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Supplementary appendix

APPENDIX

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

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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

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 diagnosed 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. Infectious individuals transit, after passive case detection into either of two treatment compartments, reflecting completed treatment or incomplete treatment. Individuals who complete their treatment are allocated to an intervention arm or non-intervention arm. In the non-intervention arm, adults transit to a latently infected state (i.e. consistent with many TB models, we assume that sterilizing cure is not achieved). From latent infection, they may progress to infectious TB either via disease reactivation (relapse) or following reinfection, and infectious individuals may be passively detected and transition again into either of the treatment compartments.

Similar transitions apply to individuals 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-ups. Furthermore, we allow rates of relapse and reinfection to differ from those in the non-intervention arm to account for the effect of secondary preventive therapy.

Individuals in whom treatment remains incomplete may reach a latent compartment or transition directly into an infectious compartment (i.e. reflecting those who remained infectious). Differential rates of relapse and reinfection apply to latently infected individuals after incomplete 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.

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 a given time. 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. Upon developing active disease, children may move into a recovered state after being found and treated.

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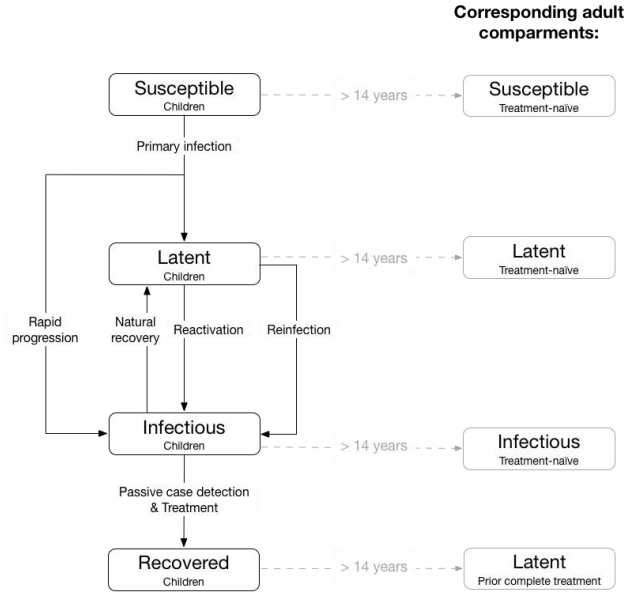
Figure S1. Model subcomponent for children aged 0-14 years
Not shown are mortality rates; grey dashed arrows indicate age transition into the corresponding compartments of the adult component of the model (see Figure 1, main manuscript)

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.

Model subdivisions for time after TB treatment completion: We distinguish two subdivisions reflecting the time that has passed since the successful completion of TB treatment (Figure 1, main manuscript). Latently infected and infectious individuals after complete treatment in both the intervention and non-intervention arm transition from a subdivision reflecting the first year post-TB treatment and into a subdivision reflecting the time later than the 1st year.

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	Ref 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 [0·0016-0·0018]	Estimated from unpublished census data, City of Cape Town
Annual natural death rate among adults (≥15 years)	0·009 [0·0086-0·0096]	Experiments with the model
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	4·0 [3·7-4·2]	Refs 16,17

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 susceptibility to reinfection (Table S4). Parameter estimates for HIV-infected adults consider 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[18,19] (Table S2), a higher probability of reactivation of latent infection[20] (Table S3) and higher susceptibility to reinfection (Table S4).

We assumed that children were less likely to transmit TB by the ratio 0·12 [0·03-0·31] (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.[21]

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]	Refs 22-24
Adults, susceptible/treatment-naïve/HIV+/non-immunocompromised	0·33 [0·18-0·51]	Refs 22-24
Adults, susceptible/treatment-naïve/HIV+/immunocompromised	0·805 [0·75-0·91]	Refs 22-24
Children, susceptible	0·118 [0·09-0·14]	Estimated from ref 25

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]	Refs 23,24,26,27
Adults, latently infected/treatment-naïve/HIV+/non-immunocompromised	0·003 [0·001-0·006]	Refs 23,24,26,27
Adults, latently infected/treatment-naïve/HIV+/immunocompromised	0·1275 [0·080-0·200]	Refs 23,24,26,27
Children, latently infected	0·001 [0·0003-0·0024]	Assumption

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Table S4: Model Parameters – Relative susceptibility among latently infected people (reference: susceptible, treatment-naïve people)

Subgroup	Value [Interval]	Source
Adults, latently infected/HIV-	0·35 [0·13-0·63]	Refs 24,26,28-30
Adults, latently infected/HIV+/non- immunocompromised	0·65 [0·32-0·77]	Refs 24,26,28-30
Adults, latently infected/HIV+/ immunocompromised	0·75 [0·61-0·86]	Refs 24,26,28-30
Children, latently infected	0·35 [0·13-0·63]	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]	Refs 23,24,28,31
Adults, infectious/treatment-naïve/HIV+/non-immunocompromised	0·1 [0·06-0·16]	Refs 23,24,28,31
Adults, infectious/treatment-naïve/HIV+/ immunocompromised	0	Refs 23,24,28,31
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 with previous TB treatment. In the absence of published estimates for many parameters, we specified prior parameter ranges and derived posterior parameter values through calibration (see below).

After TB treatment, we distinguish people during the first year after treatment and after the first year. We assumed that individuals after TB treatment were equally likely to be re-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. Due to the uncertainty about the degree to which prior disease leads to protective immunity, we specified wide ranges of relative susceptibility, allowing for some degree of protective immunity and up to 2-times higher susceptibility of previously treated people compared to susceptible, treatment-naïve people. The rate of TB resulting from reinfection was assumed to be independent of the time that had passed since the completion of treatment.

After treatment completion, people may reactivate tuberculosis. We specified a prior range of reactivation (relapse) in the first year after TB treatment completion of 2.1%-18.9%, an estimate informed by a molecular study conducted in the setting (Table S7).[14] We assumed that the rate of reactivation (relapse) was higher in the first year than in the time after the first year, consistent with the literature (Table S7).[6,32] We allowed for higher relapse rates among individuals with HIV infection.

We specified identical prior ranges for the rate of TB reactivation after incomplete treatment. However, based on data from a retrospective cohort study from 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), effectively resulting in higher rates of TB after incomplete treatment.

We finally assumed treatment-experienced cases of TB are equal to 1·5-times more likely to transmit TB compared to treatment-naïve TB cases. This assumption is based on findings from TB prevalence surveys that treatment-experienced TB cases were more likely to be coughing and more likely to be sputum smear-positive.[33]

Table S6: Model Parameters – Relative susceptibility after previously treated active TB (reference: susceptible, treatment-naïve people)

Subgroup	Value [Interval]	Source
Adults, latently infected/prior complete or incomplete treatment/HIV-	[0·13-3·00]	Assumption
Adults, latently infected/ prior complete or incomplete treatment/HIV+/non-immunocompromised	[0·32-3·00]	Assumption
Adults, latently infected/ prior complete or incomplete treatment/HIV+/ immunocompromised	[0·61-3·00]	Assumption

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

Subgroup	Value [Interval]	Source
Adults, prior treatment/any HIV status, first year after treatment completion/HIV-	[0·021 - 0.189]	Based on data from ref 6
Adults, prior treatment/any HIV status, first year after treatment completion/HIV+/ non-immunocompromised	[0·021 - 0.378]	Assumption
Adults, prior treatment/any HIV status, first year after treatment completion/HIV+/ immunocompromised	[0·021 - 0.756]	Assumption
Ratio, relapse rate after year vs. first year	[0 - 0·5]	Assumption

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

Subgroup	Value [Interval]	Source
Adults, prior incomplete treatment/any HIV-status	[0·00-0·20]	Based on data from ref 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[34] and Zimbabwe[35].

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 - 2]	Assumption
Adults, infectious/ or prior complete or incomplete treatment/HIV-	[0.083 - 1.5]	Assumption
Adults, infectious/treatment-naïve or prior complete or incomplete treatment/HIV+	[0.083 - 1.5]	Assumption
Children, infectious	[0.083 - 2]	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 and after**	
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]	Refs 23,24
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]	Refs 24,36,37
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]	Ref 38
Survival time of HIV-infected people not on ART (years)	10·2 [9·7-10·5]	Ref 39
Annual non-immunocompromised HIV-associated excess mortality rate	0·008 [0·005-0·012]	Refs 24,40-44
Annual immunocompromised HIV-associated excess mortality rate	0·24 [0·192-0·288]	Calculated from estimated survival time, see above
Annual HIV-associated excess mortality rate while on ART	0·008 [0·005-0·012]	Refs 24,40-44
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]	Ref 45

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[46], 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.

S4. Model implementation and simulation approach

The model was implemented in C# (https://github.com/yaesoubilab/APACEc) and the cost-effectiveness analysis and data visualization were conducted in Python (https://github.com/yaesoubilab/APACEVisualization).

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 $H = \{I_{\text{TN}}, I_{\text{TI}}, I_{\text{TC}}\}$ 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 ($h \in \{S_{\text{Ch}}, L_{\text{Ch}}\}$) at time t as:

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

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

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

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

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.[47]

Finally, based on estimates from a molecular epidemiological study conducted in the setting[6], we calibrated the model to observed fractions of recurrent TB cases occurring in the first year, and the fractions of recurrent TB cases during and after the first year that were due to reactivation.

Calibration targets, data sources, and specified feasible ranges are shown in Tables S15, S16.

Table S15: Overview of calibration targets and data sources

Description	Year(s)	Value	95% Confidence Interval	Source
Total adult population	2002-2008	Time-varying	-	City of Cape Town*
Total child population	2002-2008	Time-varying	-	City of Cape Town*
Number of children who started TB treatment	2002-2008	Time-varying	-	TB treatment register database used in ref 6
Number of treatment-naïve adults who started TB treatment	2002-2008	Time-varying	-	TB treatment register database used in ref 6
Number of treatment-experienced adults who started TB treatment	2002-2008	Time-varying	-	TB treatment register database used in ref 6
Percentage TB treatment-experienced adults	2002-2008	9·70	[8·70 - 10·90]	Ref 8
Percentage TB prevalence, treatment-naïve adults	2002	0·51	[0·26 - 0·76]	Ref 8
Percentage TB prevalence, treatment-experienced adults	2002	2·99	[1·14 - 4·77]	Ref 8
Percentage HIV prevalence, adults	2002	5·20	[4·2 - 6·2]	Estimated from ref 47
Fraction of adult TB cases who previously completed TB treatment that occur in the first year post-treatment	2002[†]	0·33	[0·27 - 0·40]	Ref 6
Fraction of TB cases occurring in the first year after treatment completion that are due to reactivation[‡]	2002[†]	0·80	[0·68 - 0·92]	Ref 6
Fraction of TB cases occurring after the first year post-treatment that are due to reactivation[‡]	2002[†]	0·34	[0·24 - 0·44]	Ref 6

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

[†] as opposed to disease progression following reinfection

[‡] mid-year of the study period

Table S16: 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 - 1·5
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 included all uncertain parameters described in in Tables S2-S14 in the calibration. We used a Bayesian calibration approach[48] to identify parameters sets that result in simulated trajectories with good fit to the calibration targets described above. To implement this approach, we used a 'sampling-importance-resampling' algorithm:

- Sampling: Uniform prior distributions were specified for each parameter, and multiple parameters sets were then randomly and independently selected from these distributions.
- Importance: The fit of each simulated trajectory was assessed in a two-step process. As a first step, we rejected parameter sets if resultant projections fell outside broad ranges pre-specified as feasible ranges (Table S16). The purpose of this step is to eliminate parameter sets with very poor fit to the calibration data in order to improve computational efficiency of the calibration process. We initially sampled a total of 897 704 parameter sets until 20 000 simulated trajectories were obtained that did not violate the feasibility ranges. As a second step, we estimated the goodness of these remaining simulations against the calibration targets. For each remaining simulated trajectory, the likelihood of observations was 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 $0.05 N_t / z_{1-\alpha/2}$ 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.

- Resampling: A subset of 1,000 parameter sets was then resampled (with replacement), with sampling probability proportional to goodness of fit. This subset was then used for final analysis.

To ensure that we have obtained enough simulated trajectories to calibrate our model, we later repeated the calibration procedure using a similar number of completely different parameter sets and different random number seeds. Projections under this repeated analysis (Figure S7) show that the comparative performance of the strategies considered is robust to the set of simulated trajectories selected for projecting cost-effectiveness outcomes.

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S6. Posterior parameter estimates

Sampled posterior means and corresponding 95% uncertainty intervals for some of the key model parameters describing differences in the natural history of TB between treatment-naïve and treatment-experienced people are provided below (Table S17).

Table S17: Comparison of prior and 95% posterior intervals for key model parameters describing differences in the natural history of TB between naïve and treatment-experienced people

Parameter	Prior values		Posterior values	
	Mean	*Uncertainty range*	*Mean*	*Uncertainty range*
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	4·00	(3·70 - 4·20)	3·95	(3·71 - 4·19)
Ratio of infectiousness, TB treatment-experienced adults to treatment-naïve adults	-	(1·00 - 1·50)	1·24	(1·01 - 1·49)
Relative susceptibility towards reinfection compared to primary infection				
- Adults, latently infected/treatment-naïve/HIV-	0·35	(0·13 - 0·63)	0·31	(0·15 - 0·56)
- Adults, latently infected/prior treatment/HIV-	-	(0·13 - 3·00)	1·26	(0·46 - 2·52)
- Adults, latently infected/treatment-naïve/non-immunocompromising HIV infection	0·65	(0·32 - 0·77)	0·54	(0·34 - 0·76)
- Adults, latently infected/prior treatment/non-immunocompromising HIV infection	-	(0·32 - 3·00)	1·61	(0·37 - 2·91)
- Adults, latently infected/treatment-naïve/immunocompromising HIV infection	0·75	(0·61 - 0·86)	0·73	(0·62 - 0·85)
- Adults, latently infected/prior treatment/immunocompromising HIV infection	-	(0·61 - 3·00)	1·79	(0·66 - 2·94)
Rate of reactivation of latent TB infection				
- Adults, latently infected/treatment-naïve/HIV-	0·001	(0·0003 - 0·0024)	0·0014	(0·0004 - 0·0023)
- Adults, latently infected/treatment-naïve/non-immunocompromising HIV infection	0·003	(0·001-0·006)	0·0034	(0·0011 - 0·0059)
- Adults, latently infected/treatment-naïve/immunocompromising HIV infection	0·128	(0·080 - 0·200)	0·1411	(0·0836 - 0·1973)
Rate of reactivation after completion of TB treatment (first year)				
- Adults, prior treatment/treatment-naïve/HIV-	-	(0·021 - 0·189)	0·1035	(0·0250 - 0·1837)
- Adults, latently infected/prior treatment/non-immunocompromising HIV infection	-	(0·021 - 0·378)	0·2058	(0·0330 - 0·3702)
- Adults, latently infected/prior treatment/immunocompromising HIV infection	-	(0·021 - 0·756)	0·3897	(0·0396 - 0·7340)
Ratio of reactivation rate, first year vs. >1 year after TB treatment	-	(0 - 0·50)	0·17	(0·06 - 0·33)
Time to passive TB case detection (years)				
- Adults, infectious/treatment-naïve/HIV-	-	(0·083 - 2·000)	0·4585	(0·0980 - 1·0746)
- Adults, infectious/treatment-naïve/non-immunocompromising HIV infection	-	(0·083 - 2·000)	0·9824	(0·1128 - 1·9475)
- Adults, infectious/treatment-naïve/immunocompromising HIV infection	-	(0·083 - 2·000)	1·0295	(0·1219 - 1·9387)
- Adults, infectious/prior treatment/HIV-	-	(0·083 - 1·500)	0·5826	(0·1176 - 1·3431)
- Adults, infectious/prior treatment/non-immunocompromising HIV infection	-	(0·083 - 1·500)	0·7464	(0·1187 - 1·4605)
- Adults, infectious/prior treatment/immunocompromising HIV infection	-	(0·083 - 1·500)	0·7532	(0·1184 - 1·4530)

S7. 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).

S8. Choice of diagnostic (screening) algorithms

We conducted a separate analysis to explore the characteristics and costs of different diagnostic test algorithms to screen for recurrent active TB among people who previously completed TB treatment.

Diagnostic algorithms considered

Xpert MTB/RIF Ultra (Ultra) is currently recommended as the primary tool for routine diagnosis of TB amongst presumptive TB cases in South Africa. Its advantage is the good accuracy and relatively rapid turnover which makes this test interesting for screenings. A major concern of Ultra is the high probability of false-positive (culture-negative) test results among individuals with a history of recent TB treatment because as Ultra can detect old DNA from non-viable, non-intact bacilli.[49,50] One in 7 Xpert-positive patients were found to be culture-negative in the study area, and our preliminary diagnostic accuracy data suggest that, for patients with previous TB within the last two years, the false-positive rate may be as high as 50%.

Another concern is the relatively suboptimal sensitivity of Ultra for detecting TB among HIV-infected individuals, especially when early stage disease is present and symptoms are mild. This suboptimal sensitivity is why *M.tb* culture is currently recommended to verify Ultra-negative test results among HIV-infected presumptive TB patients in South Africa, although follow-up via culture is currently inconsistently done.[51]

We simulated screening among people with recent TB treatment (1 year after completion) using Ultra as the only screening tool (*Algorithm 1*) and the following three alternative algorithms using *M.tb culture* (*Algorithms 2-4*). We did not evaluate the previous-generation Xpert test, as this is in the process of being phased out by the manufacturer.

> *Algorithm 1.*   Xpert ultra for everyone.
>
> *Algorithm 2.*   *M·tb* culture for everyone.
>
> *Algorithm 3.*   Xpert ultra for HIV-uninfected people. Culture for HIV-infected people.
>
> *Algorithm 4.*   Xpert ultra for everyone, positive results are confirmed by *M.tb* culture.

Simulation method and parameters

We conducted a Monte Carlo simulation of follow-up screenings for TB among a hypothetical population of 1,000 individuals who completed an episode of TB treatment 12 months before the screening took place. It was assumed that 17% of the 1,000 individuals were HIV-infected (ETR.net, 2013), and that by the end of the first year, 5.0% of HIV-uninfected and 10.0% of HIV-positive people had a true episode of recurrent TB. These assumptions form the basis for the choice of the parameters for the probabilities of TB and HIV in the screening population (see below). Costs for the tests represent current NHLS estimates. Finally, test characteristics were derived from the literature, an ongoing study (G. Theron et al.), or were assumed (Table S18).

Table S18: Parameters for sub-analysis

A: Probabilities of TB and HIV

#	Parameter	Value	Uncertainty interval	Source
1	Recurrent TB after 12 months	0·06	0·04 – 0·08	Assumption
2	HIV-infected individuals among recurrent TB cases	0·29	0·25 – 0·35	Assumption
3	HIV-infected individuals among recurrent TB-free individuals	0·17	0·14 – 0·18	Assumption (Data from ETR.net)

B: Costs of Xpert ultra and culture (in US-Dollar)

#	Parameter	Value	Uncertainty interval	Source
4	Xpert ultra	7·53	-	NHLS
5	M·tb (liquid) culture	14·71	-	NHLS

C: Test characteristics (people with recent TB treatment)

#	Parameter	Value	Uncertainty interval	Source
6	Xpert ultra: Sensitivity HIV-uninfected people	0·91	0·86 - 0·95	Ref 52
7	Xpert ultra: Sensitivity HIV-infected people	0·90	0·83 - 0·95	Ref 52
8	Xpert ultra: Specificity HIV-uninfected people	0·68	0·57 - 0·79	Unpublished data*
9	Xpert ultra: Specificity HIV-infected people	0·71	0·55 - 0·84	Unpublished data*
10	*M·tb* culture: Sensitivity HIV-uninfected people	0·95	-	Ref 53
11	*M·tb* culture: Sensitivity HIV-infected people	0·90	-	Assumption
12	*M·tb* culture: Specificity HIV-uninfected people	0·996	-	Ref 54
13	*M·tb* culture: Specificity HIV-infected people	0·996	-	Ref 54 (assumption)

* Based on individuals treated within the last two years. More distant previous TB will be associated with higher specificity.

Analysis methods

For the Monte Carlo simulation, a total of 1,000 sets of parameters were randomly selected from uniform distributions of values within the uncertainty intervals shown in the tables. (Point estimates were used for parameters where no intervals are shown.)

Results (Table S19) are presented as median (best estimate) with the uncertainty interval representing the 2·5th and 97·5th percentile of the outcome values. The following outcome parameters are simulated:
(1) Positive predictive value
(2) Negative predictive value
(3) Total costs (USD) per 1,000 screenings
(4) Total costs (USD) per 1 recurrent TB case detected

Figure S2 shows expected numbers of true- and false-positive test results per 1,000 screenings for Xpert and Culture.

Table S19: Results of the sub-analysis

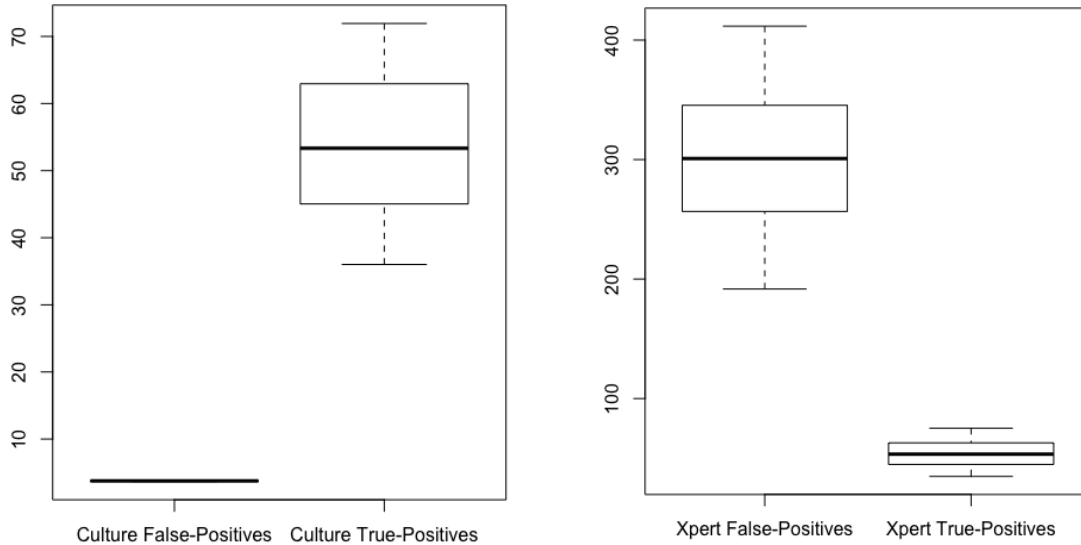| Outcome	1 Xpert	2 Culture	3 Xpert (HIV-) / Culture (HIV+)	4 Xpert / Xpert+ conf. via culture
Positive predictive value (%)	15·0 (9·6 – 23·5)	93·4 (90·5 – 95·1)	17·5 (11·0 – 27·4)	93·4 (90·5 – 95·1)
Negative predictive value (%)	99·1 (98·4 – 99·5)	99·4 (99·1 – 99·6)	99·2 (98·6 – 99·6)	99·4 (98·9 – 99·7)
Median costs per 1,000 screenings (USD)	14,709	7,533	13,503	17,382
Median costs per 1 detected TB case (USD)	275 (207 – 401)	141 (106 – 207)	251 (189 – 368)	324 (244 – 473)

Figure S2. Expected numbers of positive test results per 1,000 screenings; left: Culture, right: Xpert (note: different scale)

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Conclusions
Ultra as a screening tool has a high cost per TB case detected and results in a high number of false-positive test results at screening which would require further testing and diagnostic follow-up. In our setting, culture-based screening is therefore likely to be more acceptable to individuals and health-care services and more cost-effective, even though positive results would have to be communicated with a delay of up 2-6 weeks (until culture results become available). The effect of diagnostic delay associated with culture will be mitigated by potentially frequent early-phase disease (and hence reduced infectiousness) in previously treated patients, especially if they are not yet symptomatic. The effectiveness of the screening program would depend on whether culture-positive individuals can be successfully recalled for treatment.

S9. Methods for estimating disability-adjusted life years (DALYs)

Disability-adjusted life years form a composite of the years of life lost due to premature death (YLL) and the years of life lost due to disability (YLD).

$$DALYs = YLL + YLD$$

Estimates of YLL

First, using data from the Global Burden of Disease Study 2016[1] we obtained an estimate of the average age at death from HIV and TB among adults in South Africa:

> Death due to HIV: 40·5 years
> Death due to TB: 51·0 years

We then used synthetic life tables[1] for South Africa to estimate the average YLL:
> YLL due to HIV: 33·8
> YLL due to TB: 26·8

Estimates of YLD

YLD were estimated using model outputs and disability weights:

YLD = average time in the respective model state x disability weight

The following disability weights were used (Table S20):

Table S20: Disability weights

	Value	Uncertainty interval	Source
Latent TB infection	0		
Untreated active TB, HIV-negative	0·333	0·224 - 0·454	Ref 55
HIV, non-immunocompromised	0·012	0·006 - 0·023	Ref 55
HIV, immunocompromised	0·428	0·274 - 0·582	Ref 55
HIV, on antiretroviral treatment	0·078	0·052 - 0·111	Ref 55

We used estimates of disutility from HIV and active TB to estimate the disutility of having both HIV and active TB: 1 – (1-HIV disutility) * (1-TB disutility).

S10.   Sensitivity analysis

To assess how sensitive the projected health impact (DALYs averted) and incremental costs of the interventions were to the input parameters of our model, we calculated partial rank correlation coefficients. In this analysis we focused on the most expensive intervention strategy, 'annual follow-up with continuous 2°IPT' and refer to the base-case scenario as a reference. 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.

Sensitivity analysis (Table S.21) showed that projections of incremental health impact and incremental costs under the 'annual follow-up with continuous 2°IPT' scenario (relative to base-case) were most sensitive to the average time to passive TB case detection among previously treated TB cases (incremental health impact only), the rate of reactivation (relapse) and the relative susceptibility to reinfection post-treatment, and the efficacy of 2°IPT.

Table S21: Sensitivity analysis: Partial Rank Correlation Coefficients (PRCC) for parameters describing the natural history of TB among treatment-experienced people

Model parameter	Incremental DALYs averted		Incremental costs	
	Coefficient	P-Value	Coefficient	P-Value
Excess mortality among treatment-experienced people				
Natural death rate ratio, TB treatment-experienced adults to treatment-naïve adults	0·007	0·829	0·022	0·485
Rate of Reactivation of active TB after treatment				
Adults, prior complete treatment/1st year/HIV-	0·156	<0·001	-0·040	0·208
Adults, prior complete treatment/>1 year/HIV-	0·127	<0·001	-0·077	0·014
Adults, prior complete treatment/1st year/HIV+/non-immunocompromised	0·018	0·568	0·054	0·090
Adults, prior complete treatment/>1 year/HIV+/non-immunocompromised	0·004	0·902	-0·002	0·955
Adults, prior complete treatment/1st year /HIV+/immunocompromised	-0·023	0·466	0·014	0·654
Adults, susceptible/prior complete treatment/>1 year /HIV+/immunocompromised	-0·013	0·690	-0·016	0·609
Ratio reactivation 1st year vs. >1 year	0·001	0·980	-0·036	0·258
Relative susceptibility towards reinfection (treatment-experienced)				
Adults, latently infected/treatment-experienced/HIV-	0·154	<0·001	-0·196	<0·001
Adults, latently infected/ treatment-experienced/HIV+/non-immunocompromised	-0·036	0·258	-0·044	0·168
Adults, latently infected/treatment-experienced/HIV+/immunocompromised	-0·033	0·300	0·012	0·713
Baseline time between disease onset and passive case detection (years)				
Adults, infectious/prior complete treatment/HIV-	0·415	<0·001	-0·055	0·085
Adults, infectious/prior complete treatment /HIV+/non-immunocompromised	-0·056	0·079	-0·016	0·624
Adults, infectious/prior complete treatment /HIV+/immunocompromised	-0·041	0·199	0·008	0·803
Cost estimates				
Cost of DS-TB treatment	-0·005	0·869	-0·054	0·086
Cost of DR-TB treatment	-0·027	0·397	0·041	0·190
Cost of ART (per month)	0·004	0·902	0·051	0·106
Cost of IPT (including outpatient visits)	-0·001	0·976	0·033	0·299
Cost of management of DILI events	<0·001	0·990	-0·019	0·555
Cost for hospitalization (severe DILI)	-0·019	0·540	0·029	0·353
Efficacy of 2°IPT				
Reduction in TB reactivation rate	0·087	0·006	-0·064	0·043
Reduction in probability of fast progression to TB after reinfection	0·017	0·595	-0·010	0·745
Infectiousness				
Ratio: adults, treatment-experienced to adults, treatment-naïve	0·006	0·850	-0·050	0·111

S11. **Overview of intervention scenarios and projected epidemiologic impact**

Figure S3 shows an overview of the interventions modeled.

Figure S4 shows model projections of TB incidence over time under each model scenario.
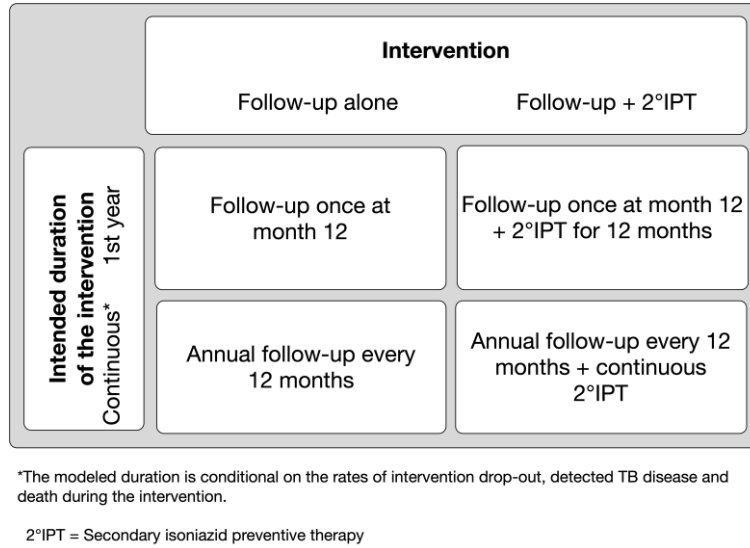

*The modeled duration is conditional on the rates of intervention drop-out, detected TB disease and death during the intervention.

2°IPT = Secondary isoniazid preventive therapy

Figure S3. Two-by-two design of modelled intervention scenarios
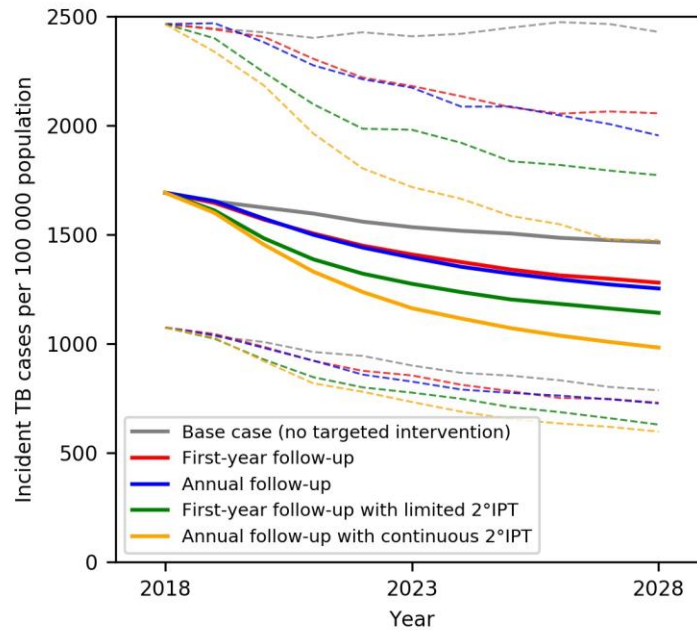
Figure S4. Best estimates of TB incidence in the general population (calculated as the mean of 1000 simulated trajectories) under different scenarios of post-treatment follow-up and secondary preventive therapy among adults who completed tuberculosis treatment in a high-incidence setting in suburban Cape Town, 2019–2028; thick lines represent means, dashed lines upper and lower bounds of 90% uncertainty intervals.

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S12. Pairwise comparison of intervention scenarios and results of secondary analysis

Figures S5 shows a pairwise comparison of the intervention scenarios in terms incremental costs and DALYs averted.

Figures S6 and S7 show model projections for scenarios in which we varied the uptake of and drop out from follow-up and secondary isoniazid preventive therapy.

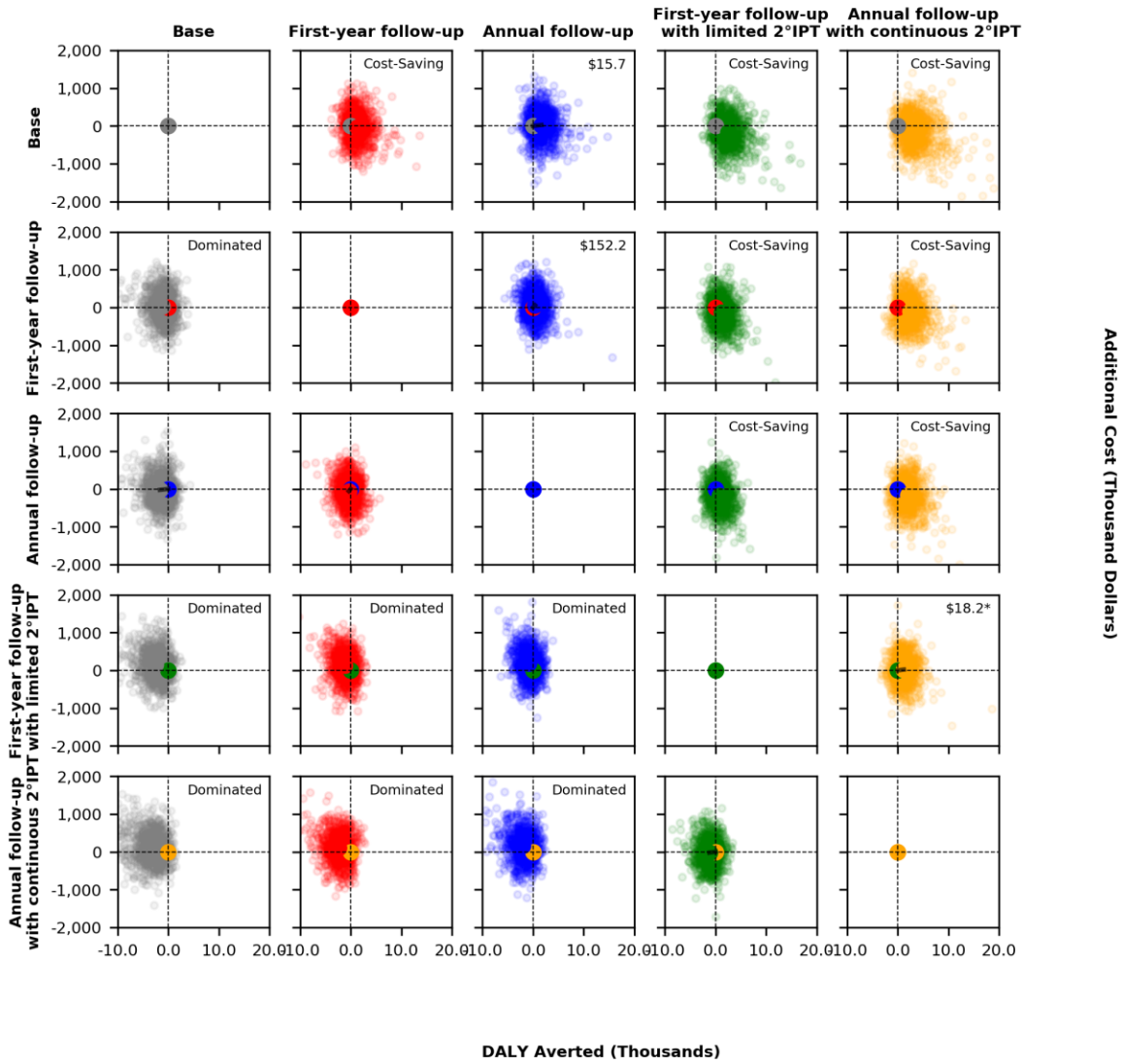Figure S8 shows a secondary analysis in which we resampled the initial parameter sets.

Figure S5. Pairwise comparison of intervention strategies
Each panel shows the additional cost and DALYs averted of strategies listed on the top of each column with respect to strategies listed on the left hand-side of each row. The label on each figure summarizes the results of the cost-effectiveness analysis: **Dominated** if the strategy listed on top is dominated by the strategy listed on left; **Cost-saving**, if the strategy listed on top is expected to avert DALYs and to result in lower cost; and the **ICER** is reported if the strategy listed on top is expected to avert DALYs and to increase the cost. The asterisks represent comparisons between two strategies that are on the cost-effectiveness frontier.
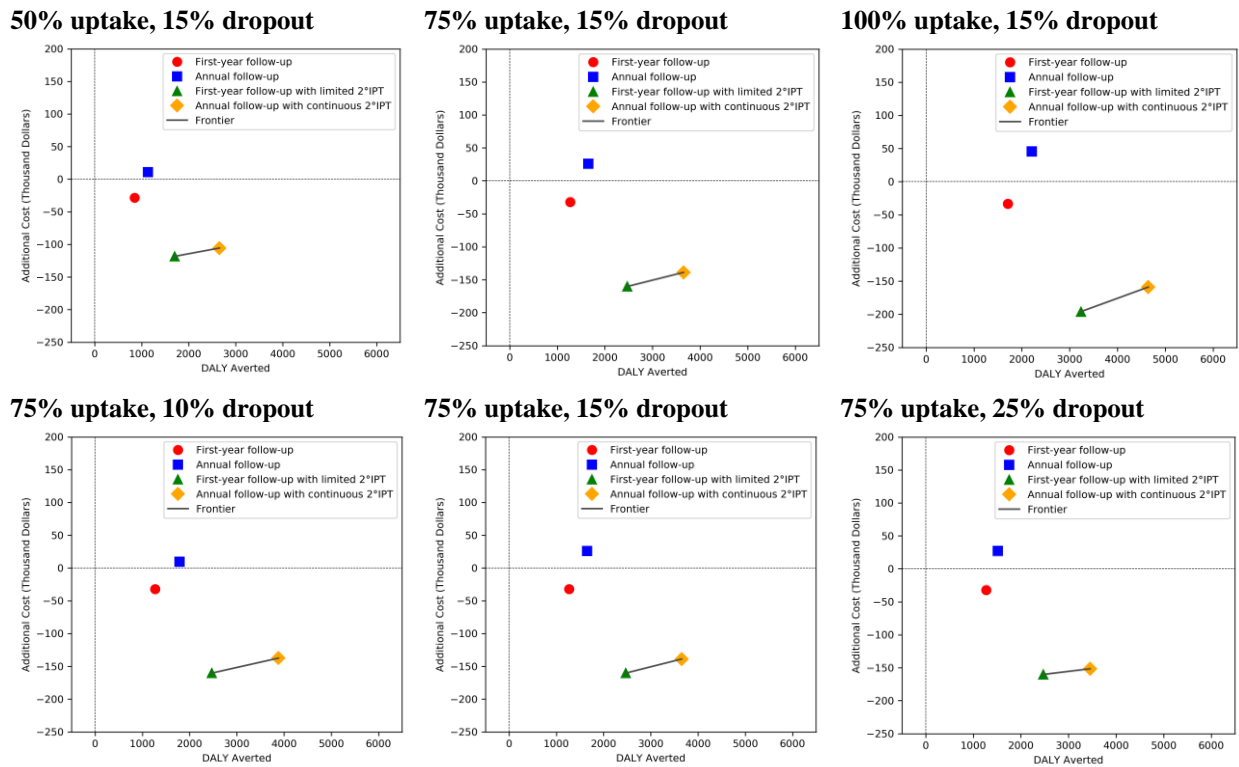
Figure S6. Secondary analysis: Additional costs and DALYs averted by varying uptake of and drop out from follow-up and secondary isoniazid preventive therapy; drop-out rates are per annum
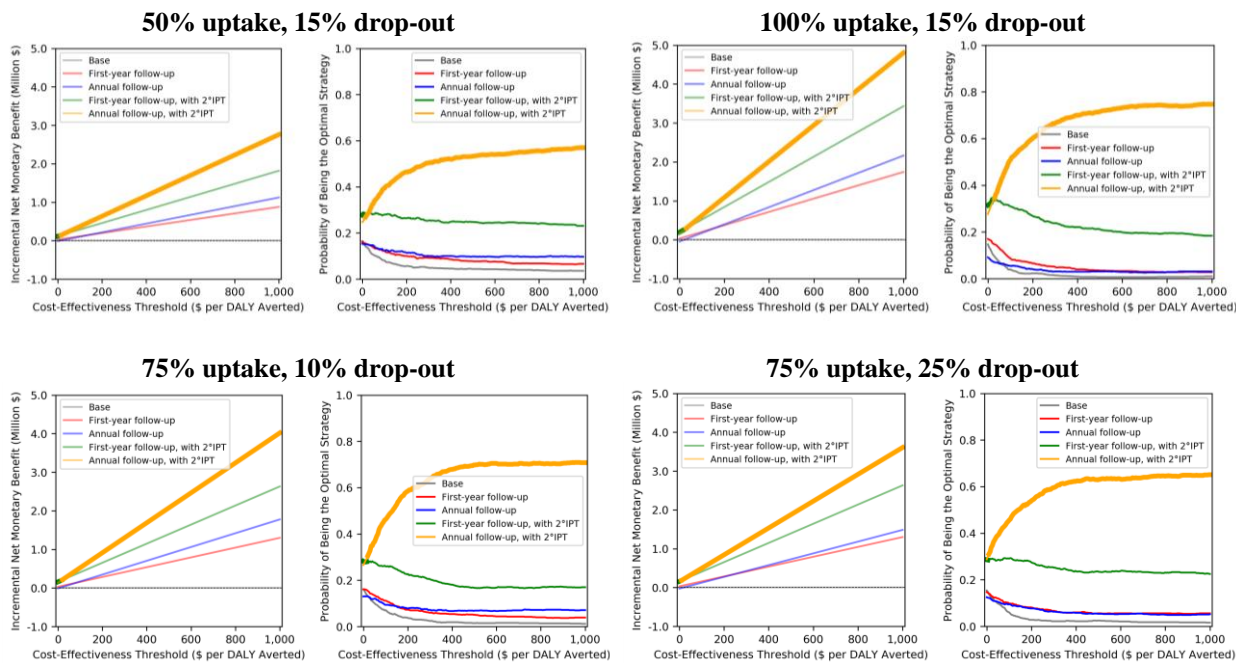

Figure S7. Secondary analysis: Cost-effectiveness acceptability by varying uptake of and drop out from follow-up and secondary isoniazid preventive therapy; drop-out rates are per annum

Original analysis

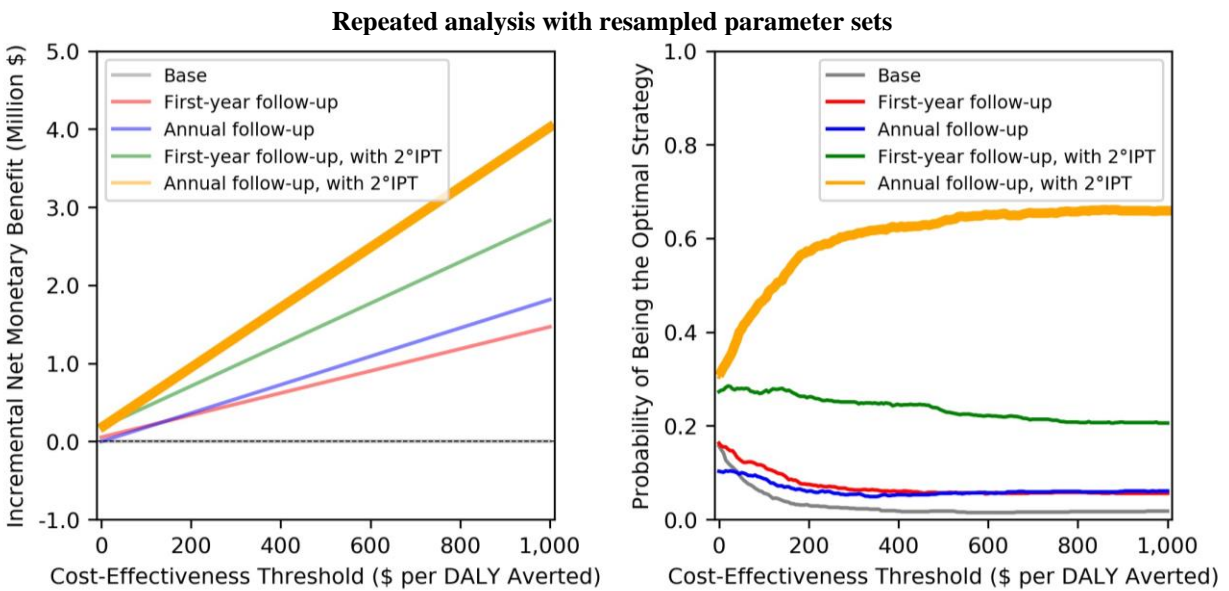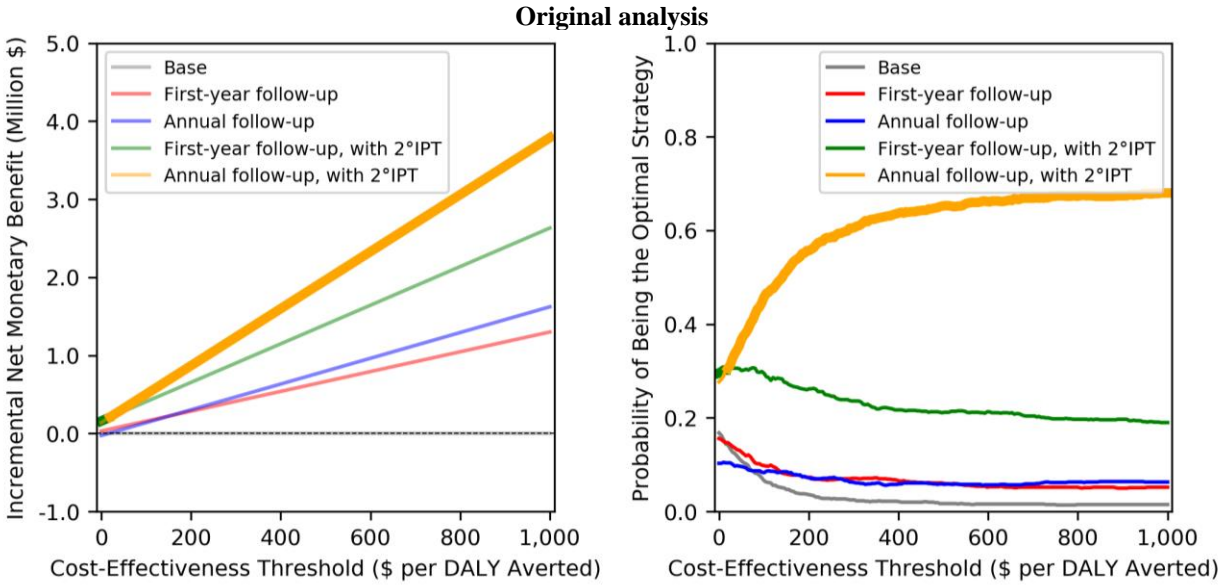**Repeated analysis with resampled parameter sets**

Figure S8. Secondary analysis: Cost-effectiveness analysis of modelled interventions for the original analysis and for a repeated analysis for which we resampled a similar number of parameter sets with different random seeds. The left panels show the expected incremental net-monetary benefit (NMB) 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 NMB). The right panes display the probability that a strategy results in the highest NMB for various cost-effectiveness thresholds. The strategy with the highest expected NMB is represented by the bold curve.

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