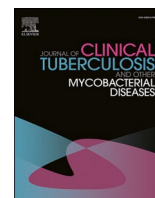




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Cost effectiveness of three months of rifapentine and isoniazid for latent tuberculosis in Syrian refugees

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ABSTRACT

Background: Latent Tuberculosis infection (LTBI) has a large global burden especially among refugees. We aimed to test the cost effectiveness of weekly rifapentine plus isoniazid for 3 months (3HP) versus nine months of daily isoniazid (INH-9) to treat LTBI in Syrian refugees residing in Turkey.

Methods: We used a Markov state transition model to estimate the incremental cost-effectiveness of 3HP relative to INH-9 using a simulated cohort of Syrian refugees. Both cost and effectiveness were assessed assuming that LTBI screening would be performed, with treatment of those who screen positive. Costs were measured in 2017 US dollars, and effectiveness was estimated as quality adjusted life years (QALYs) gained. An annual discount rate of 3% was applied to future costs and QALYs over the analytical time horizon of 20 years.

Results: Per 100 individuals screened at age 30 in the base case scenario, treating LTBI with 3HP rather than INH-9 resulted in a gain of 0.08 QALYs (95% uncertainty interval: -0.007, 0.221) and savings of \$1421 (\$483, \$3478). Assuming a value of \$100000 per QALY, the incremental net monetary benefit of 3HP was \$9772 (\$639, \$24517). Findings were robust to sensitivity analyses except when treating older individuals.

Conclusions: 3HP is likely to save costs and improve health compared to INH-9 when used for LTBI treatment among Syrian refugees in Turkey.

1. Introduction:

Tuberculosis (TB) remains the single most important infectious cause of death in the world causing 1.4 million deaths in 2019 [1]. Latent Tuberculosis infection (LTBI) serves as a large reservoir for tuberculosis with an estimated global burden of 1.7 billion individuals [2]. Turkey's share of that burden has increased since the start of the Syrian Civil War in 2011. As of May 2020, Turkey hosts more than 3.5 million Syrian refugees [3] who have a higher prevalence of TB and LTBI compared to the local population [4,5]. Historically, latent tuberculosis was treated with isoniazid-based regimens that had higher rates of toxicity and long duration of treatment, which limited adherence [6]. Refugee populations tend to move frequently back and forth between their home and host countries depending on conflict situations, which may additionally reduce adherence. Recently, shorter regimens with weekly or daily dosing proved at least as safe and as effective compared to the traditional 9 months of isoniazid (INH-9) for LTBI treatment [7,8]. These regimens included rifapentine in combination with isoniazid either daily for a month or weekly for three months. The price point for rifapentine

dropped in 2019 from \$45 to \$15[9]. In this analysis, we aimed to evaluate the cost-effectiveness of weekly rifapentine and isoniazid for three months (3HP) compared to INH-9 to treat LTBI in Syrian refugees residing in Turkey.

2. Methods

We used a decision tree followed by a Markov state transition model to estimate the incremental cost-effectiveness of 3HP relative to INH-9 using a hypothetical cohort of Syrian refugees (50% men and 50% women). The estimated age-specific burden of LTBI in the population of Syrian refugees was calculated based on an assumption of constant annual risk of infection, assuming a median age of 30 (The median age of TB patients in Syria) and a prevalence at age 30 of 16.3% based on LTBI prevalence in the Eastern Mediterranean Region [2].

Fig. 1 shows the model structure and transition states. All individuals in the cohort underwent testing for LTBI by Tuberculin Skin Test (TST) which has an estimated sensitivity of 71% and specificity of 89% [10]. Individuals who test positive for LTBI (whether truly or falsely) are

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treated with 3HP in one scenario and with INH-9 in the alternate scenario. These two populations were further divided based on treatment completion, which was also estimated from published literature [11].

After undergoing LTBI testing and treatment (if eligible), individual trajectories were simulated using a Markov model with four transition states: LTBI, active TB, cure (of active TB) and death (due to TB or other causes). Annual probability of death in the absence of active TB was based on World Health Organization (WHO) age- and sex-specific life tables for the Syrian Arab Republic [12]. Annual transition probabilities from LTBI to active TB were derived from a randomized clinical trial in a population with low HIV prevalence [7]. Annual transition probabilities from active TB to cure and death were based on published literature [13]. Individuals with false-positive test results were assumed to have no risk of reactivation to active TB. Reinfection with TB after the testing and treatment period was assumed to occur equally in all arms and was thus not explicitly modeled.

We assumed that, in the absence of reactivation to active TB, individuals with LTBI have the same age-specific annual probability of death as the general population. We assumed the cost of LTBI treatment to include an initial outpatient visit for consultation followed by a monthly outpatient visit for follow-up and refill over the duration of treatment. We assumed that LTBI treatment would be delivered by self-administered therapy (SAT) and thus excluded costs of directly-observed therapy (DOT) and used completion rates that reflected SAT [11]. In the base scenario we assumed that the cost of incomplete treatment included the full medication cost but only half the number of outpatient visits, and that partial treatment provided no protection against future reactivation. We also performed sensitivity analyses in which incomplete treatment incurred 25% to 75% of both the cost and number of outpatient visits. We assumed that adverse events in both treatment regimens resulted in similar excess cost and morbidity and thus did not explicitly include incremental adverse events in the model [14]. Finally, we assumed that Syrian refugees residing in Turkey will experience age and gender specific mortality similar to what Syrians experienced in pre-war

Syria and that the war experience or residing in Turkey would not significantly alter those probabilities.

Table 1 shows all model parameters. The cost of the 3HP regimen was based on 36 tablets of isoniazid 300 mg at \$0.02 each plus \$15 for a course (72 tablets 150 mg each) of rifampentine with the added cost of 4 outpatient visits. The cost of INH-9 was based on 270 tablets of isoniazid 300 mg at \$0.02 each with the added cost of 10 outpatient visits [9,15]. To estimate the cost of active TB, we used an estimate of \$218 for drug cost and administration [15] and added a cost of hospitalization assuming that 50% of patients with active TB will be hospitalized with an average 5-day length of stay, based on WHO data for active TB in Turkey [13]. The cost of outpatient visits and hospitalizations was based on WHO data for healthcare delivery in Turkey [16]. All costs were measured in 2017 US Dollars after adjusting for consumer price index [17].

Effectiveness was estimated as the number of quality adjusted life years (QALYs) gained, assuming that utility for the LTBI state was similar to that of the underlying general population (0.9), whereas the utility for active TB was assumed to be 0.76 based on published literature [18]. Based on literature regarding post-TB sequelae, we also assumed a decrement in health utility of 0.053 following successful treatment of active TB [19].

Both cost and effectiveness were discounted by 3% per year based on the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine [20]. The analysis had a horizon of 20 years. The analysis was performed from the perspective of the Turkish healthcare system which allows access to Syrian refugees [21]. Net monetary benefit was calculated based on a value of \$100,000 per QALY.

Our base case was based on a population of Syrian adults 30 years of age based on the median age of TB patients in Syria [13]. In order to determine the parameters that had the most effect on model outputs, we performed a one-way deterministic sensitivity analysis by varying each parameter by +/-50% of the base value, except for the completion rates and utilities where the value was varied by 5% to avoid crossing the

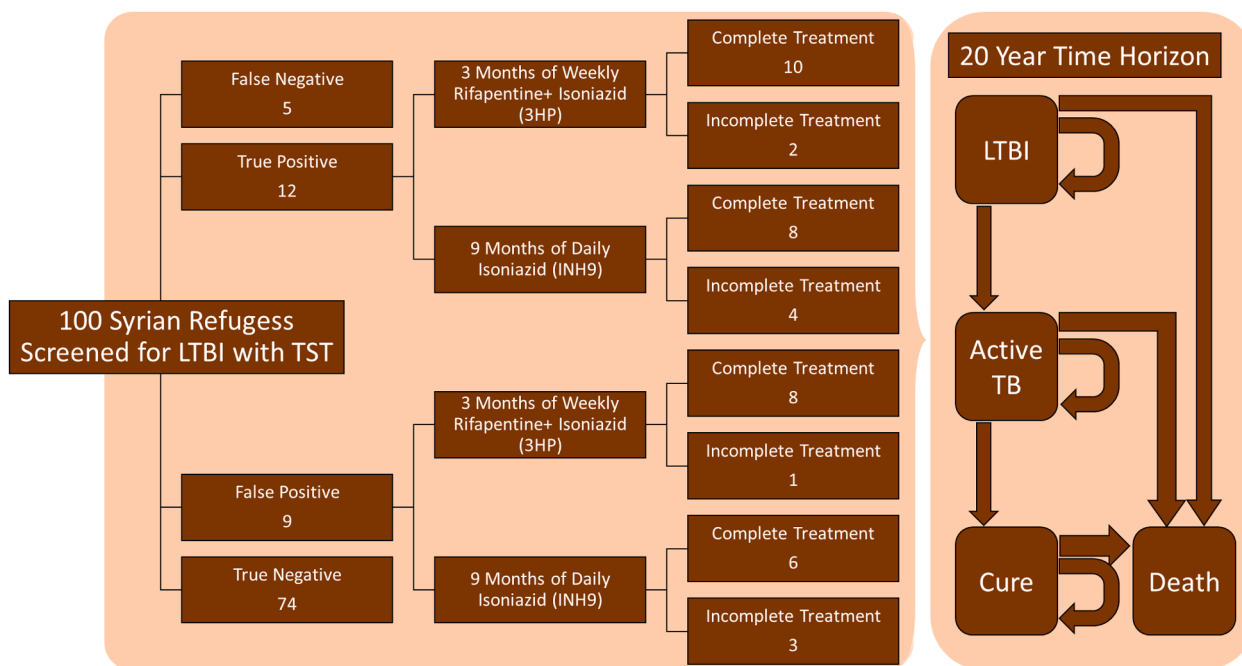


Fig. 1. Model Structure. The model first implements a decision tree among a hypothetical group of 100 Syrian refugees residing in Turkey who are screened for latent tuberculosis infection (LTBI) with the tuberculin skin test (TST). Those who screen positive are treated with 3 months of weekly rifampentine and isoniazid (3HP) in one scenario or with 9 months of daily isoniazid (INH-9) in the alternative scenario. This results in eight subgroups based on regimen and completion of treatment. Numbers in each box represent the number (rounded to the nearest whole number) of people who follow each path. Each subgroup then enters a Markov state transition model with four possible states: latent tuberculosis infection (LTBI), active tuberculosis (TB), cured from active TB (Cure) and death. This Markov process is simulated over a time horizon of 20 years.

Table 1
Model parameters.^{*,†}

Parameter	Base Case	Low Value	High Value	Source (s)
LTBI Prevalence ¹	16.30%	8.15%	24.45%	2
TST Sensitivity	71%	–	–	10
TST Specificity	89%	–	–	10
INH-9 Completion rate	65.90%	62.61%	69.20%	11
3HP Completion rate	81.90%	77.81%	86%	11
Age-specific probability of death	Life Table	–	–	12
LTBI probability of death	Life Table	–	–	12
Transition probability from LTBI to active with incomplete treatment ²	0.26%	0.13%	0.38%	7, [26]
Transition probability from LTBI to active with 3HP	0.06%	0.03%	0.10%	7
Transition probability from LTBI to active with INH-9	0.15%	0.07%	0.22%	7
Transition probability from active TB to death	6.90%	3.45%	10.35%	13
Transition probability from active TB to cure	86.05%	81.74%	90.35%	13
3HP drug cost ³	\$ 15.72	\$ 7.86	\$ 23.58	9
INH-9 drug cost ⁴	\$ 5.40	\$ 2.70	\$ 8.10	15
Outpatient visit cost	\$ 16.25	\$ 8.13	\$ 24.38	16
Cost of active TB regimen and administration	\$ 218	\$ 109	\$ 327	15
%of active TB cases hospitalized	50%	25%	75%	13
Average cost of hospitalization	\$ 664	\$ 332	\$ 996	16
Utility LTBI	0.9	0.855	0.945	18
Utility Cure ⁵	0.85	0.80	0.89	18, 19
Utility Active TB	0.76	0.722	0.798	18
Discount Rate (Cost and outcome)	3%			20

¹ LTBI prevalence was calculated based on age. The annual infection rate was based on a median age of 30 in the base case scenario.

² Transition probability from LTBI to active with incomplete treatment was also based on 0.57 improvement of INH-9 over placebo (26).

³ The total upfront cost per person for 3HP was estimated at \$80.72 for complete treatment and \$48.22 for incomplete treatment assuming total cost of pills and 2 outpatient visits for incomplete treatment compared to 4 visits for complete treatment.

⁴ The total upfront cost per person for INH-9 was estimated at \$167.90 for complete treatment and \$86.65 for incomplete treatment assuming total cost of pills and 5 outpatient visits for incomplete treatment compared to 10 visits for complete treatment.

⁵ Utility of cure was based on an assumed decrement of 0.053 compared to utility of LTBI (19).

^{*} For probabilistic analyses, TST sensitivity and specificity were not varied, age was varied randomly between 18 and 64, cost parameters followed a gamma distribution and the remaining variables followed a beta distribution.

[†] All transition probabilities are on an annual basis.

logical upper bound. We also performed multivariate probabilistic sensitivity analysis (PSA) based on 1000 trials. In each trial, parameters were varied according to an appropriate statistical distribution (Gamma distribution for cost parameters and beta distribution for all other parameters) to account for uncertainty. Age was randomly selected between 18 and 64 at the time of cohort treatment for each trial. The PSA was used to generate a cost effectiveness plane comparing the 2 interventions. We used our PSA to calculate uncertainty ranges at the 2.5th and 97.5th percentile for each reported value. A probabilistic one-way sensitivity analyses (POSA) was then conducted to quantify the effect of each parameter value (in deciles) on net monetary benefit. We also performed deterministic two-way sensitivity analyses to evaluate the effect of varying the two most relevant parameters simultaneously. For this analysis, we selected three scenarios: all other parameters as in the base case, other parameters set to favorable values for 3HP, and other parameters set to unfavorable values for 3HP. All analyses were performed using Microsoft Excel 2019 (Microsoft, Redmond, Washington) software and STATA 16 (StataCorp LLC, College Station, TX).

Institutional review board (IRB) approval was not required according to guidelines from the Johns Hopkins School of Public Health IRB office, as this research did not involve human subjects.

3. Results

In the base case, for every 100 individuals (age 30) tested for LTBI, treating those who test positive with 3HP compared to INH-9 resulted in 0.09 (-0.006, 0.25) fewer active TB cases, 0.003 (-0.002, 0.007) fewer deaths and 0.08 (-0.007, 0.221) QALYs gained (Table 2). We estimated that 3HP resulted in savings of \$1421 (\$482, \$3478) per 100 people tested, compared to INH-9. Assuming a value of \$100,000 per QALY, this translated into a net monetary benefit (NMB) of \$9772 (\$639, \$24516) per 100 people tested for 3HP compared to INH-9.

Two parameters – the cost of outpatient visits and LTBI prevalence – had strongest influence on the estimated cost-effectiveness and cost-benefit of 3HP relative to INH-9 (Fig. 2). For example, increasing the cost of outpatient visit by 50% resulted in a 55% increase in costs saved. In a similar fashion, changing LTBI prevalence by 50% changed NMB by 46% in the same direction. Nevertheless, probabilistic one-way sensitivity analysis illustrated that 3HP was projected to offer net monetary benefit over INH-9 across a wide range of parameter values (Fig. 3). For example, after incorporating a range of reasonable values for LTBI prevalence, only 1% of simulations projected NMB less than \$4,000.

Fig. 4 shows the variation in costs saved and net monetary benefit according to LTBI prevalence and the estimated cost of an outpatient visit. Cost savings and net monetary benefit associated with 3HP increased as LTBI prevalence and cost of outpatient visit increased. In the 3HP-favorable scenario, the effect of changing LTBI prevalence on NMB was more prominent while in the 3HP-unfavorable scenario, the estimated cost of an outpatient visit on NMB was more influential.

In probabilistic uncertainty analysis (Fig. 5), all simulations projected 3HP to be less costly than INH-9. Across all simulations, 93% suggested that 3HP would also be more effective than INH-9 (Fig. 5B), whereas INH-9 was projected to be more effective in 7% (Fig. 5C). In simulations that found INH-9 to be more effective, the age of patients treated (median 59 years) and the assumed effectiveness of INH-9 (median annual risk of reactivation after completing INH-9: 0.07%) was higher than for those simulations in which 3HP was more effective (median 40 years, annual risk of reactivation after INH-9: 0.14%).

4. Discussion

To date, few analyses have estimated the comparative cost-effectiveness of two regimens for LTBI treatment in refugee populations. Our analysis suggests that, following testing with TST, treating Syrian refugees in Turkey with 3HP rather than INH-9 is likely to generate important cost savings (due to fewer outpatient visits) with a corresponding small gain in QALYs. These estimates are robust to variation of parameters across wide ranges. The cost-benefit of 3HP increases with increasing LTBI prevalence and cost of outpatient visit and decreases with increasing age. These findings can help to inform policy to reduce the burden of LTBI and TB reactivation in this epidemiologically important population.

Our results are consistent with those performed in other populations. An analysis by Holland et al. found that newer and shorter regimens that included rifapentine were both more effective and cost saving compared to the standard INH-9 in the United States [22]. Another analysis by Johnson et al among people living with HIV in a high-burden setting showed that 3HP was cost effective over INH-9 only if the price of rifapentine would drop below \$20 per treatment course and high completion rate of 85% can be achieved [15]. Johnson et al performed their analysis prior to the change in rifapentine price and did not use a test and treat approach due to the high prevalence of LTBI in their setting. Our population had a negligible prevalence of HIV according to WHO data [13]. A cost-benefit analysis by Wingate et al. investigated

Table 2
Incremental cost-effectiveness of 3HP in Syrian refugees.

	People Treated	Cases of Active TB	All-Cause Deaths	Cost (Discounted US dollars)	QALY (Discounted)	NMB (Thousands of US dollars)
3HP	21	0.10 (0.03, 0.21)	3.77 (2.38, 17.81)	\$1,629 (755, 3505)	219.11 (134, 311)	\$21,909 (13404, 31048)
INH-9	21	0.19 (0.05, 0.44)	3.77 (2.38, 17.81)	\$3,050 (1256, 7116)	219.02 (134, 310)	\$21,899 (13403, 31041)
(3HP)-(INH-9)	0	-0.09 (-0.25, 0.006)	-0.003 (-0.007, 0.002)	-\$1,421 (-3478, -483)	0.08 (-0.007, 0.221)	\$9.77 (0.64, 24.52)

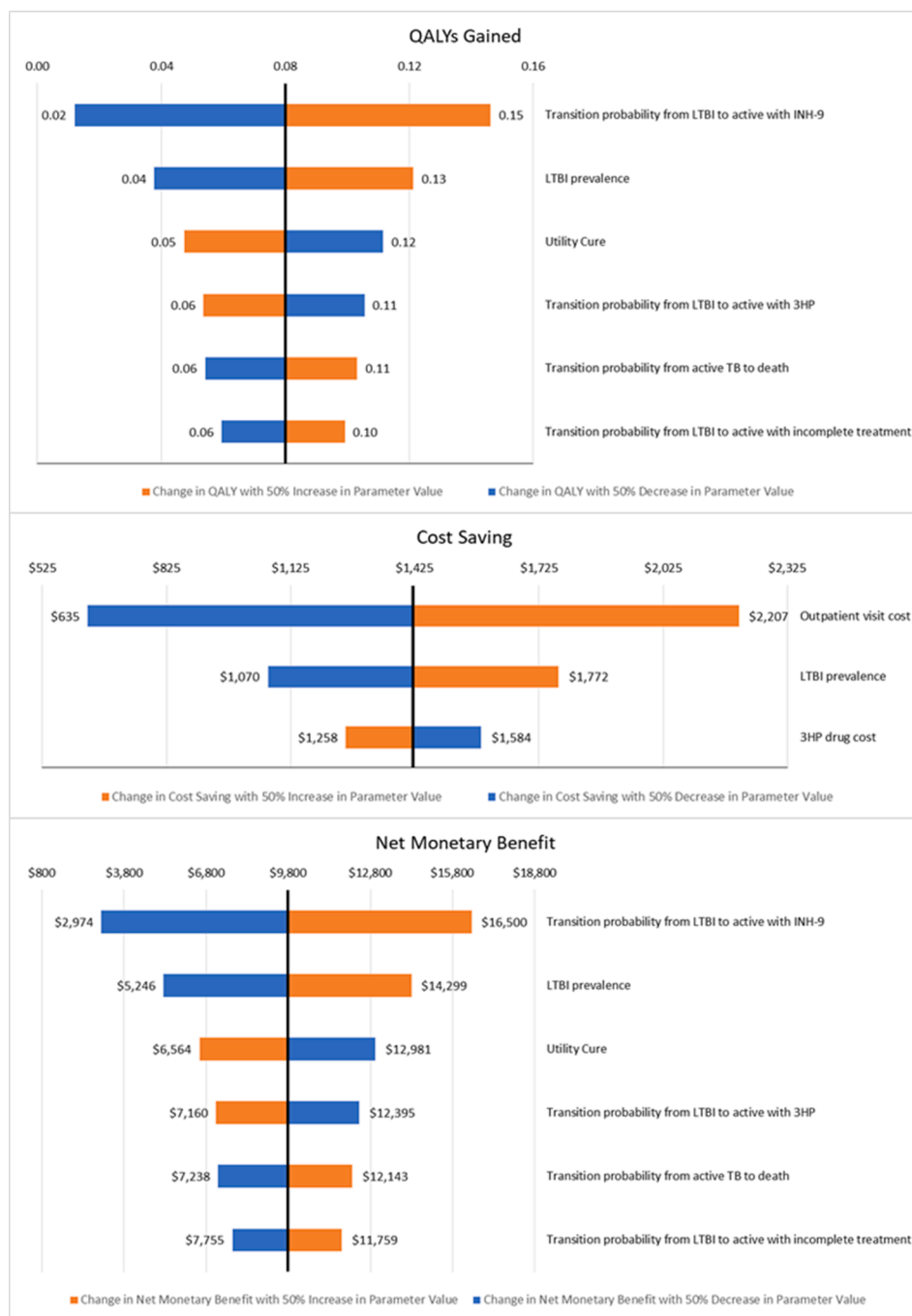


Fig. 2. One-way sensitivity analyses. Scenarios consider outcomes when 100 Syrian refugees residing in Turkey are tested with tuberculin skin testing (TST) and provided treatment for latent TB infection (LTBI) if positive, comparing the use of 12 weeks of isoniazid and rifampin (3HP) versus nine months of isoniazid (INH-9). Panel A shows quality adjusted life years (QALYs) gained, panel B shows costs saved and panel C shows incremental net monetary benefit (NMB), under high and low values of each model parameter (varied in deterministic fashion). Orange bars represent the outcome when the parameter's value is increased by 50% while the blue bars represent the outcome when the parameter's value is decreased by 50%. Utility parameters were only varied by 5% to avoid violating logical bounds. All model parameters were analyzed, but this figure only includes parameters that produced a change in outcome that is greater than 10% of the outcome in the base case scenario (shown as a dark vertical line in each panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

LTBI screening for refugees to the United States before compared to after arrival followed by 3HP treatment for those who tested positive. The analysis found the intervention beneficial for refugees coming from countries with moderate to high prevalence of LTBI (defined as TST

positive of 35% and 55% respectively) [23]. This analysis compared screening strategies rather than treatment strategies and thus is not directly comparable to the results presented here.

While our analysis assumed equal rates of adverse events between

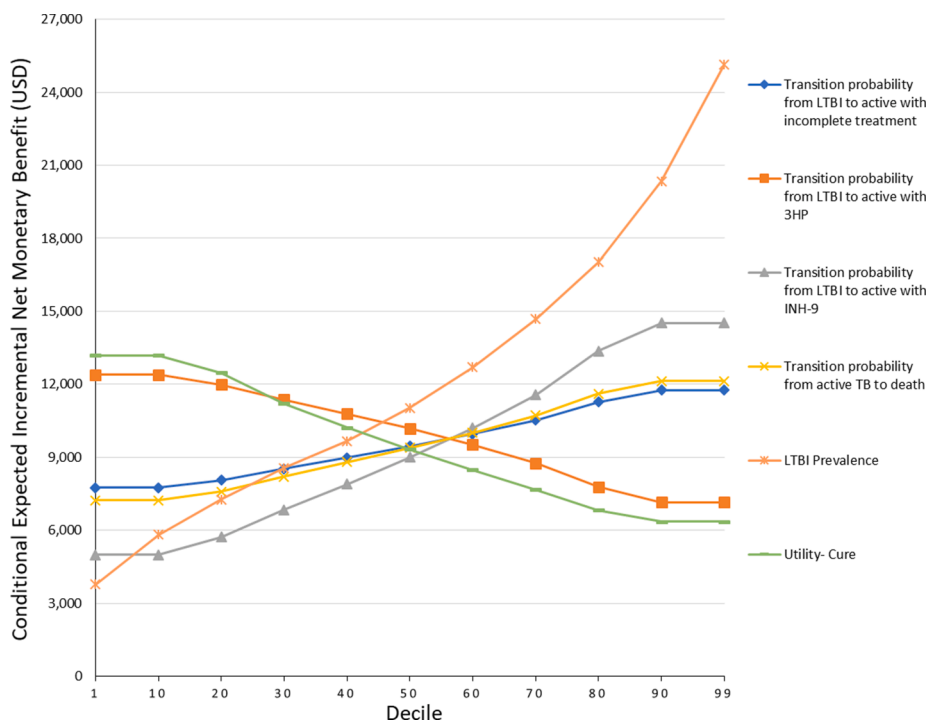


Fig. 3. Probabilistic one-way sensitivity analysis. 100,000 simulations were performed in a probabilistic analysis that included all model parameters. Deciles of each parameter were then defined and plotted on the x-axis. The corresponding conditional expected incremental net monetary benefit (cNMB) is shown on the y-axis. As with panels A-C, this analysis included all model parameters, but only parameters from panel C (i.e., those most influential on net monetary benefit) are shown.

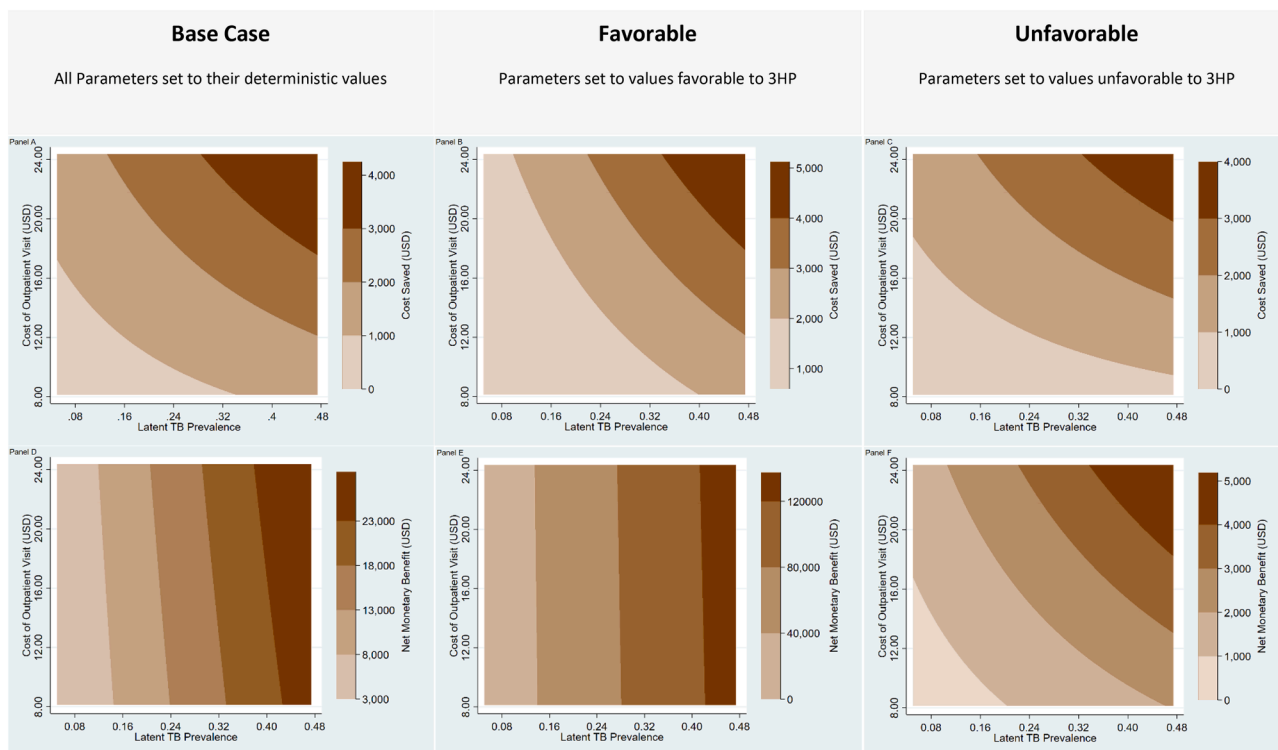


Fig. 4. Two-way sensitivity analysis on the effect of cost of outpatient visit and latent TB prevalence on net monetary benefit. Contours show the net monetary benefit (NMB) in 2017 US dollars, evaluating a scenario where 100 Syrian refugees residing in Turkey are tested with tuberculin skin testing (TST) and provided treatment for latent TB infection (LTBI) if positive and comparing the use of 3HP to INH-9. Darker shades represent scenarios in which 3HP is more cost-saving and more effective than INH-9. The x-axis shows a reasonable range of prevalence of LTBI in this population, and the y-axis shows a corresponding range of per-visit costs for outpatient treatment. Panels A, B & C show costs saved, without reference to non-monetary benefit. Panels D, E & F show changes in net monetary benefit assuming a value of \$100,000 per quality adjusted life year (QALY) gained. The favorable scenarios assume high values for all parameters except utilities of active TB and cure, age, 3HP cost, INH-9 completion and transition probabilities from LTBI to active TB with 3HP, whereas the unfavorable scenarios assume the opposite. The most favorable scenarios for 3HP are those in which both the prevalence of LTBI and the cost of outpatient treatment are high.

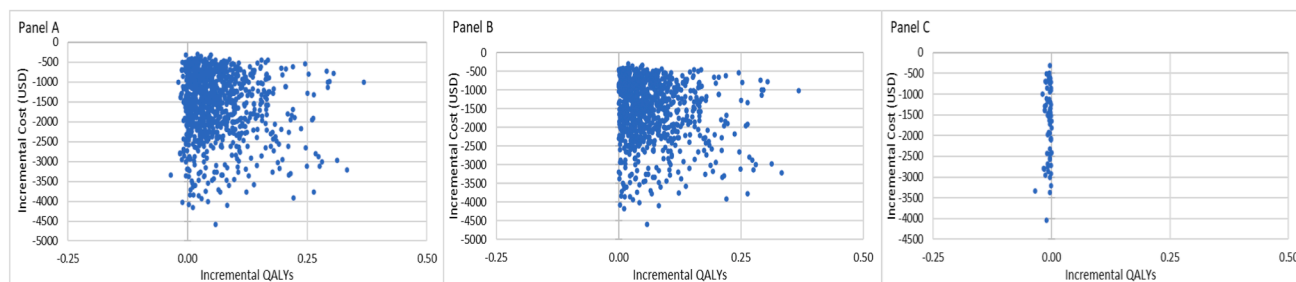


Fig. 5. Multivariate probabilistic sensitivity analysis. This figure shows 1,000 probabilistic trials evaluating the cost effectiveness of TB preventive therapy with 12 weeks of isoniazid and rifapentine (3HP) versus nine months of isoniazid (INH-9) where 100 Syrian Refugees residing in Turkey are tested with tuberculin skin test (TST) and provided treatment for latent TB infection (LTBI) if positive. In order to account for uncertainty in parameter value, in each trial all model parameters were chosen in a probabilistic fashion following a beta distribution for all parameters except for age which was selected randomly between 18 and 64 and cost parameters which were varied according to gamma distribution. The x-axis shows incremental gains in quality adjusted life years (QALYs) and the y-axis shows a corresponding incremental cost in 2017 US dollars, comparing 3HP to INH-9. Panel A shows all 1000 simulations. Panel B shows the 929 simulations where 3HP resulted in incremental QALY gain relative to INH-9, which occurred with lower ages (median age 40) and more reasonable transition probabilities from LTBI to active TB with INH-9 (median 0.14% per year). Panel C shows the 71 simulations where 3HP resulted in incremental QALY loss relative to INH-9, which occurred at higher ages (median age 59) and lower transition probabilities from LTBI to active TB with INH-9 (median 0.07%/year).

the two regimens, we still found that older adults were unlikely to benefit from LTBI treatment, as the disutility of treatment outweighed its benefits. This finding is consistent with the published literature. For example, in a systematic review, Hosford et al found that older individuals (over the age of 60) had higher rates of hepatotoxicity when treated for LTBI with isoniazid monotherapy regimens [24]. Other rifampin-based regimens such as rifampin for 4 months have been shown to be non-inferior to INH-based regimen with a better safety profile [25], but these were not included in our analysis as they are not currently in wide use in Turkey or in many high-TB-burden countries such as Syria. Given the evidence on safety and efficacy of these isoniazid-free regimens, it is hoped that they will find broader use in settings with low prevalence of rifampin resistance (such as Turkey) in the future.

Strengths of this analysis include its epidemiologically important population of refugees and extensive sensitivity analyses indicating consistent results over a large number of plausible clinical scenarios. Nevertheless, our analysis also has important limitations. First, we relied solely on published literature which had a paucity of data particular to our target population. For example, we applied the LTBI prevalence of the WHO Eastern Mediterranean region which might underestimate the true LTBI prevalence in our refugee population. Because of this, we varied LTBI prevalence across a wide range in our sensitivity analysis. Second, while the completion estimates of both 3HP and INH-9 are consistent with published literature, they might overestimate the true completion rate in our highly mobile refugee population. Third, we did not include opportunity cost for treatment from the patient perspective because many Syrian refugees in Turkey are not authorized to participate in the formal labor market. Thus, our findings from the Turkish healthcare perspective might underestimate the benefits of shorter-course treatment as measured from a societal perspective. We did not compare either INH-9 or 3HP against a no-screening scenario; thus, this analysis speaks only to the regimen that should be used if screening is undertaken. We also did not explicitly include secondary transmission in this analysis; from this perspective, our results are likely to be conservative, underestimating the benefit of 3HP in averting these transmission events.

These results suggest that 3HP is likely to be cost saving and more effective than INH-9 among Syrian refugees living in Turkey. Our estimates could be improved by targeted surveys to estimate the prevalence of LTBI in this population and through pilot studies to evaluate the cost of outpatient visits and adherence to treatment under programmatic conditions. Nevertheless, our sensitivity analyses suggest that these revisions are unlikely to change the ultimate direction of our findings.

In summary, this simulation analysis suggests that using three

months of weekly rifapentine and isoniazid is likely to improve health and save costs compared to nine months of daily isoniazid when used for treatment of Syrian refugees (Especially age 59 and younger) residing in Turkey who test positive with TST. These findings are robust to wide parameter variation and argue for consideration of short-course treatment of LTBI in this highly mobile population.

Credit authorship contribution statement

Ghassan Ilaiwy: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **David W. Dowdy:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jctube.2021.100262>.

References

- [1] World Health Organization. Tuberculosis. 2020; Available at: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>. Accessed June 20, 2021.
- [2] Houben, Rein MGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med.* 2016;13(10):e1002152.
- [3] UNHCR. Syrian Regional Refugee Response. 2020; Available at: <https://data2.unhcr.org/en/situations/syria/location/113>. Accessed June 3, 2020.
- [4] Doganay M, Demiraslan H. Refugees of the Syrian Civil War: Impact on Reemerging Infections, Health Services, and Biosecurity in Turkey. *Health Security* 2016;14(4):22–225.
- [5] Proença R, Mattos Souza F, Lisboa Bastos M, Caetano R, Braga JU, Faerstein E, et al. Active and latent tuberculosis in refugees and asylum seekers: a systematic review and meta-analysis. *BMC Public Health* 2020;20(1):1–838.
- [6] Bloom BR, Atun R, Cohen T, Dye C, Fraser H, Gomez GB, et al. Tuberculosis. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. *Major Infectious Diseases*. 3rd ed. Washington (DC): International Bank for Reconstruction and Development / The World Bank; 2017.
- [7] Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. *New England J. Med.* 2011;365(23):2155–66.
- [8] Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. *New England J. Med.* 2019;380(11):1001–11.
- [9] UNITAID. Landmark deal secures significant discount on price of medicine to prevent TB. 2019; Available at: <https://unitaid.org/news-blog/landmark-deal>

- secures-significant-discount-on-price-of-medicine-to-prevent-tb/#en. Accessed June 3, 2020.
- [10] Tasillo A, Salomon JA, Trikalinos TA, Horsburgh CR, Marks SM, Linas BP. Cost-effectiveness of Testing and Treatment for Latent Tuberculosis Infection in Residents Born Outside the United States With and Without Medical Comorbidities in a Simulation Model. *JAMA Internal Med.* 2017;177(12):1755–64.
- [11] Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. *Am. J. Prev. Med.* 2018;55(2):244–52.
- [12] World Health Organization. Global Health Observatory data repository. Life tables by country, Syrian Arab Republic. Available at: <https://apps.who.int/gho/data/?theme=main&vid=61620>. Accessed February 12, 2020.
- [13] World Health Organization. WHO TB burden estimates. 2020; Available at: <https://www.who.int/tb/country/data/download/en/>. Accessed February 11, 2020.
- [14] Bliven-Sizemore EE, Sterling TR, Shang N, Benator D, Schwartzman K, Reves R, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int. J. Tuberculosis Lung Disease* 2015;19(9):1039–44.
- [15] Johnson KT, Churchyard GJ, Sohn H, Dowdy DW. Cost-effectiveness of Preventive Therapy for Tuberculosis With Isoniazid and Rifapentine Versus Isoniazid Alone in High-Burden Settings. *Clinical Infectious Diseases* 2018;67(7):1072–8.
- [16] World Health Organization. Estimates of Unit Costs for Patient Services for Turkey. 2010; Available at: <https://www.who.int/choice/country/tur/cost/en/>. Accessed February 12, 2020.
- [17] U.S. Bureau of Labor Statistics. CPI Inflation Calculator. Available at: https://www.bls.gov/data/inflation_calculator.htm. Accessed February 12, 2020.
- [18] Guo Na, Marra Carlo A, Marra F, Moadebi S, Elwood RK, FitzGerald JM. Health State Utilities in Latent and Active Tuberculosis. *Value in Health* 2008;11(7):1154–61.
- [19] M. Quaipe, R. Houben, B. Allwood, T. Cohen, A. Coussens, A. Harries et al. Post-tuberculosis mortality and morbidity: valuing the hidden epidemic. *The Lancet Respiratory* 2020 February 10.
- [20] Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276(15):1253–8.
- [21] Asylum Information Database. Health care: Conditions for free health care in Turkey.
- [22] Holland DP, Sanders GD, Hamilton CD, Stout JE. Potential Economic Viability of Two Proposed Rifapentine-Based Regimens for Treatment of Latent Tuberculosis Infection. *PloS one* 2011;6(7):e22276.
- [23] Wingate LT, Coleman MS, de la Motte Hurst, Christopher, Semple M, Zhou W, Cetron MS, et al. A cost-benefit analysis of a proposed overseas refugee latent tuberculosis infection screening and treatment program. *BMC Public Health* 2015; 15(1):1201.
- [24] Hosford JD, von Fricken ME, Lauzardo M, Chang M, Dai Y, Lyon JA, et al. Hepatotoxicity from antituberculous therapy in the elderly: A systematic review. *Tuberculosis (Edinburgh, Scotland)* 2015;95(2):112–22.
- [25] 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. *New England J. Med.* 2018;379(5):440–53.
- [26] Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf Marieke J. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. *Annals of Internal Medicine* 2017;167(4):248–55.