



Published in final edited form as:

Lancet Glob Health. 2020 September ; 8(9): e1223–e1233. doi:10.1016/S2214-109X(20)30227-8.

Cost-effectiveness of post-treatment follow-up examinations and secondary prevention of tuberculosis in a high-incidence setting: a model-based analysis

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Summary

Background—In settings of high tuberculosis incidence, previously treated individuals remain at high risk of recurrent tuberculosis and contribute substantially to overall disease burden. Whether tuberculosis case finding and preventive interventions among previously treated people are cost-effective has not been established. We aimed to estimate costs and health benefits of annual post-treatment follow-up examinations and secondary preventive therapy for tuberculosis in a tuberculosis-endemic setting.

Methods—We developed a transmission-dynamic mathematical model and calibrated it to data from two high-incidence communities of approximately 40 000 people in suburban Cape Town, South Africa. We used the model to estimate overall cost and disability-adjusted life-years (DALYs) associated with annual follow-up examinations and secondary isoniazid preventive therapy (IPT), alone and in combination, among individuals completing tuberculosis treatment. We investigated scenarios under which these interventions were restricted to the first year after treatment completion, or extended indefinitely. For each intervention scenario, we projected health

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Contributors

FMM, TC, and RY conceived the study. FMM designed the study, developed the model structure, and collected the data. RY implemented the model and analysed the data. FMM wrote the first manuscript draft. All authors contributed to the study design and interpretation of the results. NAM and JAS advised the design, analysis, and interpretation of the health-economic analysis. NAM provided guidance on the Bayesian calibration approach. GT provided insights into alternative diagnostic algorithms relevant for the analysis. All authors revised the manuscript for important intellectual content and approved the final version.

Declaration of interests We declare no competing interests.

system costs and DALYs averted with respect to the current status quo of tuberculosis control. All estimates represent mean values derived from 1000 epidemic trajectories simulated over a 10-year period (2019–28), with 95% uncertainty intervals (UIs) calculated as the 2.5th and 97.5th percentile values.

Findings—We estimated that a single follow-up examination at the end of the first year after treatment completion combined with 12 months of secondary IPT would avert 2472 DALYs (95% UI –888 to 7801) over a 10-year period and is expected to be cost-saving compared with current control efforts. Sustained annual follow-up and continuous secondary IPT beyond the first year after treatment would avert an additional 1179 DALYs (–1769 to 4377) over 10 years at an expected additional cost of US\$18.2 per DALY averted. Strategies of follow-up without secondary IPT were dominated (ie, expected to result in lower health impact at higher costs) by strategies that included secondary IPT.

Interpretation—In this high-incidence setting, post-treatment follow-up and secondary preventive therapy can accelerate declines in tuberculosis incidence and potentially save resources for tuberculosis control. Empirical trials to assess the feasibility of these interventions in settings most severely affected by tuberculosis are needed.

Introduction

Considerable effort will be required to accelerate declines in tuberculosis incidence and mortality worldwide and ensure progress towards the global tuberculosis elimination targets.¹ Although estimates of tuberculosis incidence and mortality indicate declining trends in many high-burden countries over the past few years,² progress remains slow in settings with the highest incidence. Additional interventions to interrupt transmission and prevent disease progression might be necessary to effectively reduce tuberculosis in these settings.

While population-level interventions such as intensified case finding and preventive treatment are costly and have not yielded anticipated benefits,^{3,4} novel approaches that focus on groups at the highest risk of tuberculosis could be attractive alternatives. Whether targeting tuberculosis control interventions towards high-risk groups will be effective at the population level will depend on whether these groups are identifiable and accessible, and on the extent to which these groups contribute to transmission of *Mycobacterium tuberculosis* and overall tuberculosis burden.

Individuals who have previously completed an episode of tuberculosis treatment remain at high risk of developing tuberculosis again.⁵ This risk is usually highest in the first year after treatment completion, where endogenous reactivation (relapse) is the main mechanism of disease recurrence.⁶ In settings with a high force of infection, persistently high rates of recurrent tuberculosis after the first year,^{6–8} commonly due to exogenous reinfection, have been observed, which suggests that previously treated people might be especially susceptible to tuberculosis.⁸ In these settings, tuberculosis among previously treated people contributes substantially to the overall incidence and prevalence of active tuberculosis.^{9–11} Using a mathematical model of tuberculosis and HIV in suburban Cape Town, South Africa, we projected that targeting tuberculosis case finding and secondary prevention to previously treated people could yield substantial population-level reductions in tuberculosis incidence

and mortality.¹² However, it is not yet clear whether these types of targeted intervention are cost-effective options for tuberculosis control in a high-incidence setting.

In this analysis, we estimated the cost-effectiveness of targeted tuberculosis control strategies to find and prevent tuberculosis among people who have previously completed tuberculosis treatment. We considered targeted active case finding, implemented as annual post-treatment follow-up examinations, alone and in combination with secondary isoniazid preventive therapy (IPT). We also examined how variations in uptake and duration of follow-up examinations and secondary IPT affect the cost-effectiveness of these interventions.

Methods

Modelling approach

We developed and calibrated a stochastic compartmental model of the tuberculosis and HIV epidemic in a high-incidence setting of approximately 40 000 residents of two adjacent communities in suburban Cape Town, South Africa (see appendix p 2 for details on the study setting). The transmission-dynamic model is an extension of a model that we previously used to explore the impact of targeted active case finding and secondary IPT after tuberculosis treatment completion in the same study setting.¹² The tuberculosis component of the model follows the conventions of earlier models^{13–16} with additional structure to distinguish between individuals who have never been treated for tuberculosis (treatment naive) and those who have previously been treated for tuberculosis (treatment experienced; figure 1). Model transitions are fully described in the appendix (pp 2–3). Briefly, treatment-naive susceptible adults transition from the susceptible state to the latently infected state or directly into the infectious tuberculosis state after primary infection. If diagnosed, infectious adults move into one of two treatment compartments: incomplete or completed treatment. Adults in the incomplete treatment state move into a treatment-experienced latently infected state or, upon persistent disease, an infectious tuberculosis state. Infectious adults transit, after passive case detection, back into one of the two treatment compartments. Adults who complete their treatment are allocated to an intervention arm or non-intervention arm. In the non-intervention arm, the transitions are similar to those for adults in the incomplete treatment state, and infectious adults can once again be passively detected and transition into either of the treatment compartments. Similar transitions apply to adults in the intervention arm; however, an additional case-detection rate, incremental to passive case finding, is implemented to model case detection during post-treatment follow-up. Furthermore, we allow rates of relapse and disease progression following reinfection to differ from those in the non-intervention arm to account for the effect of secondary preventive therapy. Adults with completed treatment who drop out of the intervention arm move into the non-intervention arm, with its respective case detection, relapse, and reinfection rates.

For the present study, we distinguish between individuals who completed their tuberculosis treatment within the past year and those who completed treatment more than 1 year ago. Our model includes substructure for people living with HIV, who represent an important high-risk group for tuberculosis. The HIV component of our model accounts for HIV infection, progression to a state of immunocompromised HIV infection, and antiretroviral treatment (ART; figure 1). The model also includes a subcomponent for children aged 0–14 years

(appendix pp 2–3). A detailed description of our modelling approach, including model structure, parameterisation, implementation, model calibration, and parameter estimation, can be found in the appendix (pp 2–13).

Key model assumptions

We made the following six key model assumptions about differences between treatment-experienced and treatment-naive people. (1) Individuals who complete tuberculosis treatment revert to a latently infected stage that is distinct from latent infection among treatment-naive individuals. Subsequent tuberculosis is either due to endogenous reactivation (relapse) or exogenous reinfection. (2) We allow for a higher risk of tuberculosis reactivation in individuals who have completed tuberculosis treatment compared with those who are treatment naive and latently infected. We assumed that the rate of relapse after completion of tuberculosis treatment is highest in the first year and lower in subsequent years after treatment, consistent with observations from the study setting and a review of clinical trial data.^{6,17} (3) Due to the uncertainty about the degree to which previous tuberculosis disease is associated with immunity,⁸ we allow for previously treated people, when reinfected, to be equally protected against tuberculosis compared with treatment-naive latently infected people, and up to twice as susceptible compared with previously uninfected, treatment-naive people. (4) We allow for treatment-experienced people with tuberculosis to be more infectious than treatment-naive people with tuberculosis, consistent with local tuberculosis prevalence survey data showing that people with previously treated tuberculosis were more likely to report cough and to be smear positive.¹⁰ (5) We allow for differential rates of passive tuberculosis case finding among individuals with and without history of tuberculosis treatment. (6) Among individuals with incomplete tuberculosis treatment, we assumed that between 0% and 20% remained infectious, effectively resulting in higher rates of tuberculosis after incomplete treatment, consistent with findings from the study setting.¹⁸

Model initialisation and parameter estimation approach

We specified an initial population size of 32 889 people (25 903 adults and 10 427 children aged 0–14 years), intended to reflect the population size in 1992 and informed by local census data and projections of population growth. Model simulations were initiated in 1992, allowing for a 10-year burn-in period before the availability of local data for calibration, which were obtained between Jan 1, 2002, and Dec 31, 2008 (with prevalence estimates for 2002 only). This calibration period was chosen because of the availability of high-quality data. Because the values of many parameters in tuberculosis and HIV co-epidemic models are not known with certainty, we adopted a Bayesian calibration approach to identify parameter sets that resulted in simulated trajectories with good fit to demographic, programmatic, and observational study data available for our setting (appendix pp 10–11). To implement this approach, we used a sampling-importance-resampling algorithm¹⁹ under which uniform prior distributions were specified for each parameter, and multiple parameter sets were then randomly and independently selected from these distributions (sampling). We measured the goodness of fit for 20 000 simulated trajectories against the calibration targets (importance). The calibration targets were operationalised as the likelihood of observing the calibration data conditional on the simulated values. A subset of 1000 parameter sets was then resampled for final analysis with sampling probability proportional to goodness of fit

(resampling). Additional details about the parameter estimation approach and posterior distributions of key model parameters are shown in the appendix (pp 10–13). Figure 2 shows the fit of simulated trajectories against the calibration targets.

Base-case and intervention scenarios

We defined a base-case scenario of the current status quo of tuberculosis control in the study setting. Under this base-case scenario, treatment-naïve and treatment-experienced adults with infectious tuberculosis are passively detected and treated for tuberculosis with no additional interventions implemented. Rates of passive case detection were estimated through model calibration; percentages of patients completing tuberculosis treatment were informed by programmatic data from the local tuberculosis register.

We assumed that two targeted interventions—follow-up examinations and secondary IPT—were implemented complementary to routine tuberculosis services provided under the base-case scenario in the study setting. For follow-up examinations, we assumed that patients with tuberculosis who are completing tuberculosis treatment are requested to return to the clinic once at the end of every year to be re-evaluated for tuberculosis. At follow-up, individuals are asked to produce a single sputum sample for bacteriological testing (spontaneous or induced). We assumed that mycobacterial culture is used as the single diagnostic screening test, given the high false-positive rate of Xpert MTB/RIF in people with a recent history of tuberculosis treatment.²⁰ Additional considerations about the use of the screening test are provided in the appendix (pp 14–16). We modelled the effect of follow-up examinations as an additional rate of case finding (figure 1). Follow-up thus leads to more rapid initiation of tuberculosis treatment and reductions in the average diagnostic delay and expected period of infectiousness. For secondary IPT, we assumed that patients who complete tuberculosis treatment are offered isoniazid (300 mg daily) as preventive therapy. We modelled the effect of preventive therapy by reducing the rate of tuberculosis reactivation and the risk of progression to disease following reinfection. A preventive effect of 65% (uncertainty interval [UI] 45–85) was assumed, informed by two previous studies.^{21,22} These estimates consider the possibility that secondary IPT might be ineffective in a small fraction of individuals who acquired drug resistance during their first tuberculosis treatment episode.

The relative effect of preventive therapy was assumed to be independent of HIV infection, but the absolute rate and risk reduction associated with this intervention remains greater for those with HIV given their higher reactivation rate and risk of progression. We also assumed that the protective effect does not extend beyond the cessation of preventive therapy.²³

When modelling intervention scenarios, we considered a 2×2 factorial design of either annual follow-up examination alone or combined with secondary IPT and their intended duration after completion of treatment (restricted to the first year after treatment or unlimited; appendix p 20). We modelled the uptake of the interventions as a probability after tuberculosis treatment completion (figure 1). In our primary analysis, we assumed that 75% of patients with tuberculosis completing treatment would agree to receive the intervention. We allowed for dropout from the interventions by enabling transitions from the intervention into the non-intervention compartments at varying rates (figure 1). We assumed that, on

average, 15% of people currently enrolled in the interventions drop out every year (resulting in an expected duration of preventive therapy of 6.6 years). Both uptake of and dropout from the interventions were varied in secondary analyses. Individuals who were re-treated for tuberculosis were able to re-enter the interventions upon treatment completion.

Cost-effectiveness analysis

We estimated the costs for the base-case and intervention scenarios in 2018 US dollars, adopting a South African health-care system perspective (table 1). Average costs reflect 2018 estimates for tuberculosis health-care and diagnostic services in Cape Town that were obtained through review of the published literature and the official price list of the National Health Laboratory Service, South Africa. Cost estimates from previous years were converted into US dollars (where applicable) and adjusted for inflation using an average annual South African gross domestic product deflator rate of 5.71%.³¹ Costs for basic tuberculosis services reflect resources for standard tuberculosis diagnostic evaluation among individuals self-presenting to primary health care, HIV testing and ART, and tuberculosis treatment. Costs for annual follow-up examinations reflect those for follow-up visits to the local clinic and culture-based screening for active tuberculosis (table 1). Costs for secondary IPT reflect drug supply and dispensing during monthly follow-up visits as well as the evaluation and management of potential drug-induced toxicity events (table 1). We assumed that 3.0% (UI 0.2–15.0) of individuals enrolled in secondary IPT would experience drug-induced liver injury, of which 1.4% (0.005–2.5) would be severe events requiring hospitalisation, and of the latter 5.2% (0.01–10.0) would lead to death.²⁸

We further assumed that 0–2% of individuals receiving secondary IPT acquire drug-resistant tuberculosis. As the number of individuals developing drug-resistant tuberculosis through this pathway is expected to be low, we assumed that preventive therapy would not have a meaningful impact on the prevalence of drug-resistant tuberculosis. Hence, our model does not explicitly describe the dynamics of drug-resistant tuberculosis. However, we account for the treatment cost of individuals who acquired drug-resistant tuberculosis through secondary IPT (table 1).

We estimated disability-adjusted life-years (DALYs) as a measure of the health impact of the intervention scenarios (appendix p 18). Costs and health benefits were discounted at an annual rate of 3.0%. For each strategy considered here, we estimated the probability of it being the optimal strategy for a given cost-effectiveness threshold. At a cost-effectiveness threshold ω , a strategy is considered optimal if it results in the highest net monetary benefit, defined as $\omega \times (\text{DALYs averted by the strategy}) - (\text{incremental cost of the strategy})$.

As a sensitivity analysis, we calculated partial rank correlation coefficients to assess how sensitive our model outputs were to variation in input parameters (appendix p 19).

We followed the Consolidated Health Economic Evaluation Reporting Standards³² to report the results of our study. Model projections were made for the time period Jan 1, 2019 to Dec 31, 2028; estimates beyond would have come with considerable additional uncertainty for this relatively small study population. All estimates from the model are presented as the

mean and 95% UIs (the 2.5th and 97.5th percentiles) of 1000 epidemic trajectories simulated over the 10-year period.

The model is coded in C# (release 8) and the analyses were done in Python (version 3.8).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Under the base-case scenario, we estimated that in 2019, the incidence of tuberculosis in the population studied was 1624 cases (95% UI 890–2687) per 100 000 population. Tuberculosis incidence was 1218 cases (691–2098) per 100 000 treatment-naive people and 7551 cases (3931–12 531) per 100 000 treatment-experienced people. Among incident tuberculosis cases who had previously completed tuberculosis treatment, 48% (32–62) were due to reactivation of tuberculosis (as opposed to reinfection). Identified posterior estimates for key parameters describing the natural history of tuberculosis among treatment-experienced and treatment-naive individuals stratified by HIV status are provided in the appendix (p 13).

Epidemiological projections of tuberculosis incidence under the base-case scenario and under each intervention scenario are shown in the appendix (p 20). We estimated an expected annual decline in tuberculosis incidence between 2019 and 2028 of 1.32% (95% UI –2.07 to 3.84) under the base-case scenario (no targeted intervention), of 2.28% (–0.24 to 4.61) under follow-up examinations limited to the end of the first year after treatment, and of 2.44% (–0.06 to 4.79) under continuous annual follow-up. The expected annual decline in tuberculosis incidence would be 2.91% (0.64 to 5.12) under combined follow-up and secondary IPT restricted to the first year, and 3.79% (1.73 to 5.62) under annual follow-up and continuous secondary IPT.

A combination of follow-up and secondary IPT limited to the first year is expected to avert 14.3% (95% UI 0.1 to 28.0) of incident tuberculosis cases and 12.2% (–3.9 to 27.1) of tuberculosis deaths estimated to occur under the base-case scenario over the 10-year period (figure 3). Continuous use of annual follow-up and secondary IPT is expected to avert 20.4% (5.9 to 35.9) of incident tuberculosis cases and 18.2% (0.7 to 34.2) of deaths (figure 3).

We project that follow-up with secondary IPT limited to the first year after treatment would avert 2472 DALYs (95% UI –888 to 7801) over a 10-year period and be cost saving compared with the base-case scenario (table 2). Sustained annual follow-up with continuous secondary IPT is estimated to avert an additional 1179 DALYs (–1769 to 4377) at an additional cost of \$18.2 per DALY averted. Follow-up alone, whether limited to the first year or not, was dominated (ie, expected to result in lower health impact at higher costs) by strategies that included secondary IPT (table 2).

For cost-effectiveness thresholds higher than \$18.2 per DALY averted, sustained annual follow-up with continuous secondary IPT had the highest expected net monetary benefit and the highest probability of being the optimal strategy among the strategies considered (figure 4). A pairwise comparison of the intervention strategies in terms of additional costs and DALYs averted is shown in the appendix (p 21).

Sensitivity analysis showed that our projections of incremental health impact and incremental costs under the scenario of annual follow-up with continuous secondary IPT were most sensitive to the average time to passive tuberculosis case detection among treatment-experienced people (incremental health impact only), the rate of relapse (first year: incremental health impact only), the relative susceptibility in HIV-negative people to reinfection after treatment, and the efficacy of secondary IPT (appendix p 19). Scenarios of lower uptake of the interventions (50% uptake among patients completing treatment *vs* 75% in the primary analysis) would result in lower health impact and reduce total costs estimated for the combined intervention of follow-up and secondary IPT; however, the combined intervention remained the optimal strategy (appendix p 22). Higher dropout rates (25% *vs* 15% per year in the primary analysis) would reduce impact and costs of the lifelong combined strategy but have little impact on the first-year combined strategy (appendix p 22).

Discussion

In this study, we used a calibrated transmission-dynamic model of tuberculosis in a high-incidence setting to estimate whether interventions targeted to previously treated people would be cost-effective for tuberculosis control. Our analysis suggests that a combined strategy of annual post-treatment follow-up examinations and secondary preventive therapy among individuals who completed their tuberculosis treatment has a high probability of being cost-saving for tuberculosis control if implemented in addition to current tuberculosis control efforts in this setting. With a cost-effectiveness threshold greater than \$18.2 per DALY averted, sustained annual follow-up coupled with continuous secondary IPT is expected to be the optimal strategy.

While follow-up and secondary IPT limited to the first year after treatment is expected to minimise tuberculosis control costs and produce health gains relative to the status quo, sustained annual follow-up with continuous secondary IPT will result in the greatest health impact for a relatively low additional cost. Our projection that the combined intervention is cost-effective even when extended beyond the first year after treatment relates to the observation that, in this high-incidence setting, the risk of tuberculosis among those completing tuberculosis treatment remains elevated beyond the first year after treatment due to exogenous reinfection.⁶

To our knowledge, our study is the first to estimate the cost-effectiveness of interventions targeted to people with a history of previous tuberculosis treatment in a high-incidence setting. It extends findings of an earlier modelling study,¹² in which we found that offering tuberculosis case finding and secondary IPT to people previously treated for tuberculosis could greatly accelerate declines in tuberculosis incidence and mortality in this setting. Both studies support the proposition that in settings with a high incidence of tuberculosis,

previously treated people constitute an important group that might be especially attractive for targeted interventions given their high risk of recurrent tuberculosis and their probable role in transmission of *M tuberculosis* in the population.

Rigorous implementation of case finding and secondary prevention is necessary to maximise population-level benefits of these targeted interventions.¹² However, the results from our sensitivity analysis suggest that these interventions might be cost-effective even with lower uptake or retention, given that resources for individuals declining to participate or dropping out over time could be saved.

We note the following limitations to our study. Uncertainty around parameters of the natural history of tuberculosis, particularly those determining reinfection, disease progression, and mortality among previously treated individuals, as well as the quality of future case finding and tuberculosis care in our setting, leads to substantial uncertainty in the modelled outcomes. We aimed to reduce this uncertainty by calibrating our model to several targets based on observational data from our study setting including rates of recurrent tuberculosis due to reactivation (relapse) and reinfection as estimated in a large cohort analysis.⁶ While we allowed for differential susceptibility to tuberculosis among treatment-experienced and treatment-naive individuals, we did not explicitly model differential risk of exposure as a possible driver for recurrent disease.

As noted for our previous modelling study,¹² this study was based on a high-incidence setting; therefore, estimates of population-level impact and cost-effectiveness might not be readily generalisable to other settings. We expect interventions among previously treated people to be less cost-effective in settings with lower tuberculosis incidence, and where a smaller proportion of the tuberculosis burden and transmission is attributable to people who have previously had tuberculosis. In particular, sustaining annual follow-up and continuous secondary IPT might be less attractive in lower-transmission settings, where reinfection after tuberculosis treatment might be less common.

We were unable to address several practical aspects that could represent challenges to successful implementation of follow-up examinations and secondary IPT. For example, given the low specificity of Xpert MTB/RIF for the diagnosis of recurrent tuberculosis in recently treated people,^{20,33} we considered the use of *M tuberculosis* culture as the screening test at follow-up. The expected duration between follow-up and confirmation of tuberculosis via culture result (usually 2–3 weeks) means that culture-positive individuals would have to be contacted to start their re-treatment. Initiation of presumptive re-treatment might be considered for individuals with a high clinical suspicion of recurrent tuberculosis. However, re-treatment would have to be discontinued in the event of a negative culture result. More complex screening algorithms—for example ruling in possible tuberculosis cases via Xpert MTB/RIF and ruling out via culture—might prove more practicable but come with increased costs.

There is uncertainty about the extent to which risk factors for isoniazid-induced toxicity events such as alcohol abuse, malnutrition, or a past history of toxicity³⁴ might affect eligibility for preventive therapy after treatment, which would reduce uptake. Also,

implementing these interventions requires that drug toxicity events be successfully detected and managed.

Finally, our study did not take into account potential additional disability related to the burden of post-tuberculosis lung disease. There is consistent evidence from studies for an association between repeated episodes of tuberculosis and deteriorating lung function or chronic lung disease.³⁵ Preventing recurrent and first-time tuberculosis through targeted interventions might therefore produce additional health benefits not accounted for by our study.

In conclusion, our analysis suggests that interventions to detect and prevent recurrent tuberculosis among previously treated people would be cost-effective for tuberculosis control, and that practical efforts to assess their feasibility in high-incidence settings are warranted. Empirical trials of the feasibility, impact, and cost-effectiveness of follow-up examinations and secondary preventive therapy are needed to assess whether these targeted interventions could support tuberculosis control in populations most severely affected by tuberculosis. Efforts to better understand the factors that predispose patients with tuberculosis to a high risk of recurrent tuberculosis after completion of treatment could help to prioritise those who would benefit the most from interventions after completing treatment. Additional research is also needed to identify more sensitive, specific, and rapid diagnostic algorithms to detect recurrent tuberculosis. Other treatment regimens and strategies to prevent recurrent tuberculosis, including the recently recommended shorter preventive treatment regimens (eg, daily rifampicin for 4 months,³⁶ weekly rifapentine/ isoniazid for 3 months³⁷), could be considered. Preventing and detecting recurrent tuberculosis should become part of an integrative post-tuberculosis care strategy that also addresses other long-term adverse health consequences including the burden of post-tuberculosis lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Karen Jennings and Judy Taylor (City Health, City of Cape Town, South Africa) for their support. This work was supported through a grant provided jointly by the Günther Labes Foundation and the Oskar Helene Heim Foundation to FMM, and grants provided by the National Institutes of Health (NIH) to TC, JAS, and NAM (R01 AI112438-01) and to RY (1K01AI119603). FMM was supported through the I3D Exchange of the International Clinics on Infectious Disease Dynamics and Data Program (NIH award number R25GM102149 to J R C Pulliam and A Welte). GT acknowledges funding from the EDCTP2 program supported by the EU (grant SF1401, OPTIMAL DIAGNOSIS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Funding:

National Institutes of Health, Günther Labes Foundation, Oskar Helene Heim Foundation.

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Research in context

Evidence before the study

High rates of recurrent tuberculosis after completion of standard antituberculosis treatment have been reported from several settings with high tuberculosis incidence. To our knowledge, no empirical studies have been done to measure the population-level effect of interventions that aim to prevent recurrent disease or more rapidly detect tuberculosis in previously treated people. In a modelling study of a South African community with high tuberculosis incidence, we projected that targeting active case finding and preventive therapy among individuals who had previously completed a course of tuberculosis treatment could accelerate reductions in tuberculosis incidence and mortality. However, whether such interventions would be cost-effective remains unaddressed.

To establish whether other population-based mathematical models have been employed to estimate the effect of tuberculosis interventions targeted to previously treated people, we updated an earlier PubMed search of relevant articles published in any language up to June 1, 2020, using the following search: (tuberculosis) AND (recurren* OR relapse OR reinfection OR re-infection OR re-treatment OR previous treatment) AND (model* OR simulation). We found no other modelling study has addressed the population-level effects and cost-effectiveness of interventions targeted to people previously treated for tuberculosis.

Added value of this study

We used a calibrated transmission-dynamic mathematical model of tuberculosis among treatment-naïve and treatment-experienced people in a high-incidence setting in suburban Cape Town, South Africa, to understand whether two targeted interventions—post-treatment follow-up examinations and secondary isoniazid preventive therapy (IPT)—among people who had completed tuberculosis treatment would be cost-effective if implemented alongside existing tuberculosis control efforts. We found that a strategy combining targeted follow-up examinations and secondary IPT for 1 year after treatment completion would both improve health (estimated as disability-adjusted life years [DALYs] averted) and reduce tuberculosis control costs. Compared with this strategy, annual follow-up with continuous secondary IPT is expected to cost an additional US \$18.2 per DALY averted. Follow-up examination alone, whether limited to or extended beyond the first year after treatment was dominated (ie, expected to result in lower health impact at higher costs compared to the other strategies modelled). The comparative performance of these strategies in terms of cost and health benefits is expected to be maintained even at reduced uptake (50%) of or high dropout (25% per year) from the targeted interventions.

Implications of all the available evidence

This study shows that, in tuberculosis-endemic and HIV-endemic settings, former patients with tuberculosis constitute an important risk group that would derive substantial health benefits from targeted interventions, at comparatively low cost. Our results suggest

that post-treatment follow-up and secondary preventive therapy offered to people who have completed tuberculosis treatment would be cost-effective and potentially cost-saving for tuberculosis control. Empirical trials of these targeted interventions are now needed to assess their feasibility and benefits in populations most severely affected by tuberculosis.

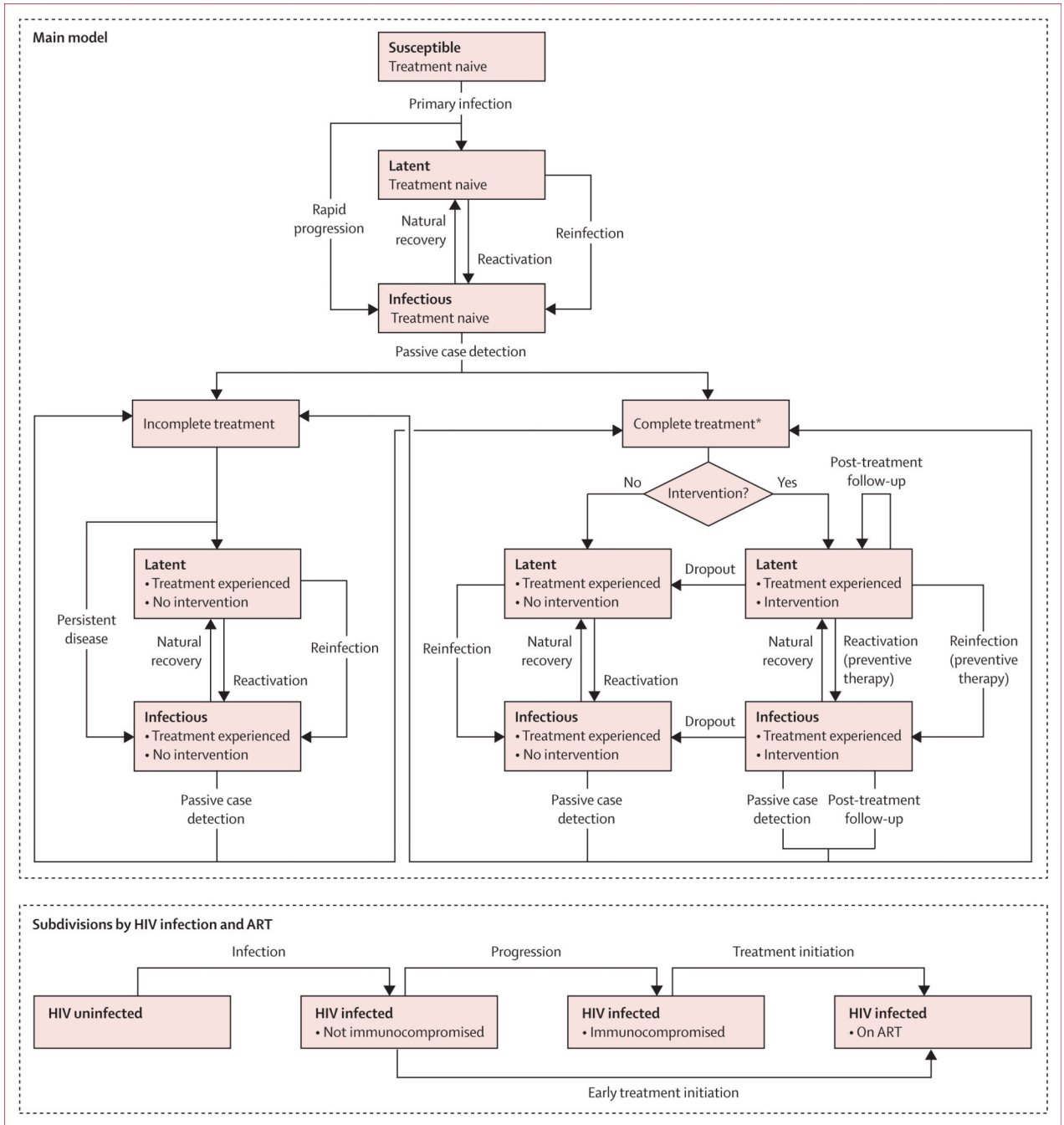


Figure 1: Structure of the mathematical model

Mortality rates are not shown. The childhood subcomponent and corresponding transitions are shown in the appendix (p 3). ART=antiretroviral treatment. *Latently infected and infectious individuals after complete treatment in both the intervention and non-intervention arms transition from a subdivision reflecting the first year after completing tuberculosis treatment into a subdivision reflecting more than 1 year after completing tuberculosis treatment.

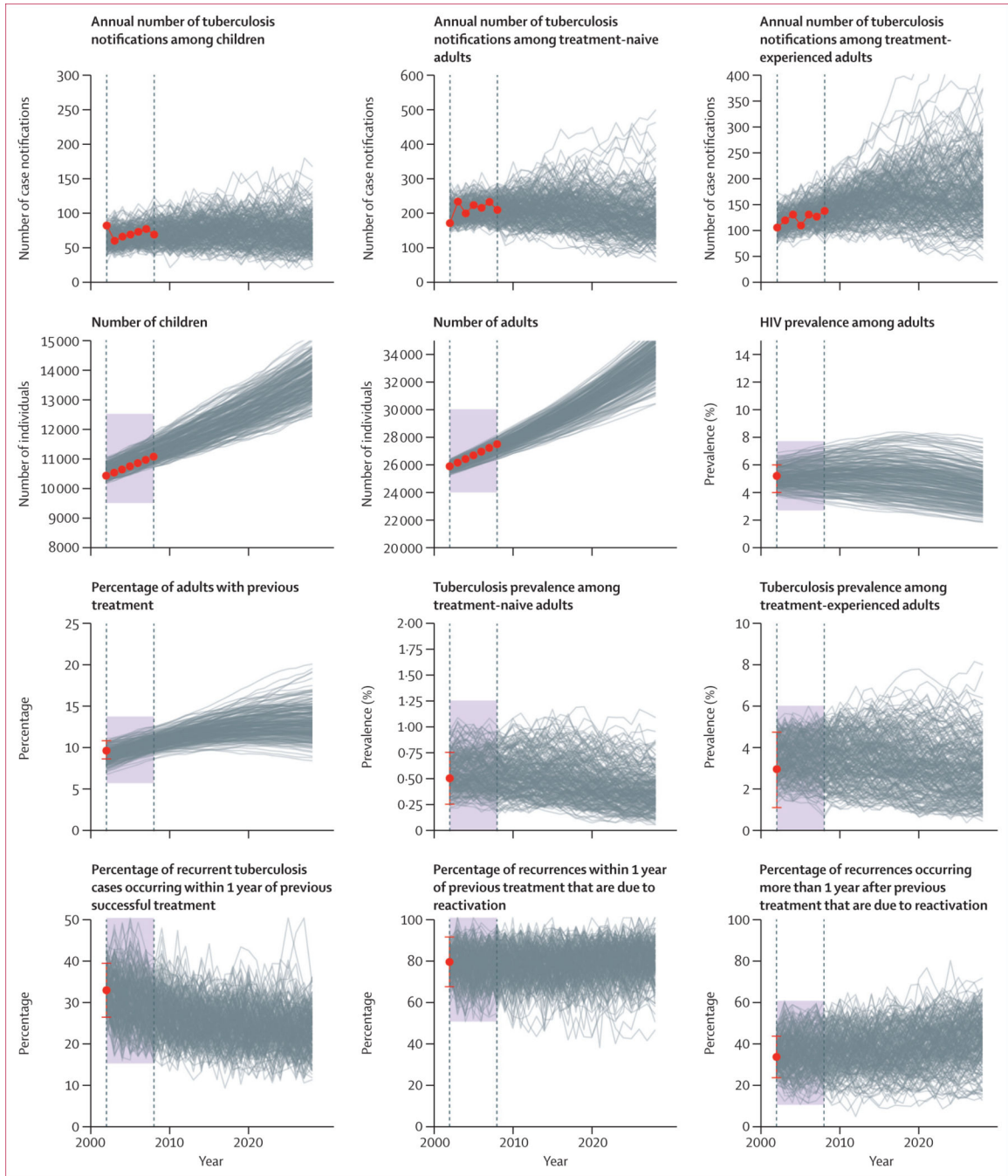


Figure 2: Overview of calibration targets and fitted model trajectories

Red dots denote the 12 calibration targets, with error bars representing 95% CIs where applicable; grey lines represent 250 simulated trajectories produced by the calibrated model; the simulated trajectories that fell outside of the feasible regions (shaded areas) were considered extremely unlikely and were eliminated by the calibration method. The interval between the dashed vertical lines shows the model calibration period (2002–08).

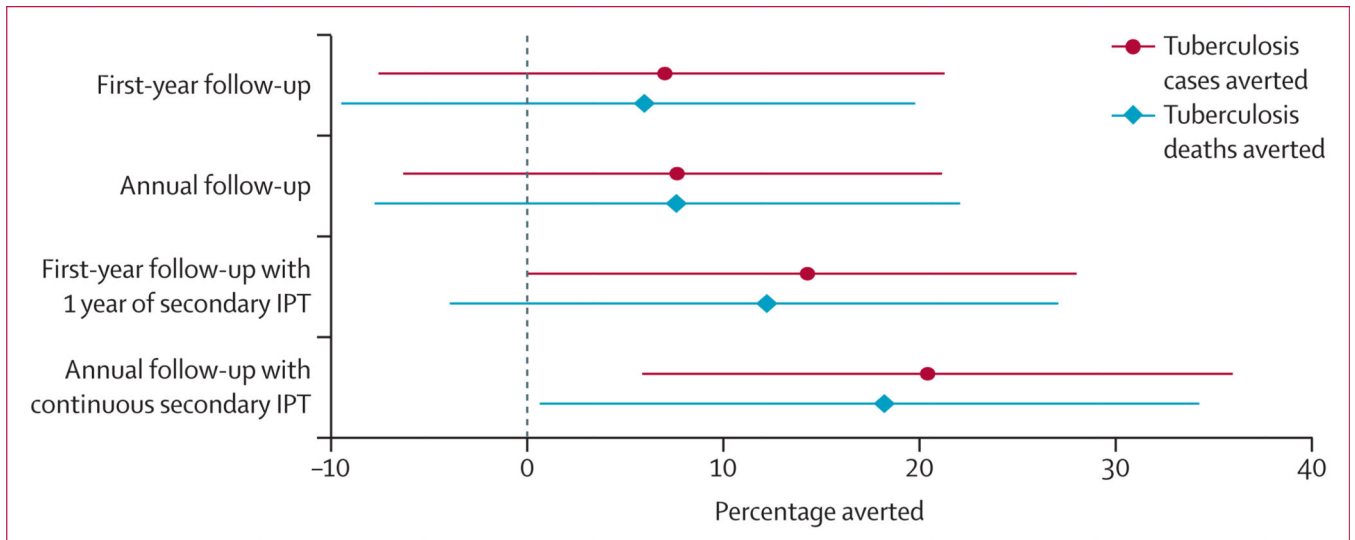


Figure 3: Incident tuberculosis cases and deaths averted under different scenarios of post-treatment follow-up and secondary preventive therapy among adults who completed tuberculosis treatment in a high-incidence setting in suburban Cape Town, 2019–28

Error bars denote 95% uncertainty intervals. IPT=isoniazid preventive therapy.

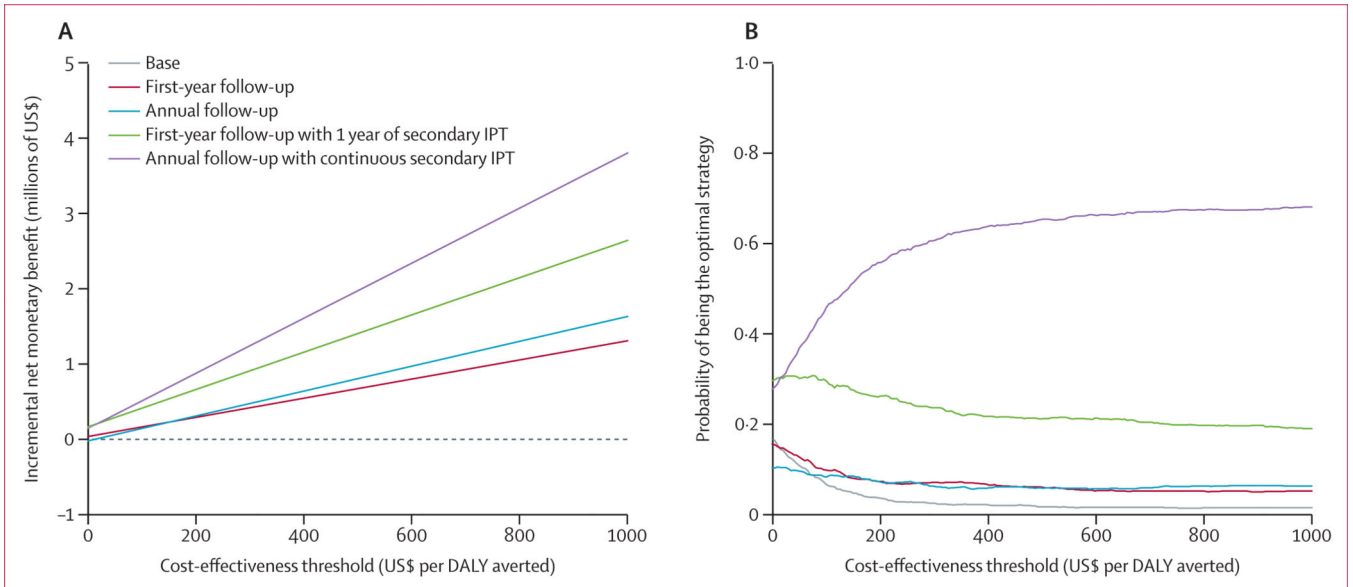


Figure 4: Cost-effectiveness analysis of modelled interventions

(A) Expected incremental net monetary benefit of each strategy with respect to the base-case strategy (for a given cost-effectiveness threshold, the optimal strategy is the one with the highest expected incremental net monetary benefit). (B) Probability that a strategy results in the highest net monetary benefit for various cost-effectiveness thresholds. IPT=isoniazid preventive therapy. DALY=disability-adjusted life-year.

Table 1:

Parameters for costs and disability weights

	Value	Source
Costs*		
Standard diagnostic evaluation (passive case finding)		
Clinic visit for initial diagnosis (excluding tests)	\$14.36	Sinanovic et al (2015) ²⁴
Xpert MTB/RIF (treatment naive only)	\$14.80	NHLS state price list ²⁵
<i>Mycobacterium tuberculosis</i> culture (treatment experienced only)	\$7.58	NHLS state price list ²⁵
Drug-susceptibility testing	\$14.99	NHLS state price list ²⁵
Smear microscopy	\$1.34	NHLS state price list ²⁵
Chest x-ray	\$23.84 (16.22–33.85)	Menzies et al (2012) ¹⁵
Tuberculosis or HIV treatment		
Drug-susceptible tuberculosis, full course	\$708.15 (477.30–939.00)	Vassall et al (2011), ²⁶ Pooran et al (2013) ²⁷
Multidrug-resistant tuberculosis, full course	\$5446.85 (3225.68–7669.57)	Vassall et al (2011), ²⁶ Pooran et al (2013) ²⁷
ART, per month	\$151.98 (122.47–184.44)	Menzies et al (2012) ¹⁵
Post-treatment follow-up examination		
Follow-up clinic visit	\$6.46	Sinanovic et al (2015) ²⁴
<i>Mycobacterium tuberculosis</i> culture screening for tuberculosis	\$7.58	NHLS state price list ²⁵
Secondary IPT		
IPT including monthly outpatient follow-up, per year	\$20.25 (11.97–34.11)	Kim et al (2018), ²⁸ Johnson et al (2018) ²⁹
Management of drug-induced liver injury, per event	\$35.86 (24.22–90.06)	Kim et al (2018) ²⁸
7-day hospitalisation costs per severe drug-induced liver injury event	\$813.05 (334.60–886.48)	Kim et al (2018) ²⁸
Disability weights		
Latent tuberculosis infection	0	..
Untreated active tuberculosis, HIV negative	0.333 (0.224–0.454)	GBD 2016 ³⁰
HIV positive, non-immunocompromised	0.012 (0.006–0.023)	GBD 2016 ³⁰
HIV positive, immunocompromised	0.428 (0.274–0.582)	GBD 2016 ³⁰
HIV positive, on ART	0.078 (0.052–0.111)	GBD 2016 ³⁰

Data in parentheses are uncertainty intervals. Price estimates for diagnostic tests were obtained from the NHLS price list and do not contain uncertainty intervals. NHLS=National Health Laboratory Service. IPT=isoniazid preventive therapy. ART=antiretroviral treatment. GBD=Global Burden of Disease Study.

* Published cost estimates were converted into US dollars and inflated to 2018 price levels.

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Incremental costs, life-years saved, DALYs averted during 10 years, and ICERs for each of the intervention scenarios compared with the base case

Table 2:

	Expected cost, thousands	Expected DALYs	Expected incremental cost, thousands*	Expected incremental DALYs averted*	ICER*
First-year follow-up with 1-year of secondary IPT	\$17 765 (10 419 to 27 039)	29 476 (18 283 to 45 819)	Cost saving
Annual follow-up with continuous secondary IPT	\$17 787 (10 419 to 27 129)	28 296 (17 665 to 43 464)	\$21 (-720 to 708)	1179 (-1769 to 4377)	\$18.2 [‡]
First-year follow-up	\$17 894 (10 373 to 27 272)	30 679 (18 760 to 48 808)	Dominated
Base case	\$17 926 (10 498 to 27 023)	31 947 (18 909 to 51 664)	Dominated
Annual follow-up	\$17 951 (10 516 to 27 168)	30 299 (18 661 to 48 344)	Dominated

Intervals in brackets denote 95% uncertainty intervals. Strategies are listed in increasing order of expected cost. ICERs are US\$ per DALY averted. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. IPT=isoniazid preventive therapy.

* Estimates of incremental cost, incremental DALYs averted, and ICER are calculated only for non-dominated and non-cost-saving strategies. For annual follow-up with continuous secondary IPT, these estimates are calculated with respect to the first-year follow-up with 1 year of secondary IPT strategy as reference.

[‡]The uncertainty interval of this ICER estimate cannot be calculated since the estimates of incremental costs and DALYs averted were negative for some model trajectories.