high and low values assume ±10% to the 3HP estimate.

‖Represents hypothetical scenario with higher initiation and completion rates.

¶Represents increased latent tuberculosis infection screening, by 3.5-times the baseline, in addition to high initiation and completion rates (Scenario H).

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