Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study

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Summary

Background In high-incidence settings, recurrent disease among previously treated individuals contributes substantially to the burden of incident and prevalent tuberculosis. The extent to which interventions targeted to this high-risk group can improve tuberculosis control has not been established. We aimed to project the population-level effect of control interventions targeted to individuals with a history of previous tuberculosis treatment in a high-incidence setting.

Methods We developed a transmission-dynamic model of tuberculosis and HIV in a high-incidence setting with a population of roughly 40 000 people in suburban Cape Town, South Africa. The model was calibrated to data describing local demography, TB and HIV prevalence, TB case notifications and treatment outcomes using a Bayesian calibration approach. We projected the effect of annual targeted active case finding in all individuals who had previously completed tuberculosis treatment and targeted active case finding combined with lifelong secondary isoniazid preventive therapy. We estimated the effect of these targeted interventions on local tuberculosis incidence, prevalence, and mortality over a 10 year period (2016–25).

Findings We projected that, under current control efforts in this setting, the tuberculosis epidemic will remain in slow decline for at least the next decade. Additional interventions targeted to previously treated people could greatly accelerate these declines. We projected that annual targeted active case finding combined with secondary isoniazid preventive therapy in those who previously completed tuberculosis treatment would avert 40% (95% uncertainty interval [UI] 21–56) of incident tuberculosis cases and 41% (16–55) of tuberculosis deaths occurring between 2016 and 2025.

Interpretation In this high-incidence setting, the use of targeted active case finding in combination with secondary isoniazid preventive therapy in previously treated individuals could accelerate decreases in tuberculosis morbidity and mortality. Studies to measure cost and resource implications are needed to establish the feasibility of this type of targeted approach for improving tuberculosis control in settings with high tuberculosis and HIV prevalence.

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See Comment page e361

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Introduction

Worldwide, an estimated 10·4 million people developed tuberculosis and 1·8 million deaths were attributable to the disease in 2015.[1] Substantial innovation in tuberculosis control is needed to reach the targets of the new global End TB Strategy, which aims to eliminate the disease by the year 2035.[2] The rates of tuberculosis decline must accelerate in settings with the highest disease incidence, some of which are located in southern Africa and are facing the dual burden of tuberculosis and HIV.[3] In these settings, the prevalence of untreated tuberculosis remains high, and conventional control approaches that rely on passive case finding can fail to identify infectious cases early enough to prevent transmission.[4–6]

Active case finding and wide-scale use of preventive therapy have been considered as enhanced activities for improving tuberculosis control, but these approaches require substantial investment.[7] Furthermore, disappointing results from community-randomised trials of population-wide case finding and preventive therapy interventions[8,9] have tempered enthusiasm for untargeted use of these interventions. It remains unknown whether targeting of case finding and preventive therapy to high-risk groups could be an effective approach for disease control in communities. The broader effect of a targeted approach depends on whether it is possible to prevent disease or reduce the duration of infectiousness among an easily identifiable subgroup that experiences a high relative risk of disease and is responsible for a substantial proportion of transmission.

One subgroup that might be attractive for targeted interventions is individuals with a history of previous tuberculosis treatment.[10] Studies from southern Africa show a high incidence of recurrent tuberculosis even

Research in context

Evidence before the study

Up to now, no empirical studies have been done of the population-level effect of interventions that aim to prevent recurrent disease or more rapidly detect tuberculosis in previously treated people. To establish whether population-based mathematical models have been employed to estimate the effect of tuberculosis interventions targeted to previously treated people, we did a PubMed search of relevant articles published in any language through March 7, 2017, using the search terms "(tuberculosis) AND (recurren* OR relapse OR reinfection OR re-infection OR re-treatment OR previous treatment) AND (model* OR simulation)". We also reviewed titles and abstracts of mathematical modelling studies identified through an earlier comprehensive systematic literature review of studies describing mathematical and economic modelling of tuberculosis published through March 30, 2013 (conducted by Tuberculosis Modeling and Analysis Consortium [TB-MAC]). While mathematical models have considered the effect of improving treatment outcomes as a means of reducing relapse and associated transmission, none has addressed preferential targeting of tuberculosis control interventions to former tuberculosis patients.

Added value of this study

We developed a transmission-dynamic mathematical model of the tuberculosis epidemic and calibrated it to epidemiological and demographic data from a setting with a high incidence of tuberculosis in suburban Cape Town, South Africa. High rates of recurrent tuberculosis and a high prevalence of tuberculosis in previously treated people have previously been reported from this setting. We presented estimates of the potential effect of tuberculosis interventions targeted to people who completed an episode of tuberculosis treatment and noted that targeted prevention and case finding efforts could yield substantial benefits for tuberculosis control at the population level.

Implications of all the available evidence

Our results suggest substantial public health potential for control interventions targeted towards individuals with a history of previous tuberculosis treatment in settings with a high disease incidence. In these settings, previously treated people are especially attractive for targeted control interventions because they remain at an increased risk of active tuberculosis after apparent cure, contribute substantially to onward transmission, and should be readily identifiable by national tuberculosis programmes. Efforts to establish the feasibility and costs of such targeted interventions are needed to establish their cost-effectiveness in tuberculosis and HIV endemic settings.

after previous successful treatment,[11–14] resulting from both endogenous reactivation and exogenous re-infection.[15] We recently documented a large burden of prevalent tuberculosis in previously treated adults in 24 high tuberculosis burden communities in southern Africa, consistent with the hypothesis that this risk group drives a substantial proportion of transmission in these settings.[16]

In this study, we used a transmission-dynamic model to project the effect of two targeted control interventions—targeted active case finding and secondary isoniazid preventive therapy—in individuals who previously completed tuberculosis treatment in a high-incidence setting in suburban Cape Town, South Africa. We estimated the effect of these targeted interventions on tuberculosis incidence, prevalence, and mortality over a 10-year period.

Methods

Modelling approach

We developed a stochastic compartmental transmission-dynamic model of the tuberculosis and HIV epidemic in a high-incidence setting of roughly 40 000 residents in suburban Cape Town, South Africa; the appendix provides details about the study setting. The tuberculosis component of our model followed the conventions of earlier models,[17–21] with additional structure to distinguish between individuals who were never treated for tuberculosis (treatment-naive) and those who were previously treated for tuberculosis (treatment-experienced; figure 1).

See Online for appendix

We adopted previous ranges for parameters that allowed for differential partial immunity against re-infection and differential reactivation rates in treatment-experienced and treatment-naive, latently infected individuals, and differential delay in detecting tuberculosis in individuals with and without history of tuberculosis treatment (table 1). We also allowed for higher infectiousness in treatment-experienced compared with treatment-naive tuberculosis cases, as suggested by local tuberculosis prevalence surveys that reported that treatment-experienced individuals with tuberculosis were more likely to report cough and more likely to be smear-positive than treatment-naive individuals without the disease.[16] Among individuals with incomplete tuberculosis treatment, we assumed that up to 20% remained infectious, consistent with findings from a retrospective cohort study done in the study setting.[26] Table 1 shows a list of key model parameters describing differences in treatment-naive and treatment-experienced individuals.

The HIV component of the model accounts for HIV infection, progression to a state of immunocompromised HIV infection, and antiretroviral treatment (ART;

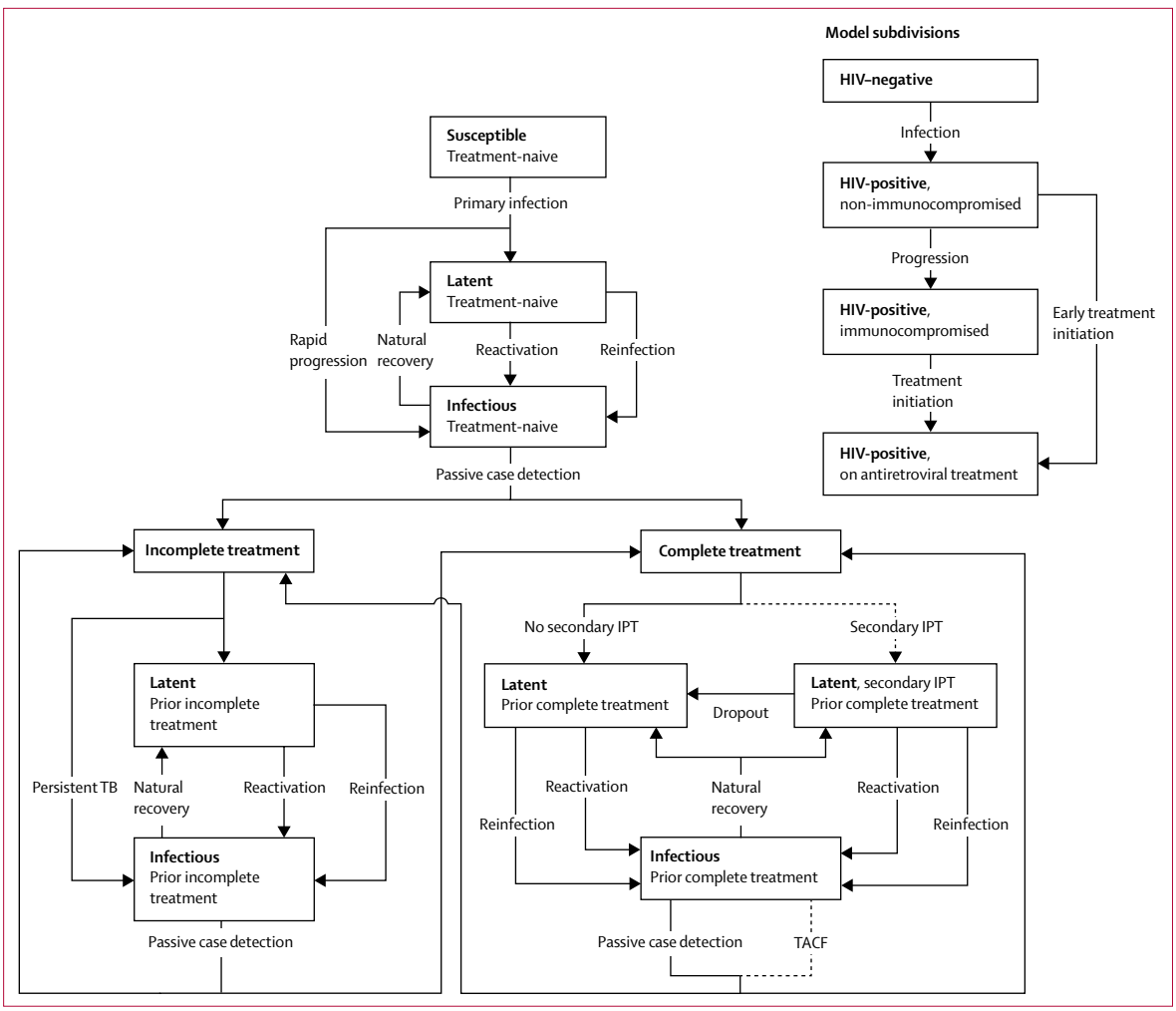

Figure 1: **Structure of the mathematical model**
Dashed arrows are modelled interventions, 2°IPT=secondary isoniazid preventive therapy. TACF=targeted active case finding. Mortality rates are not shown. The childhood subcomponent and corresponding transitions are shown in the appendix.

figure 1). We also implemented a model subcomponent for children aged 0–14 years. Additional model details including the subcomponent for children are described in the appendix.

Model initialisation and parameter estimation approach

We calibrated the model to data between 2002, and 2008; model simulations were initiated in 1992 to allow for a 10-year burn-in period. We specified an initial population size of 32 889 (25 903 adults and 10 427 children aged 0–14 years), informed by local census data and projections of population growth. The values of many parameters in tuberculosis and HIV co-epidemics models are not known with certainty. Therefore, we adopted a Bayesian calibration approach[27] to identify parameter sets that resulted in simulated trajectories with good fit to available epidemiological data (table 2). To implement this approach, we specified previous distributions for each parameter. Multiple parameters sets were randomly and independently selected from these distributions. We used each of these parameter sets to simulate epidemic trajectories, and measured the goodness-of-fit for each of these simulations against several calibration targets. These calibration targets were operationalised as the likelihood of recording the epidemiological data conditional on the simulated values. The appendix provides additional details about the likelihood function used and the methods to characterise the posterior parameter distributions. Figure 2 displays the fit of simulated trajectories against the calibration targets listed in table 2.

Interventions

We used the model to project the effect of two targeted interventions: targeted active tuberculosis case finding and secondary isoniazid preventive therapy. For

	Uniform prior distribution	Source
Relative infectiousness of treatment-experienced *vs* treatment-naive adults with active tuberculosis (ratio)	1·000 to 1·500	Assumption, based on findings from Marx et al[16]
Percentage reduction in susceptibility due to partial immunity (HIV-negative adults)		
During latent tuberculosis infection (tuberculosis treatment-naive)	0·370 to 0·870	Menzies et al,[20] Dye and Williams,[22] Dye and Espinal,[23] Cohen et al,[24] Dowdy and Chaisson[25]
After complete tuberculosis treatment	0·370 to 0·870	Assumption
After incomplete tuberculosis treatment	0·370 to 0·870	Assumption
Annual rate of tuberculosis reactivation (HIV-negative adults)		
Latent infection	0·0003 to 0·0024	Menzies et al,[20] Dye and Williams,[22] Dye and Espinal,[23] Cohen et al,[24] Dowdy and Chaisson[25]
Previously treated active tuberculosis	0·0003 to 0·048	Assumption
Baseline time (years) between onset of tuberculosis and detection (adults, independent of tuberculosis treatment history)		
Treatment-naive, HIV-negative adults and children	0·083 to 3·000	Menzies et al,[20] Dye and Williams,[22] Dye and Espinal,[23] Cohen et al,[24] Dowdy and Chaisson[25]
Treatment-experienced, HIV-negative adults	0·083 to 2·000	Assumption
HIV-positive adults	0·083 to 2·000	Assumption
Percentage tuberculosis treatment completion		
Treatment-naive adults	Time-varying	Estimated from tuberculosis treatment register database used in Marx et al.[14]
Adults after previous complete tuberculosis treatment	Time-varying	..
Adults after previous incomplete tuberculosis treatment	Time-varying	..
Probability of persistent active tuberculosis following incomplete tuberculosis treatment (adults, any HIV status)	0 to 0·200	Based on data from Marx et al[26]

***Table 1*: Selected model parameters describing differences between treatment-experienced and treatment-naive individuals**

	Value	95% confidence interval	Source
Total population (2002)			
Adults	25 903	..	City of Cape Town*
Children	10 427	..	City of Cape Town
Percentage tuberculosis treatment-experienced adults (2002)	9·70	8·70–10·90	den Boon et al[28]
Percentage tuberculosis prevalence, treatment-naïve adults (2002)	0·51	0·26–0·76	den Boon et al[28]
Percentage tuberculosis prevalence, treatment-experienced adults (2002)	2·99	1·14–4·77	den Boon et al[28]
Percentage HIV prevalence, adults (2002)	5·20	..	Assumption, based on data from Western Cape Department of Health[29]
Number of children who started tuberculosis treatment (2002–08)	Time-varying	..	Tuberculosis treatment register database used in Marx et al.[14]
Number of treatment-naive adults who started tuberculosis treatment (2002–08)	Time-varying	..	Tuberculosis treatment register database used in Marx et al.[14]
Number of treatment-experienced adults who started tuberculosis treatment (2002–08)	Time-varying	..	Tuberculosis treatment register database used in Marx et al.[14]

*Unpublished end-of-year estimates (community level) from the 2001 South Africa population census provided by the City of Cape Town.

***Table 2*: Overview of calibration targets and data sources**

targeted active case finding we assumed that all adults who previously completed tuberculosis treatment were re-evaluated for active tuberculosis on average once per year and referred for tuberculosis treatment. We modelled targeted active case finding by increasing the rate of diagnosis, resulting in reductions in the average diagnostic delay, and the expected period of infectiousness (figure 1).

For secondary isoniazid preventive therapy, in the first year of intervention, we modelled a catch-up treatment campaign that reached 90% of individuals with previously completed tuberculosis treatment in the population. Subsequent to this catch-up period, we assumed that secondary isoniazid preventive therapy was offered to individuals after the completion of a full course of tuberculosis treatment and that an average of 90% of individuals completing treatment were enrolled. Secondary isoniazid preventive therapy reduces the rate of tuberculosis reactivation and the risk of progression to disease following re-infection. We allowed the

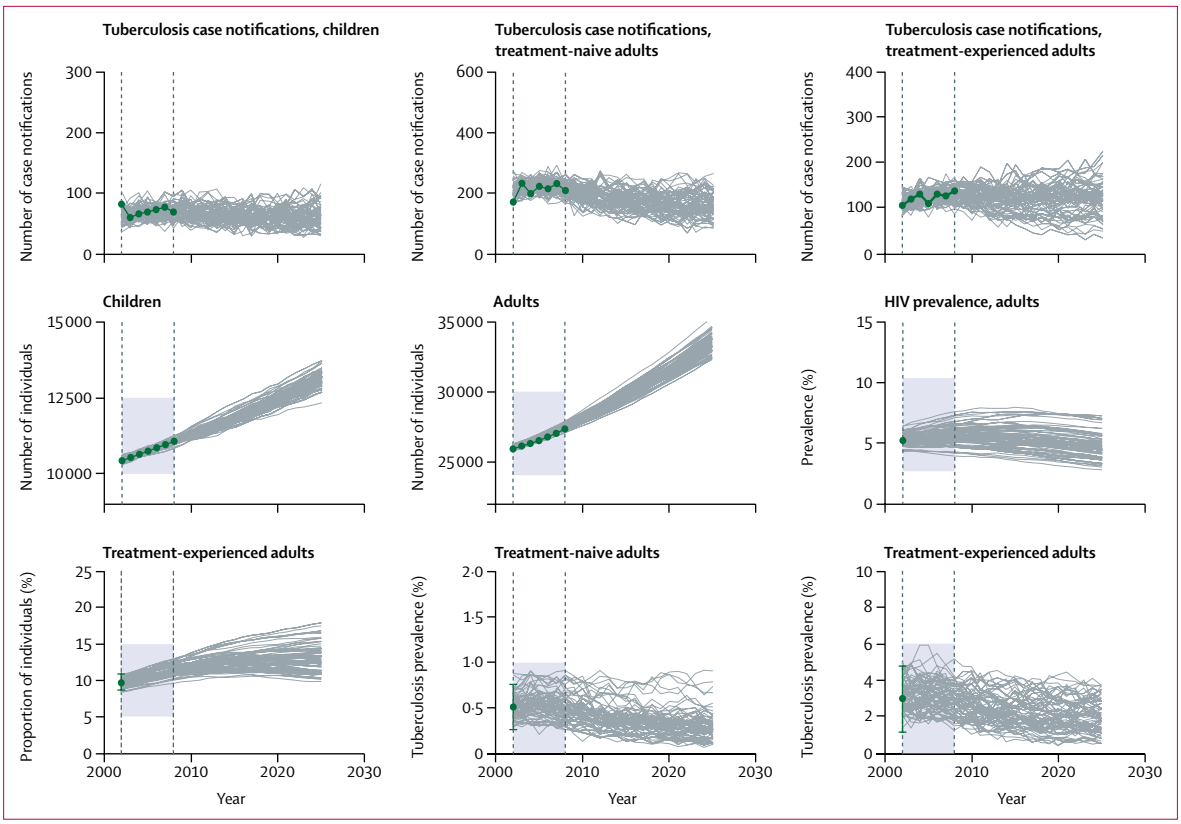

Figure 2: **Calibration targets and fitted model trajectories**

Green dots denote the nine calibration targets, with error bars representing 95% CIs where applicable; grey lines represent 100 simulated trajectories produced by the calibrated model; the simulated trajectories that fell outside 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).

preventive effects of secondary isoniazid preventive therapy to vary between 45% and 85%, a range informed by two previous studies.[30,31] We assumed that the relative effect of secondary isoniazid preventive therapy was independent of HIV infection, but the absolute effect associated with this intervention remains greater for those with HIV in view of their higher reactivation rate and risk of progression.

Secondary isoniazid preventive therapy was intended as a lifelong intervention but we assumed that, on average, 15% of people currently on secondary isoniazid preventive therapy drop out every year (resulting in an expected duration of 6·6 years of secondary isoniazid preventive therapy), and that the protective effect of secondary isoniazid preventive therapy does not extend beyond the cessation of treatment.[32]

Model outcomes and data analysis

We projected trends in tuberculosis incidence, prevalence, and mortality for 10 consecutive years—ie, 2016–25, under the baseline scenario and under two interventions scenarios: targeted active case finding alone and targeted active case finding plus secondary isoniazid preventive therapy. The effect of these interventions was defined as the cumulative number of tuberculosis cases and deaths averted during the 10-year period relative to the baseline scenario. The results are presented as the mean and 95% uncertainty intervals (the 2·5th and 97·5th percentiles of outcome values derived from 1000 simulated trajectories).

Sensitivity and scenario analyses

To assess how sensitive the projected effect of targeted active case finding and secondary isoniazid preventive therapy was to input parameters of our model, we calculated partial rank correlation coefficients.[33,34] The coefficients measure the correlation between an input parameter and the projected model outcome (number of incident tuberculosis cases averted) while adjusting for other parameters in the model. Additionally, we did the following types of scenario analyses: the projected effect of both targeted interventions under different periodicities of targeted active case finding (every 6 *vs* 12 and 24 months on average), different probabilities of secondary isoniazid preventive therapy enrolment (none *vs* 50%, 75%, and 90%), and different annual rates of drop-out from secondary isoniazid preventive therapy (5% *vs* 15% and 25%) were assessed. Furthermore, to provide additional insight on how well these targeted interventions might perform in

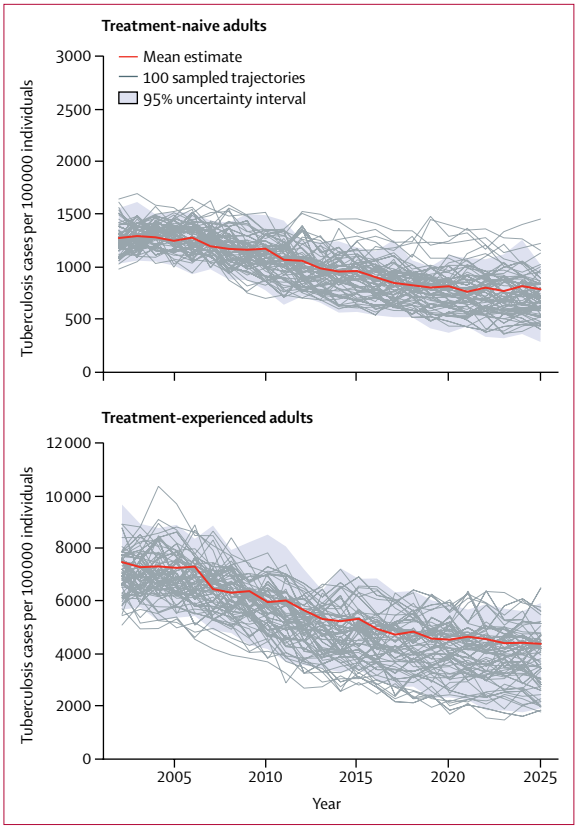

Figure 3: **Tuberculosis incidence among treatment-naive and treatment-experienced adults between 2003 and 2025, projected under the baseline scenario**

Mean estimates (bold red line) represent the mean prediction at any given year. The 100 trajectories shown represent a random subset of the 1000 trajectories selected for analysis.

communities with lower transmission rates, we report results for a hypothetical scenario where we reduced the force of infection by 50% relative to that in our study setting.

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

We estimated that in 2016, 13% (95% uncertainty interval [UI] 11–16) of all adults in this population had previously been treated for active tuberculosis. The estimated prevalence of untreated tuberculosis was 2·2% (95% UI 0·9–3·8) in treatment-experienced adults, about 5·5 times higher than that in treatment-naive adults (0·4%, 0·1–0·8).

The identified parameter posterior distributions suggested that HIV uninfected treatment-experienced people were, on average, 1·6 times (95% UI 0·4–3·4) more susceptible to re-infection than were HIV uninfected people who were latently infected and tuberculosis treatment-naive. HIV uninfected adults who had completed tuberculosis treatment experienced, on average, a 35 times (95% UI 3·2–104·0) higher rate of tuberculosis reactivation than people who were latently infected and tuberculosis treatment-naive. The appendix provides posterior distributions of key parameters of the natural history of tuberculosis for treatment-experienced and treatment-naive individuals.

In the absence of targeted interventions, we projected 4457 (95% UI 2741–6723) incident tuberculosis cases and 623 (328–1031) tuberculosis-associated deaths between 2016 and 2025. In this period, 1423 (95% UI 670–22 311) incident tuberculosis cases will occur among adults who had completed a prior episode of treatment, representing 32% (20–39) of all incident cases.

Figure 3 shows trends in tuberculosis incidence projected for treatment-naive and treatment-experienced adults over a 25-year period. Among treatment-naive adults, mean tuberculosis incidence per 100 000 people was 903 (95% UI 541–1147) in 2016 and was projected to decrease to 787 (287–1020) by 2025 (figure 3). Mean tuberculosis incidence among treatment-experienced adults was 4926 (95% UI 2949–6857) per 100 000 people in 2016, 5·5-times higher than among treatment-naive adults, and is expected to fall to 4353 (1874–5917) by 2025. The projected average annual decrease in tuberculosis incidence between 2016 and 2025 was 1·3% in treatment-naive and 1·2% in treatment-experienced adults.

With regards to the epidemiological effect of the interventions, our model suggests that annual targeted active case finding among individuals who had completed tuberculosis treatment would reduce the average duration of infectious disease in this group from 9·7 months (95% UI 2·3–17·5) to 5·0 months (1·9–7·1).

Figure 4 shows trends in tuberculosis incidence, prevalence, and mortality under the baseline scenario, under targeted active case finding alone, and under combined targeted active case finding and secondary isoniazid preventive therapy. The average annual decline in tuberculosis incidence between 2016 and 2025 relative to 2015 was 1·6% at baseline (no intervention), 3·0% under annual targeted active case finding, and 5·4% under annual targeted active case finding in combination with secondary isoniazid preventive therapy. Targeted active case finding alone would avert a total of 621 (95% UI 13–1355) incident tuberculosis cases between 2016 and 2025, 14% (0·4–28·0) of all incident tuberculosis cases projected under the baseline scenario. Over the same time period, targeted active case finding would avert a total of 138 (95% UI 13–296) tuberculosis deaths, 21% (2·5–39·0) of all tuberculosis deaths projected under the baseline scenario. The

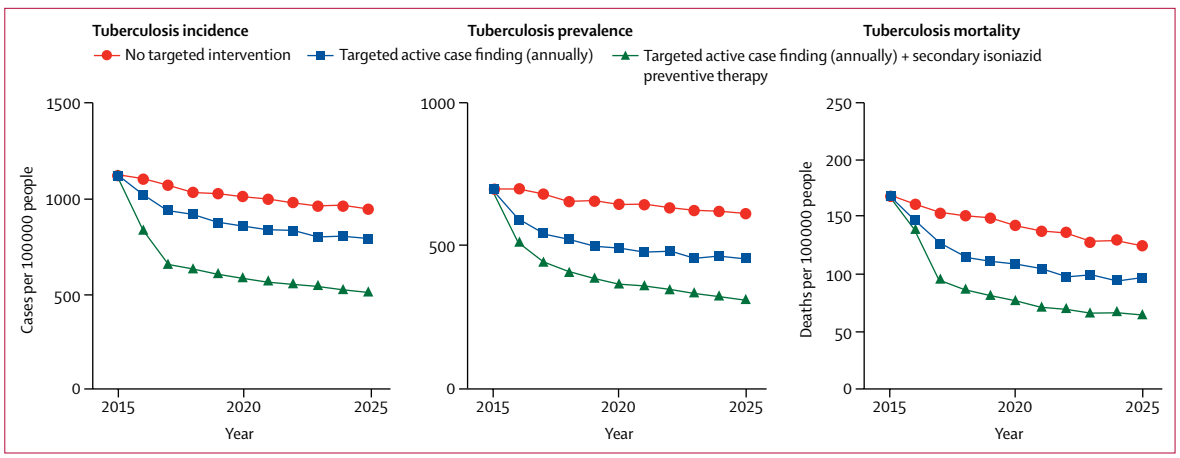

Figure 4: **Projected epidemiological effect of interventions targeted to individuals with a history of previous complete tuberculosis treatment in a high-incidence setting in suburban Cape Town, 2016–2025**

implementation of targeted active case finding in combination with secondary isoniazid preventive therapy would avert 1805 (95% UI 565–2952) incident tuberculosis cases between 2016 and 2025, 40% (21–56) of all incident tuberculosis cases projected under the baseline scenario. The combined targeted intervention would avert a total of 267 (95% UI 70–543) tuberculosis deaths, 41% (16–55) of all tuberculosis deaths projected under the baseline scenario.

Findings of sensitivity analysis showed that the projected effect of targeted active case finding and secondary isoniazid preventive therapy was most sensitive to the tuberculosis reactivation rate after completion of tuberculosis treatment, the time between tuberculosis disease onset and detection in the target group, the natural mortality rate in treatment-experienced relative to treatment-naive adults, and the efficacy of secondary isoniazid preventive therapy, among other parameters (appendix p 18). Lower periodicity of targeted active case finding (every 24 *vs* 12 months) and lower uptake of secondary isoniazid preventive therapy, as well as higher drop-out from secondary isoniazid preventive therapy, resulted in reduced effect (appendix p 19). In a hypothetical scenario in which we reduced the force of infection to 50% of the baseline value, we noted that annual targeted active case finding in combination with secondary isoniazid preventive therapy averted 34% (95% UI 16–54) of 2811 (1742–4503) incident tuberculosis cases and 36% (14–56) of 444 (231–760) tuberculosis deaths estimated at baseline (appendix p 19).

Discussion

In this study, we used a calibrated population-based mathematical model to project the effect of two types of interventions targeted to previously treated people in a tuberculosis high-incidence setting. Our data suggest that, if targeted active case finding and secondary isoniazid preventive therapy were introduced to complement existing tuberculosis control efforts in this setting, the burden of tuberculosis could be substantially reduced. Our study supports the idea that efforts for prevention and prompt detection of recurrent tuberculosis[35] could offer novel opportunities for tuberculosis control in settings of high tuberculosis incidence.

We propose these targeted control interventions during a time when untargeted efforts, such as population-wide enhanced case finding and household-based screening[8] and mass isoniazid preventive therapy[9] have yielded insufficient evidence of effect, and where novel approaches are urgently needed to reduce the burden of tuberculosis in communities most affected by the disease. Targeting control efforts to groups at high risk of tuberculosis could enable health services to make more efficient use of available resources. In many high tuberculosis prevalence settings, previously treated people can be easily identified and experience an elevated risk of tuberculosis,[16] therefore they might be an attractive target for focused interventions.

We project that within 10 years in this setting, a combination of targeted active case finding and secondary isoniazid preventive therapy could avert more than a third of incident tuberculosis cases and tuberculosis deaths. Targeted active case finding alone could have a notable effect on tuberculosis prevalence and mortality, but is expected to have a smaller effect on incidence; our simulations suggest that a marked effect of targeted active case finding is achieved when it can be coupled with secondary isoniazid preventive therapy. Our projections show that much of the effect of targeted active case finding and secondary isoniazid preventive therapy accrues in the first few years after their implementation. The diminishing effect over time suggests a saturation effect, which might imply that such targeted interventions could be used within an adaptive control strategy.[21]

Our study constitutes a first step towards better understanding the effect of interventions targeted to previously treated people in high-incidence settings.

However, several limitations must be noted. We applied our model to a specific setting with a high tuberculosis incidence and where high rates of recurrent tuberculosis due to relapse and re-infection had been previously reported.[12,14,36] We note that the effect of interventions targeted at previously treated people, which we project for this setting, might not be easily generalised to other high-incidence settings for several reasons. High rates of recurrent tuberculosis have been reported from several other high-incidence settings.[10,11,13] However, the population-level effect of targeted interventions will also depend on the size of the target group and their contribution to tuberculosis transmission in the population. In this particular setting, persistently high rates of incident tuberculosis have generated a large subgroup of people who had previously been treated for tuberculosis (about 10% of all adults) and who constitute a substantial proportion of the prevalent tuberculosis burden in the population (about 30% of prevalent cases).

Although our projections are consistent with the epidemiology of tuberculosis in other high-incidence communities in South Africa,[5,16] we expect interventions among previously treated people to be less effective in settings with lower tuberculosis incidence, and where a smaller proportion of the tuberculosis burden is attributable to former tuberculosis patients. For example, previously treated people accounted for 4·1% of the adult population and for 13% of prevalent tuberculosis cases in Lusaka, Zambia,[6] and for 1·5% and 15%, respectively, in Nigeria[37]—two settings with lower tuberculosis incidence than our study setting. Nonetheless, given that new approaches for tuberculosis control are most needed in areas where tuberculosis incidence has been persistently high, our results suggest that efforts to both prevent and rapidly detect and treat recurrent disease will produce important health benefits. In our scenario analysis, for which we lowered the force of infection by 50%, we noted that targeted active case finding in combination with secondary isoniazid preventive therapy reduced the expected number of incident tuberculosis cases and deaths to a lesser extent, but still averted a third of incident cases.

Differences in the prevalence of HIV in a population might influence the effect of interventions targeted to previously treated people in several ways. Communities with higher HIV prevalence might experience more recurrent tuberculosis given the elevated risk of re-infection with tuberculosis among HIV-infected individuals,[38] and thus benefit more from similar interventions. Survival after a first tuberculosis episode might be reduced among those not on ART; those on ART may be subject to more regular clinical follow-up that would limit the benefit of additional case finding interventions in this group.

The population-level effect of targeted active case finding and secondary isoniazid preventive therapy will be dependent upon existing patterns of passive health-care seeking behaviour. In settings where there are longer delays to diagnosis, additional interventions to more rapidly identify and treat recurrent cases would be more effectual, whereas in areas where individuals self-present quickly after onset of symptoms, we would expect more modest returns from investment in combined targeted active case finding and secondary isoniazid preventive therapy interventions. This is consistent with our sensitivity analysis, which showed that the time to passive tuberculosis detection among treatment-experienced adults correlated with the projected effect.

Uncertainty around parameters of the natural history of tuberculosis, particularly those determining re-infection, disease progression, and mortality among previously treated individuals, leads to substantial uncertainty in the modelled outcomes. To avoid bias towards higher estimates of effect, we used conservative prior ranges of parameters for treatment-experienced adults, similar to those among treatment-naive adults. Specifically, we did not enforce higher susceptibility, lower partial immunity, or higher disease progression risk among those with a history of previous tuberculosis, but did allow posterior parameter values derived from calibration to vary by treatment history. While posterior distributions of our model are consistent with treatment-experienced people being more likely to become productively re-infected than treatment-naive people, we did not explicitly model differential risk of exposure, which could also be a mechanism driving increased risk of recurrent disease.[39]

Our study is further limited by uncertainty around the efficacy of secondary isoniazid preventive therapy towards preventing recurrent tuberculosis. As shown in our sensitivity analysis, higher effects of secondary isoniazid preventive therapy would result in higher effect at the population level. Only two studies—a randomised trial[30] and a cohort study[31]—have assessed the effect of preventive therapy on recurrent tuberculosis. Both were limited in size and focused on people living with HIV. More available data from the field would improve our projections.

We used a simple mathematical model that does not enable us to explore specific intervention designs or consider many practical issues related to implementation. In particular, in our main analysis we assumed that interventions could be aggressively rolled out in these suburban settings—ie, that individuals with previous treatment could be effectively identified, enrolled, and screened for tuberculosis on average every 12 months, that 90% could be enrolled in secondary isoniazid preventive therapy upon completing treatment, and 15% would drop out from secondary isoniazid preventive therapy every year. Although we believe high coverage levels of the interventions could be achieved in this relatively small suburban setting, the effect of these interventions would clearly be lower if interventions were less vigorously applied or if some individuals were not reachable by the intervention.

In conclusion, our study provides impetus for further research to better understand the individual and population-level benefits of tuberculosis control interventions targeted at previously treated people. Studies and trials of the feasibility, safety, effect, and population-level effect of targeted active case finding and secondary isoniazid preventive therapy in previously treated people in high-incidence settings would be particularly useful. Other interventions to prevent recurrent tuberculosis such as adjuvant immunotherapy during tuberculosis treatment,[40] extending the duration of tuberculosis treatment for certain high-risk patients,[34] or post-treatment vaccination might be considered in the future. Further mathematical modelling, in which detailed costs of interventions are also included, would be useful for policy makers as they could establish whether such interventions are cost-effective and how investment in these approaches may compare with alternatives.

Contributors

FMM and TC conceived the study. FMM designed the study and developed the model structure. FMM and NB 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, revised the manuscript for important intellectual content, and approved the final version.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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APPENDIX

Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study

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Contents

S1. **Study setting**

Our study focuses on two adjacent suburban communities with a high tuberculosis (TB) burden in Cape Town, South Africa, covering an area of 3.4 km², and with a total population of 39,930 people in 2011. The internationally-endorsed TB control strategy (DOTS) was introduced in these communities in 1996. In the first year of the program, the rate of notified TB (all forms) was 1,340 cases per 100,000 residents.[1] Treatment success rates were initially low but increased rapidly and exceeded 80% amongst smear-positive TB cases in 2003.[2] However, persistently high annual rates of infection (estimated 3·7% in 1999 and 4·1% in 2005[2]) suggest that control measures, while improving individual outcomes, did not reduce transmission.[3] High local rates of recurrent TB after previous successful treatment[4-6] and after loss to follow-up from treatment[7] have also been reported; a lung health survey conducted in 2001 identified a high prevalence of undetected TB among previously treated residents.[8]

S2. **Model structure**

Childhood subcomponent: At birth, individuals enter the childhood subcomponent of the TB model (Figure S1) in the susceptible state, where they face a time-varying risk of infection, conditional on the force of infection which is dependent on the total number of infectious cases (adults and children) at time t. Upon primary infection, children either progress rapidly to infectious TB or reach a latently infected (non-infectious) state. Children may remain in the latent state, or their infection may reactivate and progress to infectious TB. They may also become reinfected and either rapidly progress to infectious disease or remain in the latent state. Upon infectious disease, children may move into a recovered state after being found and treated.
At any state, children may leave the model subcomponent into the main (adult) component at rates reflecting their age progression beyond 14 years (Figure S1). Specifically, children transit from the susceptible state into the adult treatment-naïve susceptible state, from the latently infected state into the adult treatment-naïve latently infected state, and from the infectious state into the adult treatment-naïve infectious state. We assume that treatment of childhood TB is always complete, thus, children in the recovered state move into the adult latently infected after complete treatment state.

Main component (adults): Treatment-naïve susceptible adults transition from the susceptible state to the latently infected state or directly into the infectious TB state after primary infection (Figure 1, main manuscript). Latently infected treatment-naïve adults may experience reactivation disease and transition into the infectious TB state. If reinfected while in the latently infected state, they may progress to infectious disease or remain latently infected. Treatment-naïve infectious adults may be identified and move into either of the two treatment compartments (treatment that is completed, treatment that is incomplete). The transition into these two treatment states is determined by the case finding rate and the proportion of complete treatment among new (i.e. previously treatment-naïve) TB cases estimated for the study setting. Individuals in the incomplete treatment state move into a treatment-experienced latently infected state or, upon continuous infectious TB, directly into the infectious TB state. From latent infection, they may progress to infectious TB either via disease reactivation or following reinfection. Upon complete treatment,

all adults transition to a latently infected state (i.e. consistent with many TB models, we assume that sterilizing cure is not achieved). We introduced two different states of latent infection for those individuals completing treatment. This allows us to distinguish whether individuals were enrolled in 2°IPT. Latently infected adults after complete treatment may progress to infectious disease either via reactivation or following reinfection. Similar to treatment-naïve infectious cases, cases occurring after either incomplete or complete treatment move back into the two treatment states at rates determined by case finding rates and the proportion of complete treatment estimated for the study setting. We implemented an active case finding rate, incremental to the passive case detection rate, to simulate TACF among adults who previously completed TB treatment. Individuals may exit the model due to death from any state, with additional excess mortality rates due to TB disease and HIV infection implemented in out model.

Model subdivisions for HIV co-infection and antiretroviral treatment: Upon HIV infection (Figure 1, main manuscript), HIV-negative adults transit into a non-immunocompromised HIV infected state, and upon progression, into an immunocompromised subdivision. Upon initiation of antiretroviral treatment (ART), individuals in either of the two prior HIV-positive subdivisions may transit into a fourth subdivision. Once initiated on ART, individuals were assumed to stay on ART. We did not model HIV in children.

S3. Model parameterization

Parameter values and ranges used in the model along with their sources are provided in the subsequent sections and Tables S1-S14. Rates shown are per year unless otherwise specified.

S3.1. Demographics

Estimates for demographic parameters are based on data from the Tygerberg sub-district of Cape Town in which the study setting is situated. We assumed a constant birth rate throughout the study period which was estimated by dividing the number of life births in the study setting reported for the year 2003[9] by the projected population in 2003 (Table S1). Estimates of the natural death rates among children 0-14 years of age were derived from unpublished mortality data (for 2011) provided by the City of Cape Town Directorate of Health (Table S1). In the absence of published data, we derived an estimate of the natural mortality rate among adults through calibration, allowing for a 1·0% annual population growth, consistent with unpublished census data for the study setting (Table S1). We assumed that the rate of natural death among treatment-experienced adults was between equal and 5-times higher compared to treatment-naïve adults. This range takes into account the possibility that mortality among former TB patients may be higher[10-12] due to a variety of factors such as lung impairment and chronic pulmonary disease[13] and an elevated risk of death from lung cancer[14] compared to individuals without a history of TB.
We assumed that on average, a child would be in contact with 40 other children and 9 adults per day, and an adult would be in contact with 15 adults and 9 children per day.[15]

Table S1: Model Parameters – Demographics

Measure	Value [Interval]	Source
Annual per capita birth rate	0·0229	[9]
Annual population growth	1·0%	estimated from unpublished census data, City of Cape Town
Annual natural death rate among children (<15 years)	0·0017	estimated from unpublished census data, City of Cape Town
Annual natural death rate among adults (≥15 years)	[0·0086-0·0096]	Experiments with the model
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	[1-6]	assumption

S3.2. Natural history of TB

Estimates for transition rates between TB-related states were derived from the published literature, where available (Tables S2-S5). In accordance with prior modeling studies, we considered that distant prior (latent) infection would lead to partial immunity reducing the risk of becoming reinfected (Table S4). Parameters for HIV-infected adults take into account that HIV alters the natural history of TB. Specifically, HIV-infected individuals are subject to a higher probability of fast progression to active TB following infection[16,17] (Table S2) and a higher probability of reactivation of latent infection[18] (Table S3).

We assumed that children were less likely to transmit TB by the ratio 0·12 [0·034-0·305] (compared to treatment-naïve adults) that was based on the probability of smear-positive TB among children and adults estimated in a recent meta-analysis.[19]

Table S2: Model Parameters - Probability of Fast Progression to Active TB Upon Primary Infection

Subgroup	Value [Interval]	Source
Adults, susceptible/treatment-naïve/HIV-	0·115 [0·09-0·14]	[20-22]
Adults, susceptible/treatment-naïve/HIV+/non-immunocompromised	0·33 [0·18-0·51]	[20-22]
Adults, susceptible/treatment-naïve/HIV+/ immunocompromised	0·805 [0·75-0·91]	[20-22]
Children, susceptible	0·118 [0·09-0·14]	estimated from [23]

Table S3: Model Parameters - Rate of Reactivation of latent TB infection

Subgroup	Value [Interval]	Source
Adults, latently infected/treatment-naïve/HIV-	0·001 [0·0003-0·0024]	[21,22,24,25]
Adults, latently infected/treatment-naïve/HIV+/non-immunocompromised	0·003 [0·001-0·006]	[21,22,24,25]
Adults, latently infected/treatment-naïve/HIV+/ immunocompromised	0·1275 [0·080-0·200]	[21,22,24,25]
Children, latently infected	0·001 [0·0003-0·0024]	assumption

Table S4: Model Parameters – Percent Reduction in Susceptibility due to Partial Immunity afforded by Prior Infection (treatment-naïve)

Subgroup	Value [Interval]	Source
Adults, latently infected/HIV-	0·65 [0·37-0·87]	[22,24,26-28]
Adults, latently infected/HIV+/non-immunocompromised	0·45 [0·23-0·68]	[22,24,26-28]
Adults, latently infected/HIV+/ immunocompromised	0·25 [0·14-0·39]	[22,24,26-28]
Children, latently infected	0·65 [0·37-0·87]	assumption

Table S5: Model Parameters – Rate of Natural Recovery among Undetected Active TB Cases

Subgroup	Value [Interval]	Source
Adults, infectious/treatment-naïve/HIV-	0·2 [0·15-0·25]	[21,22,26,29]
Adults, infectious/treatment-naïve/HIV+/non-immunocompromised	0·1 [0·06-0·16]	[21,22,26,29]
Adults, infectious/treatment-naïve/HIV+/ immunocompromised	0	[21,22,26,29]
Children, infectious	0·2 [0·15-0·25]	assumption

S3.3. Natural history of TB: Characteristics of treatment-experienced adults

The model allows for specific characteristics in the natural history of TB among individuals previously treated for the disease. In the absence of published estimates for many of these parameters, we specified prior parameter ranges and derived posterior parameter values through calibration (see below).

We assumed that TB treatment-experienced people were equally likely to be exposed to an individual with infectious TB in the community compared with treatment-naïve people. However, we allowed treatment-experienced adults to differ from treatment-naïve, latently infected adults in terms of their risk of becoming reinfected upon exposure. This was achieved through differential parameters for partial immunity towards reinfection among treatment-experienced and treatment-naïve people derived through calibration (same prior ranges; Table S6, see Table S4 for comparison). Rates of reactivation TB after complete and incomplete treatment were derived from calibration. To account for the possibility of higher reactivation rates after prior treatment for active TB, we specified prior parameter ranges for reactivation rates (Table S7) with the lower boundary being equal and the upper boundary 20-times higher than that for reactivation of distant prior latent infection (compare Table S3).

Based on findings from prevalence surveys that treatment-experienced cases of TB were more likely to be coughing and to be smear-positive[30], we assumed that treatment-experienced TB cases were equal to 1·5-times more likely to transmit TB compared to treatment-naïve TB cases in terms of their potential to transmit TB.

Individuals with incomplete treatment may continue to suffer from infectious disease. Based on data from a retrospective cohort study conducted previously in the study setting[7], we assumed that between 0 and 20% of those who were lost to follow-up during treatment remained infectious and thus moved directly into the compartment of infectious TB (Table S8). We assumed that recurrent cases of TB after previous complete or incomplete treatment were equally likely to transmit compared with cases of a first episode of TB.

Table S6: Model Parameters –Percent Reduction in Susceptibility due to Partial immunity after (previously treated) active TB

Subgroup	Value [Interval]	Source
Adults, latently infected/prior complete or incomplete treatment/HIV-	- [0·37-0·87]	22,24,26-28
Adults, latently infected/ prior complete or incomplete treatment/HIV+/non-immunocompromised	- [0·23-0·68]	22,24,26-28
Adults, latently infected/ prior complete or incomplete treatment/HIV+/ immunocompromised	- [0·14-0·39]	22,24,26-28

Table S7: Model Parameters – Rate of Reactivation of active TB after treatment

Subgroup	Value [Interval]	Source
Adults, prior complete treatment/HIV-	0·001 [0·0003-0·048]	see: S3.2
Adults, prior incomplete treatment/HIV-	0·001 [0·0003-0·048]	see: S3.2
Adults, prior complete treatment /HIV+/ non-immunocompromised	0·003 [0·001-0·12]	see: S3.2
Adults, prior incomplete treatment /HIV+/non-immunocompromised	0·003 [0·001-0·12]	see: S3.2
Adults, prior complete treatment/HIV+/ immunocompromised	0·1275 [0·080-4·00]	see: S3.2
Adults, prior incomplete treatment /HIV+/ immunocompromised	0·1275 [0·080-4·00]	see: S3.2

Table S8: Model Parameters – Probability of Persistent Active TB Following Incomplete Treatment

Subgroup	Value [Interval]	Source
Adults, prior incomplete treatment/any HIV-status	[0-0·20]	based on data from [7]

S3.4. TB case detection and treatment

Parameters for TB case detection rates were derived from calibration. We allowed for shorter times to detection assuming that people who had experienced TB treatment may seek care more promptly than those without previous TB treatment. We also assumed shorter times to detection for HIV-infected people (Table S9). The prior ranges used were informed by estimates of infectious disease duration before detection from previous studies in South Africa[31] and Zimbabwe[32].

We assumed that TB cases on treatment are non-infectious, i.e. they do not contribute to transmission. The duration of complete treatment among new and re-treatment cases was estimated from treatment register data (Table S10). We assumed that treatment is either complete or incomplete. Proportions of complete treatment among treatment-naïve and treatment-experienced people between 1996 and 2008 were estimated from the TB register database (Table S11). For the years following 2008, we randomly sampled treatment completion probabilities from a uniformly distributed range of probabilities specified by the 1996 to 2008 data.

Table S9: Model Parameters – Baseline time between disease onset and detection (years)

Subgroup	Value [Interval]	Source
Adults, infectious/treatment-naïve/HIV-	[0.083-3]	assumption
Adults, infectious/ or prior complete or incomplete treatment/HIV-	[0.083-2]	assumption
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+	[0.083-2]	assumption
Children, infectious	[0.083-3]	assumption

Table S10: Model Parameters – Duration of treatment (years)

Subgroup	Value [Interval]	Source
Adults, complete treatment	0·50 (0·47-0·57)	TB program data
Adults, incomplete treatment	0·42 (0·31-0·52)	TB program data

Table S11: Probability of complete treatment

Subgroup	Year							Source
	2002	2003	2004	2005	2006	2007	2008	
Adults, treatment-naïve	91 (87-94)	98 (95-99)	97 (94-98)	94 (90-96)	97 (94-98)	99 (96-99)	98 (96-99)	TB program data
Adults, prior complete treatment	92 (82-97)	92 (83-96)	92 (85-96)	94 (86-97)	88 (79-94)	94 (87-98)	89 (80-94)	TB program data
Adults, prior incomplete treatment	60 (37-79)	84 (60-95)	82 (56-94)	65 (40-84)	83 (58-95)	55 (33-75)	77 (46-93)	TB program data

S3.5. TB-associated (excess) mortality

We considered excess mortality rates (incremental to natural death rates) for two different groups, those with untreated active (infectious) TB (Table S12) and those on TB treatment (Table S13). We assumed that the excess mortality rate among HIV-infected non-immunocompromised adults and those HIV-infected on ART was similar to that among HIV-uninfected individuals. We further assumed that the excess mortality rate among untreated children was similar to that among HIV uninfected adults, and that children would not die from TB while on treatment (Table S13).

Table S12: Model Parameters – Rate of TB-associated (excess) mortality rate, untreated TB

Subgroup	Value [Interval]	Source
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV-	0·28 [0·20-0·37]	[21,22]
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/non-immunocompromised	0·28 [0·20-0·37]	assumption, see S3.5
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/ immunocompromised	0·80 [0·47-1·27]	[22,33,34]
Adults, infectious/prior treatment-naïve or prior complete or incomplete treatment/HIV+/ART	0·28 [0·20-0·37]	assumption, see S3.5
Children, infectious	0·28 [0·20-0·37]	assumption, see S3.5

Table S13: Model Parameters – Rate of TB-associated (excess) mortality rate, on TB treatment

Subgroup	Value [Interval]	Source
Adults, infectious (any subcategory)	0·056 [0·047-0·070]	estimated from TB program data
Children, infectious	0	assumption

S3.6. Natural history of HIV infection

Adults may be infected with HIV at any state in the model and move across the HIV subdivisions. The rate of HIV transmission in the adult population was derived from calibration. Rates of progression from non-immunocompromised to immunocompromised HIV and that of HIV-associated excess mortality among non-immunocompromised people were estimated from data published in the literature (Table S14). The distinction between *non-immunocompromised* and i*mmunocompromised* HIV-infected adults was made on the basis of CD4 count cut-off level of <350/mm³. HIV-associated excess mortality among immunocompromised people was calculated from estimates of survival time among HIV-infected people not on ART, assuming that 75% of these died from HIV-related causes other than TB. It was assumed that all children in the study setting were and remained HIV uninfected.

Table S14: Model Parameters – HIV-progression, HIV-associated mortality and effect of ART

Measure	Value [Interval]	Source
Annual rate of progression to immunocompromised HIV from non-immunocompromised HIV	0·142 [0·135-0·149]	[35]
Survival time of HIV-infected people not on ART (years)	10·2 [9·7-10·5]	[36]
Annual non-immunocompromised HIV-associated excess mortality rate	0·008 [0·005-0·012]	[22,37-41]
Annual immunocompromised HIV-associated excess mortality rate	0·068 [0·062-0·074]	calculated from estimated survival time, see above
Annual HIV-associated excess mortality rate while on ART	0·008 [0·005-0·012]	[22,37-41]
Effectiveness of ART in reversing effect of HIV on TB natural history (compared to the HIV+/non-immunocompromised state, excluding mortality)	0·69 [0·47-0·81]	[42]

S3.7. Initiation of antiretroviral treatment among HIV-infected adults

Assumptions were made to consider ART initiation among HIV-infected people in the study setting.

ART among immunocompromised adults not on TB treatment. We assumed a (historical) rate of ART initiation among immunocompromised people of 0·1 per year in 2004, the year of ART roll-out in Cape Town, and a linear increase of this rate to 0·3 per year in 2016, after which the rate remains constant.

ART among non-immunocompromised adults not on TB treatment. Considering the possibility that ART is also offered to HIV-infected people above a CD4 count of 350mm³, we assumed a rate of ART initiation among non-immunocompromised people of 0·02 per year in 2004, and a linear increase of this rate in the following years to 0·1 per year in 2016, after which the rate remains constant.

ART among immunocompromised and non-immunocompromised adults starting TB treatment. In line with national TB guidelines for South Africa[43], it was considered that ART is also initiated when HIV-infected people start TB treatment. We assumed that ART was initiated among 10% of HIV-infected individuals starting TB treatment. This proportions increases linearly to 30% until 2016 and remains constant at 30% in the following years. We assumed that ART was initiated at the start of TB treatment but was not initiated at a later stage during the course of TB treatment.

Figure S2 shows the projected coverage of ART among treatment-naïve and treatment-experienced HIV-infected adults (not on TB treatment) over time derived from our model.

S4. Simulation approach

Let $\lambda_{i \leftarrow i'}$ denote the rates at which members of age group $i \in \{\text{Ch, Ad}\}$ contact members of age group $i' \in \{\text{Ch, Ad}\}$ and let $H = \{I_{TN}, I_{TI}, I_{TC}\}$ denote the set of adult compartments with infectious status (TN = treatment-naïve, TI = prior incomplete treatment and TC = prior complete treatment). We used $N_{\text{Ch}}(t)$ and $N_{\text{Ad}}(t)$ for the number of children and adults at time t, and $N_h(t)$ for the number of population members in model compartment h.

We defined the force of infection for susceptible and latent children ($h \in \{S_{Ch}, L_{Ch}\}$) at time t as:

$$F_h(t) = \beta_h \left(\lambda_{Ch \leftarrow Ch} \frac{N_{I|Ch}(t)}{N_{Ch}(t)} + \sum_{h' \in H} \lambda_{Ch \leftarrow Ad} \frac{N_{h'}(t)}{N_{Ad}(t)} \right), \quad (1)$$

and for susceptible and latent adults ($h \in \{S_{TN}, L_{TN}, L_{TC}, L_{TI}\}$) as:

$$F_h(t) = \beta_h \left(\lambda_{Ad \leftarrow Ch} \frac{N_{I|Ch}(t)}{N_{Ch}(t)} + \sum_{h' \in H} \lambda_{Ad \leftarrow Ad} \frac{N_{h'}(t)}{N_{Ad}(t)} \right). \quad (2)$$

In above equations, β_h is the transmission parameter in compartments $h \in \{S_{Ch}, L_{Ch}, S_{TN}, L_{TN}, L_{TC}, L_{TI}\}$, where S denotes susceptible, and L denotes latently infected. Based on existing survey data,[15] we assumed $\lambda_{Ch \leftarrow Ch} = 4.7$, $\lambda_{Ch \leftarrow Ad} = \lambda_{Ad \leftarrow Ch} = 3.1$ and $\lambda_{Ad \leftarrow Ad} = 10.7$.

To generate epidemic trajectories for this model, we use Monte Carlo simulation. Consider a particular compartment Z in which members may depart due to J events. For example, members of L_{TN} compartment may leave due to reactivation of latent infection, reinfection, or natural death (i.e. $J = 4$) (see Figure 1). If the number of individuals in compartment Z at time t is $Z(t)$, then the number of individuals that leave this compartment due to events $j \in \{1,2,\dots,J\}$ follows a multinomial distribution with total counts of $Z(t)$ and probabilities $(p_0, p_1, p_2, \dots p_J)$, where $p_0 = 1 - e^{\sum_{j=1}^{J} \mu_j \Delta t}$ is the probability of not leaving the compartment Z during $[t, t + \Delta t]$, and $p_j = \frac{\mu_j}{\sum_{j=1}^{J} \mu_j \Delta t} e^{\sum_{j=1}^{J} \mu_j \Delta t}$ is the probability of leaving the compartment Z during $[t, t + \Delta t]$ due to event $j \in \{1,2,\dots,J\}$. Having obtained the realizations for the number of individuals who move from one compartment to another during $[t, t + \Delta t]$, we can then update the number of individuals in each compartment at time $t + \Delta t$.

Model Initialization

In the absence of published estimates for the prevalence of HIV, active TB and treatment-experienced individuals in the year 1992 (which marks the start of our simulation warm-up period), we determined the initial size of model compartments based on the following:

1. Prevalence of immunocompromised and non-immunocompromised HIV is sampled, respectively, from uniform distributions U [%3·5; %5·0] and U [%0·5; %1·0]. The prevalence of HIV-negative was set to 1 minus the sum of the above two samples.
2. Prevalence of the treatment-experienced within each HIV subgroup was sampled from the uniform distribution U [%6·0; %10·0]. The proportion of treatment-experienced with history of complete or incomplete TB treatment was set to be equal.
3. Within the HIV-negative subgroup:
    a. the prevalence of active TB was sampled from U [%0·4; %0·6] for treatment-naïve subgroup, and from U [%1·0; %10] for treatment-experienced subgroup;
    b. the prevalence of latent-TB among treatment-naïve was sampled from U [%40; %60].
4. Within non-immunocompromised HIV+ subgroup,
    a. the prevalence of active TB was sampled from U [%0·5; %2·0] for treatment-naïve subgroup and from U [%1·0; %10] for treatment-experienced subgroup;

   b. the prevalence of latent-TB among treatment-naïve was sampled from U [%55; %65]
5. Within immunocompromised HIV+ subgroup,
   a. the prevalence of active TB was sampled from U [%0·5; %2] for treatment-naïve subgroup and from U [%1·0; %10] for treatment-experienced subgroup;
   b. the prevalence of latent-TB among treatment-naïve was sampled from U [%55; %65]
6. Among children:
   a. Prevalence of active TB was sampled from U [%0·1; %1·0],
   b. Prevalence of latent-TB was sampled from U [%30; %70],
   c. Proportion recovered was sampled from U [%2·0; %10],
   d. Proportion susceptible was set to 1 minus the sum of the three samples above.

The initial size of compartments representing "on TB treatment" was assumed to be zero at the beginning of the simulation period.

S5. Model calibration

S5.1. Calibration data sources

We calibrated the model to data from three main sources. Population census data provided by the City of Cape Town were used to obtain estimates of the size and age structure (i.e. children vs. adults) of the population in the study setting. Data from a lung health prevalence survey conducted in the study setting in 2002[8] were used to derive estimates of the proportion of adults with a history of previous TB treatment and of the prevalence of TB among treatment-naïve and treatment-experienced adults in 2002. Estimates of the crude prevalence of TB by treatment history were calculated from[8] by dividing each, the number of treatment-naïve and treatment-experienced adults detected with culture-confirmed TB by the total number of adults in the survey sample multiplied by each, the proportion of treatment-naïve and treatment-experienced adults in the survey sample, respectively. Finally, we accessed TB treatment data from an electronic TB treatment register database that had been cleaned for duplicate entries and assessed for data consistency to obtain the number of new and previously treated TB cases registered for treatment in the study setting. The proportion of new and previously treated TB patients with complete TB treatment was estimated among new and previously treated TB cases by dividing the number of TB cases with documented treatment outcome success by the total number of patients with either treatment success or treatment default (loss to follow-up; defined by treatment interruption for at least two consecutive months) in that particular year (i.e. thereby excluding TB cases with treatment failure, transfer out or unknown treatment outcome from the denominator).

To estimate parameters of HIV transmission in the community, we calibrated the model to an estimated HIV prevalence of 5·2% (4·0%-6·0%) among adults living in the study setting in 2002, assuming that HIV-prevalence was half of the 2002 antenatal survey estimate for the greater Tygerberg East Sub-district.[44]

Calibration targets, data sources, and specified feasible ranges are shown in Tables S15-S17.

Table S15: Calibration Targets for 2002

Target	Value [Interval]	Source
Number of adults in the study setting	25,903	City of Cape Town*
Number of children in the study setting	10,427	City of Cape Town*
Percentage treatment-experienced, all adults	9·7 [8·7-10·9]	[8]
Percentage prevalent TB, treatment-naive adults	0·51 [0·26-0·76]	[8]
Percentage prevalent TB, treatment-experienced adults	2·99 [1·14-4·77]	[8]

* Unpublished end-of-year estimates (community level) from the 2001 South Africa population census provided by the City of Cape Town.

Table S16: Time-varying calibration targets (2002 -2008)

Target	Value [Interval]							Source
	2002	2003	2004	2005	2006	2007	2008	
Number of treatment-naïve adults starting TB treatment	172	234	200	224	216	233	210	TB treatment register database [6]
Number of treatment-experienced adults starting TB treatment	105	119	130	109	130	126	137	TB treatment register database [6]
Number of notified TB cases, children	82	60	66	69	73	77	69	TB treatment register database [6]
Percentage HIV-positive, all adults	5·2 [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	- [4-6]	estimated from [44]

Table S17: Specified feasible ranges for calibration targets

Target	Feasible Range
Number of adults in the study setting	24,000 - 30,000
Number of children in the study setting	10,000 - 12,500
Percentage treatment-experienced, all adults	5 - 15
Percentage prevalent TB, treatment-naive adults	0 - 1·0
Percentage prevalent TB, treatment-experienced adults	0 - 6·0
Percentage HIV-positive, all adults	2·6 - 10·4

S5.2. Calibration procedure

The goal of model calibration is to use the observations gathered throughout the epidemic to reduce the uncertainty around model input parameters. We used a Bayesian calibration approach[45] where the likelihood of observations in Tables S15-16 are measured using the probability distributions described below. For a given simulated trajectory:

1. The likelihood of the observed adult population size in each year (Table S15) is measured by a normal distribution with mean equal to the adult population size generated by the simulated trajectory. In the absence of sampling distribution for the estimated population size, we approximated the standard division of these normal distributions by $0.05N_t/z_{1-\alpha/2}$ where N_t is the adult population size in year t and $z_{1-\alpha/2}$ is the $(1-\alpha/2)$ upper critical value of a standard normal distribution. We chose $\alpha = 0.05$ ($z_{1-0.05/2}$=1.96). The likelihood of observed population of children is measured using the same approach.
2. The likelihood of observed prevalence of treatment-experienced adults is measured by a binomial distribution where the number of trials is set to the number of population-based survey participants and the probability of success is set to the prevalence of treatment-experienced adults projected by the simulated trajectory. We approximate the number of survey participants from the reported confidence intervals $[L, U]$ (see Table S15) by solving $\frac{U-L}{2} = z_{1-\alpha/2}\sqrt{\frac{1}{n}\hat{p}(1-\hat{p})}$ for n, where $\hat{p}$ is the estimated prevalence provided in Table S15. The likelihood of observed HIV prevalence, percentage prevalent TB among treatment-naive adults and percentage prevalent TB among treatment-experienced adults are calculated using the approach described above.
3. The likelihood of the observed number of treatment-naïve adults starting TB treatment in each year (Table S16) is measured by a binomial distribution where the number of trials is set to the population size of treatment-naïve adults produced by the simulated trajectory and the probability of success is set to proportion of treatment-naïve adults who started TB treatment in that year of the simulation. The likelihoods of the observed number of treatment-experienced adults starting TB treatment and the number of notified cases of pediatric TB are calculated in the same way.

S6. Outcome definitions and data analysis

We projected trajectories of TB incidence, prevalence and mortality. Incident TB was defined in our model as the number of adults and children, regardless of treatment history and HIV status, who transitioned into any of the infectious TB compartments; individuals remaining infectious after incomplete treatment were not counted in incidence estimates. Prevalent TB was defined as the number of adults and children in any of the infectious compartments at a particular point in time. TB mortality was defined as the number of adults and children who died while either in any of the infectious or TB treatment compartments.

Best estimates of incidence, prevalence and mortality were derived by calculating the mean of values projected from the 1,000 sampled model trajectories. We calculated 95% percent uncertainty intervals representing the 2·5th and 97·5th percentiles of the 1,000 sampled trajectories. The impact of both interventions was defined as the cumulative number of incident

and prevalent TB cases and TB deaths that was averted in the population (compared to the baseline scenario of no targeted interventions) during a 10-year period (2016 - 2025).

S7. Posterior estimates for the natural history of TB by history of TB treatment

Posterior estimates for parameters describing the natural history of TB among treatment-experienced and treatment-naïve people are shown in Figures S3-S6.

S8. Sensitivity and scenario analyses

Detailed results for the sensitivity analysis as described in the main document are shown in Table S18 and Figure S7(A). Results from additional scenario analyses are illustrated in Figures S7(B und C), S8 and S9.

Table S18: Sensitivity analysis: Partial Rank Correlation Coefficients (PRCC)

Model parameter	PRCC	P-Value
Demographics		
Annual per capita birth rate	-0·042	0·176
Annual natural death rate among children (<15 years)	-0·126	<0·001
Annual natural death rate among adults (≥15 years)	0·001	0·977
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	-0·459	<0·001
Probability of Fast Progression to Active TB Upon Primary Infection		
Adults, susceptible/treatment-naïve/HIV-	-0·273	<0·001
Adults, susceptible/treatment-naïve/HIV+/non-immunocompromised	0·033	0·305
Adults, susceptible/treatment-naïve/HIV+/immunocompromised	-0·064	0·045
Children, susceptible	0·043	0·175
Rate of Reactivation of latent TB infection		
Adults, latently infected/treatment-naïve/HIV-	-0·220	<0·001
Adults, latently infected/treatment-naïve/HIV+/non-immunocompromised	-0·109	0·001
Adults, latently infected/treatment-naïve/HIV+/immunocompromised	0·088	0·006
Children, latently infected	0·011	0·739
Percent Reduction in Susceptibility due to Partial Immunity afforded by Prior Infection (treatment-naïve)		
Adults, latently infected/HIV-	0·277	<0·001
Adults, latently infected/HIV+/non-immunocompromised	0·076	0·016
Adults, latently infected/HIV+/immunocompromised	0·002	0·945
Rate of Natural Recovery among Undetected Active TB Cases		
Adults, infectious/treatment-naïve/HIV-	0·036	0·258
Adults, infectious/treatment-naïve/HIV+/non-immunocompromised	-0·035	0·269
Adults, infectious/ prior complete treatment/HIV-	-0·082	0·010
Adults, infectious/prior complete treatment/HIV+/immunocompromised	-0·032	0·315
Adults, infectious/ prior incomplete treatment/HIV-	0·107	0·001
Adults, infectious/prior incomplete treatment/HIV+/immunocompromised	-0·035	0·269
Children, infectious	-0·216	<0·001
Percent Reduction in Susceptibility due to Partial immunity after (treated) active TB		
Adults, latently infected/treatment-experienced/HIV-	-0·041	0·200
Adults, latently infected/ treatment-experienced/HIV+/non-immunocompromised	0·115	<0·001
Adults, latently infected/ treatment-experienced/HIV+/immunocompromised	-0·076	0·017
Adults, latently infected/ prior complete or incomplete treatment/HIV+/ART	-0·059	0·064

Rate of Reactivation of active TB after treatment		
Adults, prior complete treatment/HIV-	0·507	<0·001
Adults, prior incomplete treatment/HIV-	0·114	<0·001
Adults, prior complete treatment /HIV+/non-immunocompromised	0·008	0·805
Adults, prior incomplete treatment /HIV+/non-immunocompromised	0·121	<0·001
Adults, prior complete treatment/HIV+/ immunocompromised	-0·112	<0·001
Adults, susceptible/ prior incomplete treatment /HIV+/immunocompromised	0·134	<0·001
Probability of Persistent Active TB Following Incomplete Treatment		
Adults, prior incomplete treatment/HIV-	-0·061	0·055
Adults, prior incomplete treatment/HIV+/non-immunocompromised	0·130	<0·001
Adults, prior incomplete treatment/ HIV+/immunocompromised	0·108	0·001
Adults, prior incomplete treatment/ HIV+/ART	0·092	0·004
Baseline time between disease onset and detection (years)		
Adults, infectious/treatment-naïve/HIV-	0·018	0·575
Adults, infectious/treatment-naïve/HIV+/non-immunocompromised	0·227	<0·001
Adults, infectious/treatment-naïve/HIV+/immunocompromised	0·065	0·041
Adults, infectious/treatment-naïve/HIV+/ART	-0·064	0·043
Adults, infectious/prior complete treatment/HIV-	0·508	<0·001
Adults, infectious/prior complete treatment /HIV+/non-immunocompromised	-0·233	<0·001
Adults, infectious/prior complete treatment /HIV+/immunocompromised	-0·021	0·502
Adults, infectious/prior complete treatment /HIV+/ ART	0·118	<0·001
Adults, infectious/prior incomplete treatment/HIV-	-0·030	0·350
Adults, infectious/prior incomplete treatment /HIV+/non-immunocompromised	-0·011	0·729
Adults, infectious/prior incomplete treatment /HIV+/immunocompromised	0·068	0·033
Adults, infectious/prior incomplete treatment /HIV+/ ART	0·038	0·232
Children, infectious	0·104	0·001
Rate of TB-associated (excess) mortality rate, untreated TB		
Adults, infectious/any or no treatment history/HIV-	0·093	0·003
Adults, infectious/any or no treatment history/HIV+/non-immunocompromised	-0·090	0·004
Adults, infectious/any or no treatment history/HIV+/ immunocompromised	0·254	<0·001
Adults, infectious/any or no treatment history/HIV+/ART	-0·085	0·007
Rate of TB-associated (excess) mortality rate, on TB treatment		
Adults, infectious/any or no treatment history/HIV-	0·028	0·376
Adults, infectious/any or no treatment history/HIV+/non-immunocompromised	0·018	0·560
Adults, infectious/any or no treatment history/HIV+/immunocompromised	0·374	<0·001
Adults, infectious/any or no treatment history /HIV+/ART	-0·131	<0·001
HIV-progression, HIV-associated mortality and effect of ART		
Annual rate of progression to immunocompromised HIV from non-immunocompromised HIV	0·102	0·001
Annual non-immunocompromised HIV-associated excess mortality rate	0·035	0·270
Annual immunocompromised HIV-associated excess mortality rate	0·095	0·003
Annual HIV-associated excess mortality rate while on ART	0·223	<0·001
Effectiveness of ART in reversing effect of HIV on TB natural history (compared to the HIV+/non-immunocompromised state, excluding mortality)	-0·061	0·054
Efficacy of 2°IPT		
Reduction in TB reactivation rate	0·280	<0·001
Reduction in probability of fast progression to TB after reinfection	0·019	0·558
Susceptibility to infection		
Ratio: susceptible Children to HIV-negative, susceptible adults	0·358	<0·001
Ratio: latently infected children to HIV-negative, susceptible adults	0·143	<0·001
Infectiousness		
Adults, treatment-naïve, HIV-	-0·339	<0·001
Adults, treatment-naïve, HIV+/non-immunocompromised	0·109	0·001
Ratio: adults, HIV+/immunocompromised to adults, HIV+/non-immunocompromised	-0·003	0·926
Ratio: adults, HIV+/on ART to adults, HIV+/non-immunocompromised	0·050	0·117
Ratio: children to treatment-naïve adults	-0·087	0·006
Ratio: adults, treatment-experienced to adults, treatment-naïve	0·043	0·172

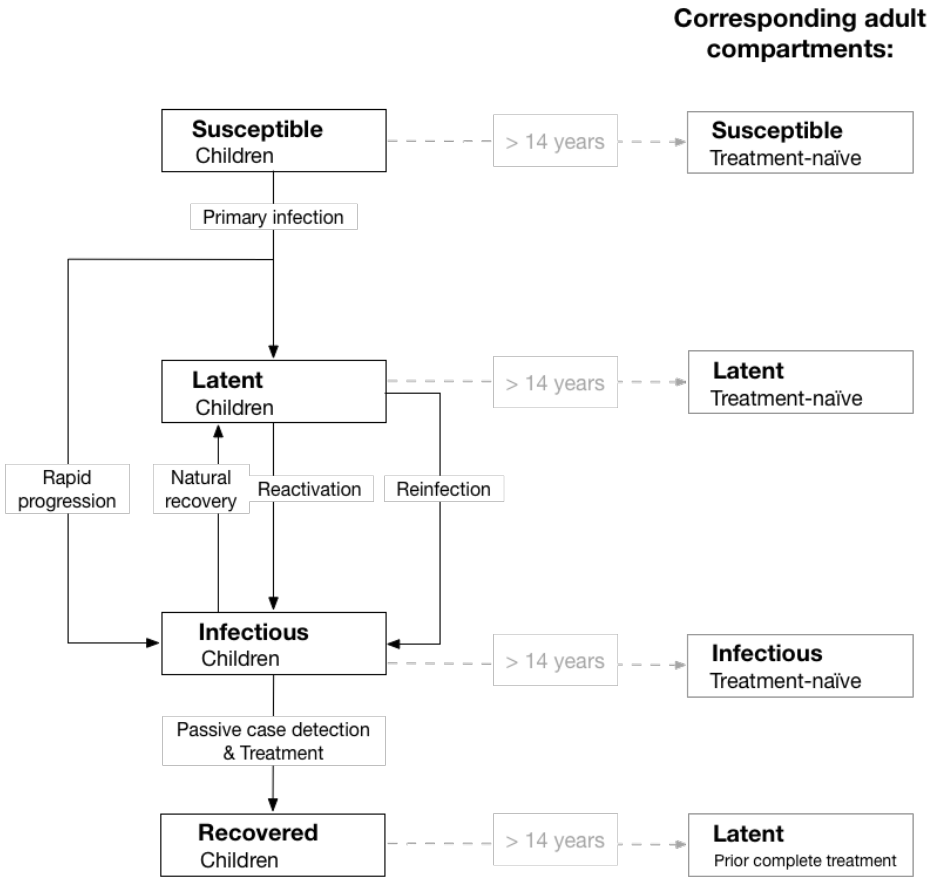

Figure S1: Model subcomponent for children aged 0-14 years
Not shown are mortality rates; grey dashed arrows indicate age transition into the corresponding compartments of the adult component of the model (see Figure 1, main manuscript)

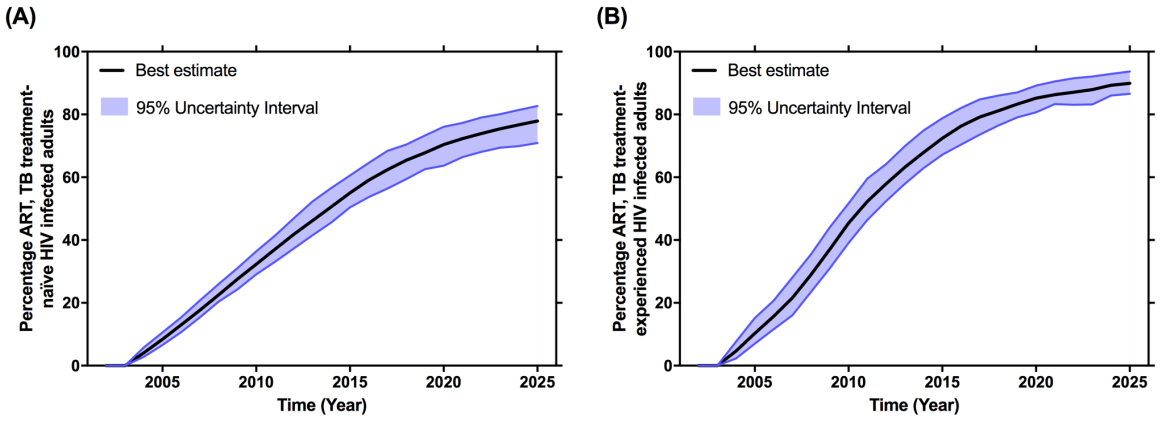

Figure S2. Projected coverage of antiretroviral treatment (ART) among HIV infected adults, 2004 - 2025
Panel A: treatment-naive adults
Panel B: treatment-experienced adults

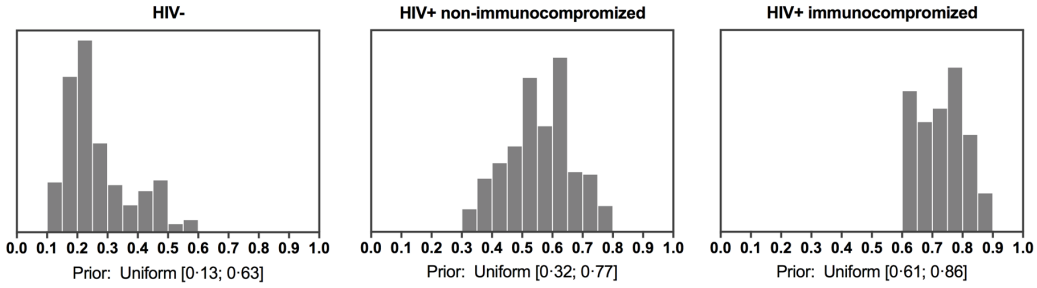

Figure S3: Posterior distribution for the relative susceptibility to reinfection among <u>treatment-naïve</u>, latently infected adults using the susceptibility to primary infection among treatment-naïve, susceptible adults as a reference (assuming partial immunity afforded by prior infection)

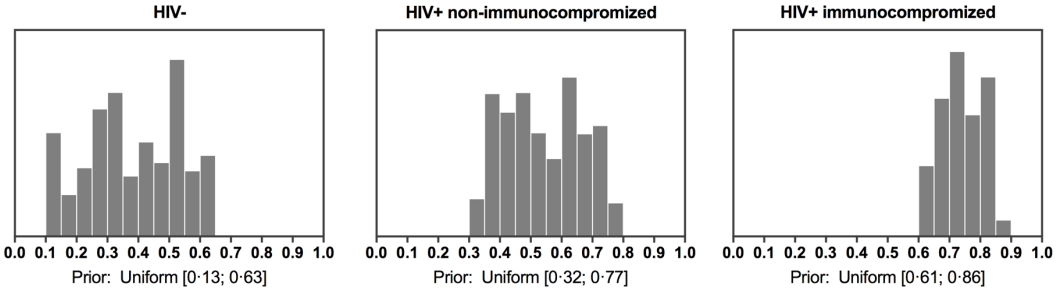

Figure S4: Posterior distribution for the relative susceptibility to reinfection among <u>treatment-experienced</u> adults using the susceptibility to primary infection among treatment-naïve, susceptible adults as a reference (assuming partial immunity afforded by prior infection)

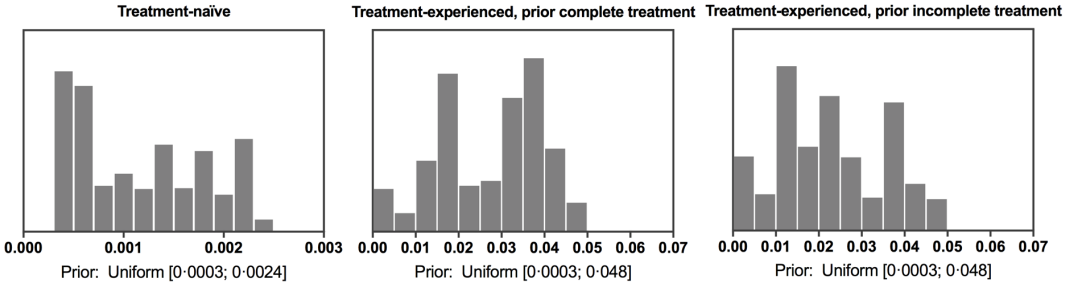

Figure S5: Posterior distribution for the annual reactivation rate among HIV-negative latently-infected adults, by history of previous TB treatment

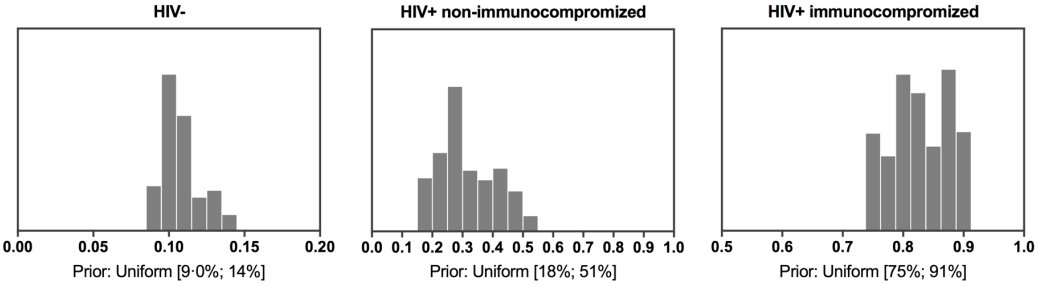

Figure S6: Posterior distribution for the probability of fast progression to active TB upon primary infection by status of HIV co-infection, treatment-naïve, susceptible adults

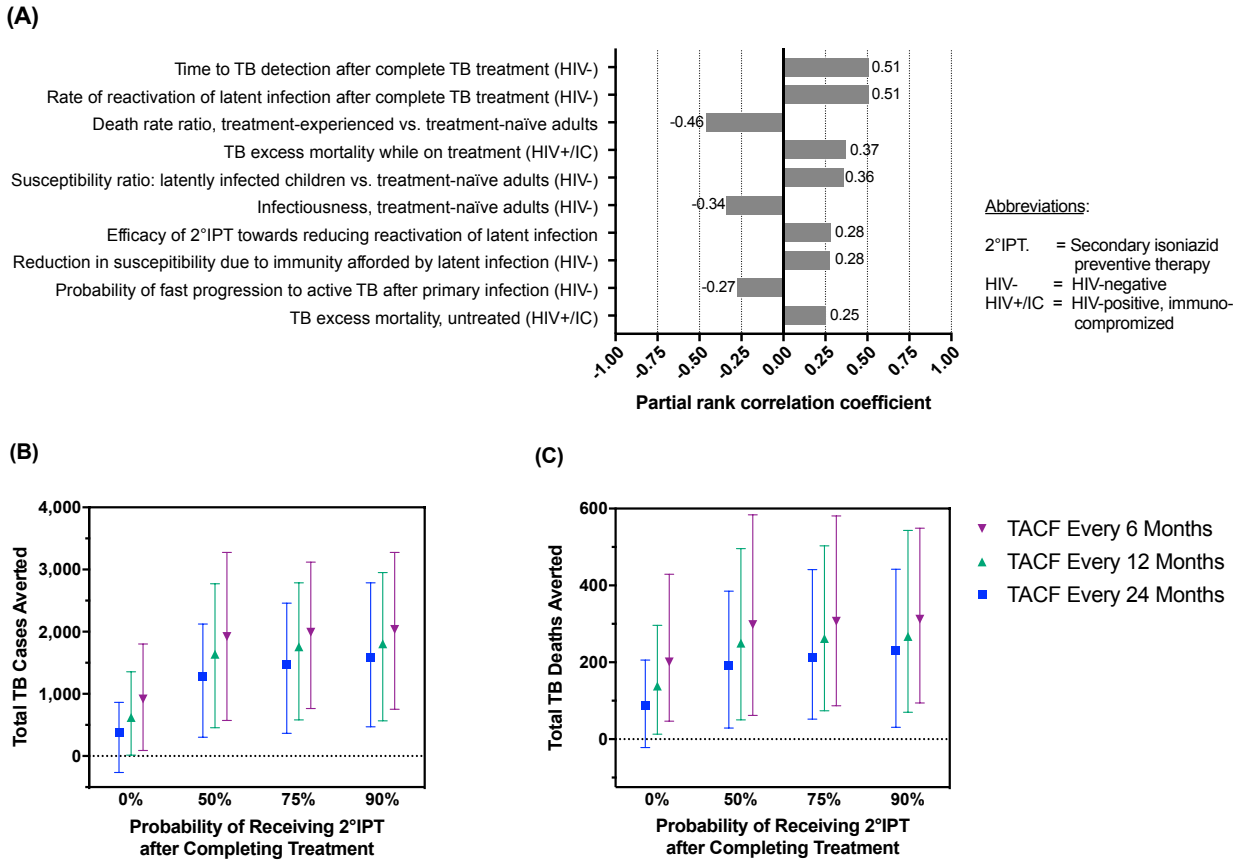

Figure S7: Sensitivity and scenario analyses: Partial rank correlation coefficients for the top 10 model parameters with the greatest influence towards the number of TB cases averted through TACF and 2°IPT interventions (5A); expected number of TB cases averted (5B) and deaths averted (5C) as the result of TACF and 2°IPT interventions with respect to the baseline scenario for varying TACF intervals and probabilities of enrollment in 2°IPT after the completion of TB treatment. Note that the space between data points for different series (5B/5C) is intended to improve readability and is not proportional to scale of the x-axis; error bars represent 95% uncertainty intervals.

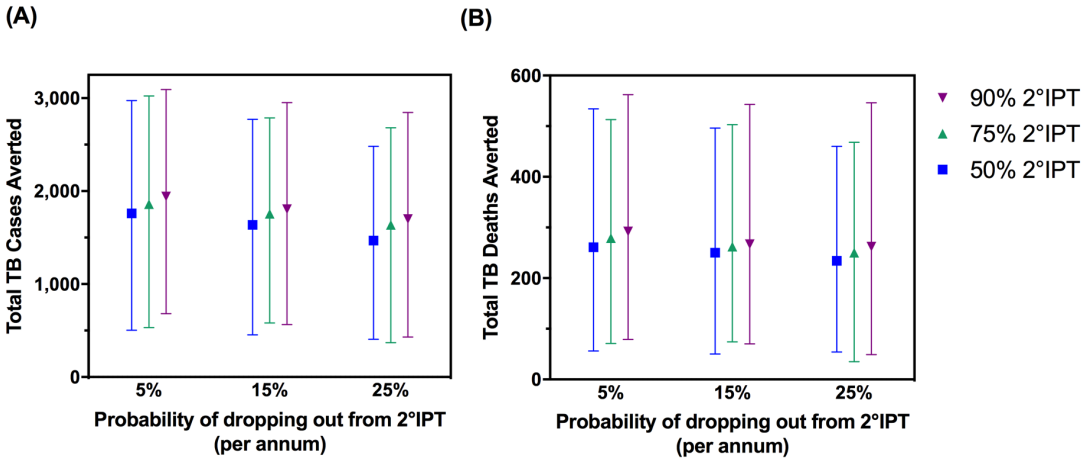

Figure S8: Expected number of TB cases (Fig. A) and deaths (Fig. B) averted with respect to the baseline scenario as the result of annual TACF and 2°IPT when the probability of annual 2°IPT drop-out varied between 5% and 25%. Series represent different probabilities of receiving 2°IPT after completing TB treatment (50%-90%; see legend); space between data points of different series is for better readability and not proportional to scale of the x-axis; error bars represent 95% uncertainty intervals.

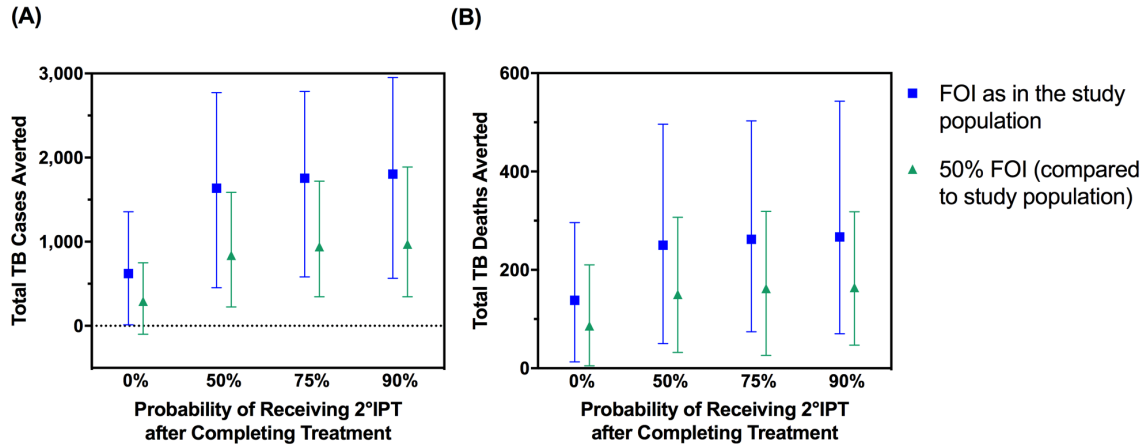

Figure S9: Expected number of TB cases (Fig. A) and deaths (Fig. B) averted as the result of annual TACF and 2°IPT interventions with respect to a scenario where the TB force-of-infection (FOI) is reduced by 50% compared to the TB force-of-infection estimated for our study population. Space between data points of different series is for better readability and not proportional to scale of the x-axis; error bars represent 95% uncertainty intervals.

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