Supplementary Methods for

Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries

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Modelling methods

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Additional results

Cost-effectiveness methods

Cost-effectiveness parameters

(1) Modelling methods in full

Methods

Two settings were considered: a base case 'no new vaccine' and a 'new vaccine' setting. BCG (the current infant TB vaccine) vaccination was assumed to continue at current levels in both settings and is included in the estimates of TB burden to which the model was calibrated. BCG has consistently been shown to be efficacious against primary progressive disease (1) and hence is likely to continue to be given even with the introduction of a TB vaccine against progression to pulmonary disease. Full parameter values are given in Table S1. The model was programmed in 'R' (2).

Population and epidemiological data

Estimates of the number of births and mortality rates (2009-2050), as well as age structure in 2009 for each country were taken from the UN population division 2010 revision (3). The background mortality rate was stratified into discrete single year levels.

Tuberculosis incidence levels were taken from WHO estimates or calculated (for PLHIV) using WHO methods (4) (for full methods see Annex 1 of the 2013 Global TB Report (5)). Due to the higher levels of uncertainty in the HIV associated levels, the range from the estimates was multiplied by a factor of five. HIV incidence was derived from UNAIDS estimates (6). It was assumed that HIV incidence remains constant at country specific 2009 levels until 2050. This assumption has been made in other models of TB (7), and was made here in the light of the uncertainty in the impact of ART scale-up (8) and in order to be conservative in vaccine impact. We explore this assumption in scenario analysis.

Future improvements in case detection rates and treatment success for TB (4), as well as ART coverage were included. High targets for TB control have been set by the WHO, hence it is unlikely that TB control will not improve before 2025. To be conservative in terms of vaccine impact this scale-up gave a bigger decrease in TB incidence than the current (2%, since 2006) annual decline, but was less than an optimistic 10% annual decline (Figure S1). It was assumed that the improvements would increase the 2009 value by half the difference between the 2009 value and 100%, allowing for smaller improvements in coverage in countries with already high levels. The improvement was assumed to happen gradually (via a non-linear generalised logistic function) over the period 2012 to 2020, with 2009 levels prior to 2012, and 2020 levels kept constant until 2050 to allow time for TB burden to stabilise prior to vaccine introduction in 2024 (Figure S2, Table S3). The same scale-up was chosen for all countries for simplicity and ease of comparison, as well as uncertainty in differences at the country level. However, the relative scale-up (i.e. taking the 2009 value for the country) allows for the scale-up to reflect both how well the country is already doing and the difficulty of increasing already high levels of control. From 2020 onwards the values for TB control parameters were kept constant so that the only change to TB control after 2024 was use of a new vaccine. The change in these parameter inputs (shown in Figure S2) is reflected in the decrease in TB burden seen in Figures 1, S1 and S6.

Income groups

World Bank income group definitions were used (9). Low-income countries were those with 2011 GNI per capita of US$ 1,025 or less; lower middle income has GNI per capita between US$ 1,026 and US$ 4,035; and upper middle-income between US$4,036 and US$ 12,475. There were 32 low-, 33 lower-middle- and 26 upper-middle-income countries in the final analysis (Table S2). The included countries account for 96.9% and 97.8% of reported TB incident cases and deaths respectively, in low- and middle-income countries in 2009.

Study time period

The study time period was from 2024, which is considered the earliest possible date for a new TB vaccine to be available (10). While a principle of economic evaluation is to include all costs and effects of any intervention being modelled, when using a transmission model there is a balance to be reached between capturing these effects and the increasing level of future uncertainty. We chose 2050 as an end point as this is the global target for TB elimination and thus best represents the current policy decision and investment timeframe. Halting the model output at 2050 caps the effect of the life-time duration of protection vaccines, making our incremental cost-effectiveness ratios (ICERs) specific to the 2024-2050 time period. However, at this time point we already have a large level of uncertainty as to the burden of TB that will exist (what new tools may be introduced other than vaccines?) and the end point is the same for all vaccine profiles and target populations considered.

We investigated altering the end point for the ICER calculation and found that the discounted cost per DALY averted decreased with longer time horizons but that the rate of decrease was slowing by 2050 likely reflecting the impact of discounting. Interestingly, the ICERs calculated for the shorter duration adult targeted vaccines in 2045 were higher than in 2040 and 2050, reflecting the costs but not the impact of the mass campaign that had yet to be seen in 2045.

An ICER was calculated for each model fit (see below for details), and the median of this set of ratios and 95% range is presented in the main text.

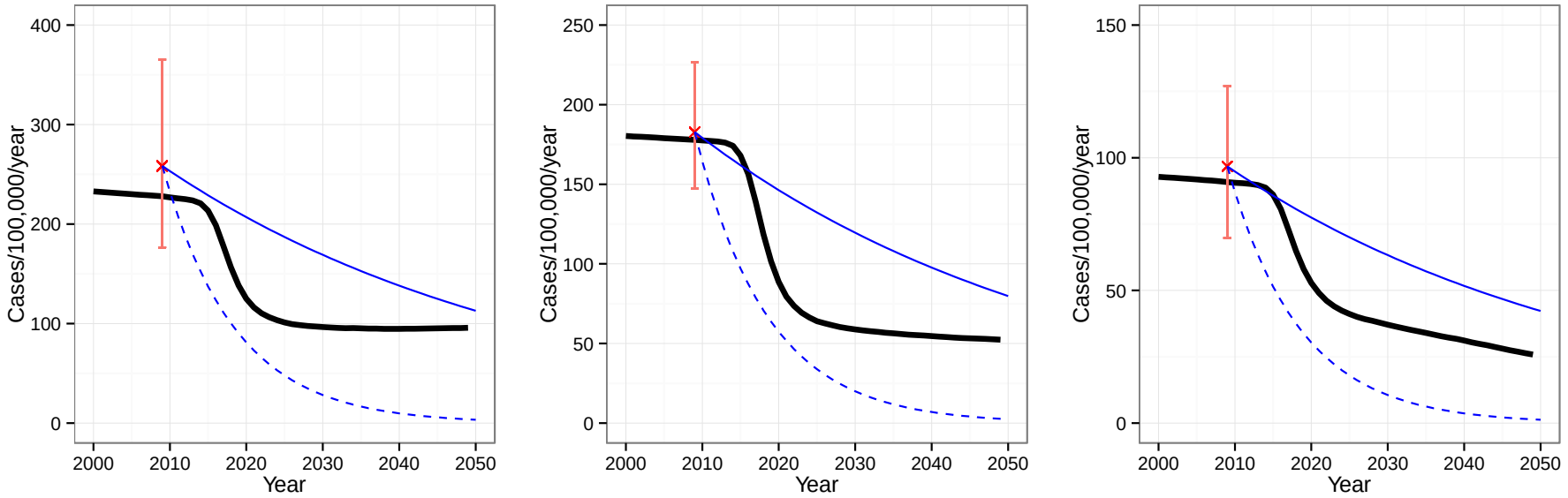

Figure S1: Comparison of model prediction of TB incidence for LICs, LMICs and UMICs with assumed scale-up in TB control versus current (2%) decline and best historically observed levels (10%). Thick black line shows median fit to data (red cross and interval) for LICs, LMICs and UMICs (left to right). The decline in median levels reflects the assumed scale-up in TB control in order to be conservative in vaccine impact. The blue solid line is the 2% decline in TB incidence per year, the dashed is the 10% decline, which has been observed historically (in Europe, with the use of chemotherapy). Over 2009-2050 a 2% decline per year would result in TB incidence in LIC, LMIC and UMIC respectively of 113, 80 and 42 cases per 100,000 population in 2050.

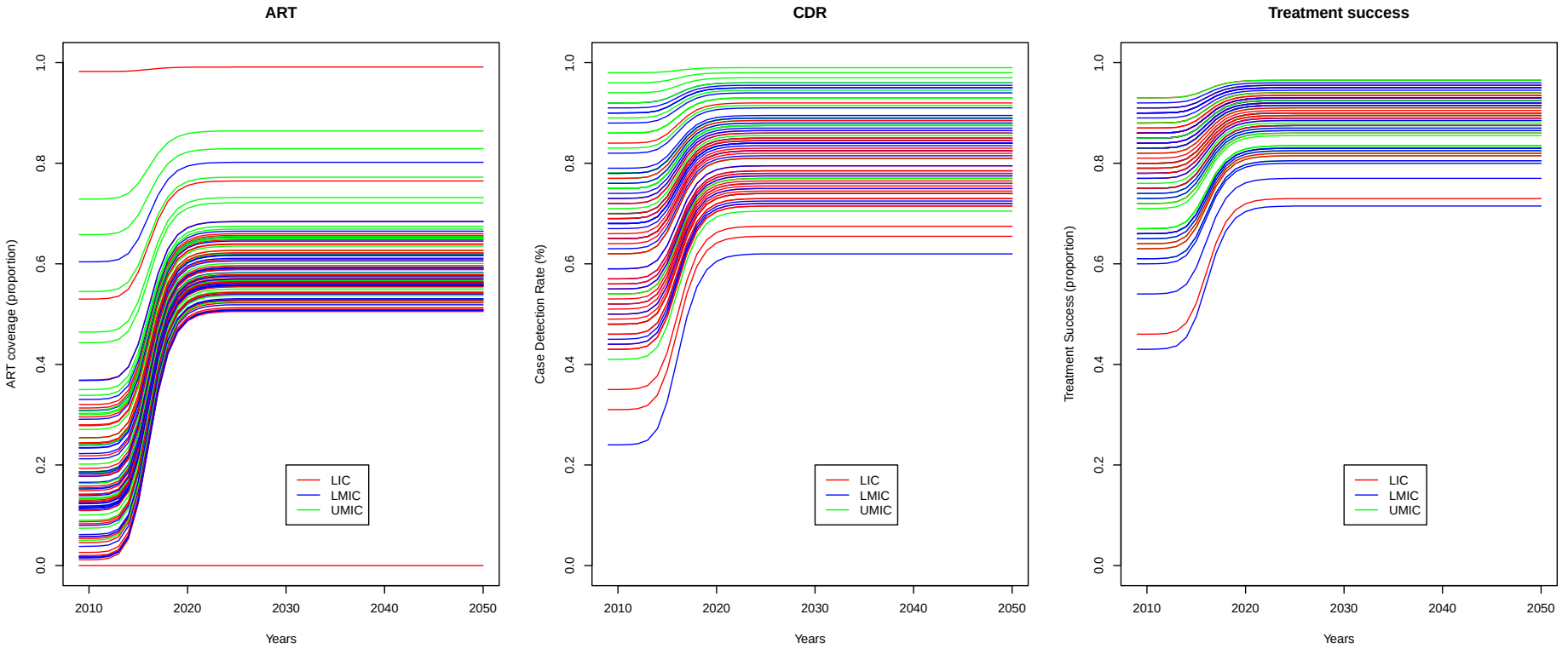

Figure S2: Future assumptions about ART, Case Detection Rate (CDR) and Treatment Success. Each line is the estimate from a different country, with colours reflecting income groups and the assumed scale-up in TB control by 2020 shown (halving of the difference between 2009 value and 100% detection, success or coverage respectively). The bottom red line (no ART coverage) is the estimate for Afghanistan where there is assumed to be negligible HIV prevalence.

Vaccine profiles

It is assumed that the vaccine prevents active disease but not infection. Hence, it has equal efficacy in TB uninfected or infected individuals. The new vaccine was assumed introduced in 2024 and two doses of the vaccine are required to obtain the assumed efficacy values. Coverage here is then taken to be those who receive both doses, i.e. although we assume that two doses would be needed in the costing we do not explicitly model two separate doses. For example, if school attendance were 80%, then 80% of school children would be assumed to receive two doses in this model.

Vaccine coverage assumptions

For the 'infant' strategy the first dose would be given at birth and the second with the third dose of diphtheria-tetanus-pertussis (DTP) vaccine around 14 weeks. Coverage was assumed similar to WHO/Unicef 2011 coverage estimates of the third dose of diphtheria-tetanus-pertussis (DTP3) vaccine (Table S3). The 'Adolescent/Adult' vaccine was targeted to 10 year olds at schools and coverage rates were based on school attendance levels in each country obtained from UNICEF (Table S3). There would be six months between the first and second dose. For the profiles with less than lifelong duration of protection, this vaccine was also assumed delivered in mass campaigns in 2024 and then with a frequency equal to every 10 years or the length of duration of protection, which ever was longer, targeting all of the population above 11 years. Coverage of mass campaigns was 20% lower than those obtained in rubella campaigns targeting women of childbearing age (Table S3).

To our knowledge, there are no `examples of mass vaccination campaigns targeting the whole population above a certain age, as modelled in this analysis. The largest vaccination campaigns conducted previously have been against rubella for all women of childbearing age and against meningococcal A for all people between 1 and 29 years in the African Meningitis Belt (11-13). While campaigns targeting an even wider age group would require substantial social mobilisation and pose logistical challenges, they are considered the only viable option for adult TB vaccine delivery in LMICs with weak health systems (14). To enable such mass campaigns to be operationally feasible, substantial TB vaccine research is focused on aerosolized vaccines that can be delivered by non health care workers and temperature stable vaccines that do not require a cold chain (15). We based our mass campaign vaccination coverage assumptions on those obtained for rubella campaigns, but since the modelled TB vaccination campaigns would target a wider age group we assumed 20% less coverage (11). Coverage rates of rubella vaccine campaigns were available for 126 countries in the WHO database (16). However, the target age groups varied considerably with some targeting women up to 45 years and others only girls between 9 months and 14 years. Mean reported coverage across the countries was 93%, with a variation of 25% in Bahamas and 116% in Nicaragua (both of these campaigns targeted girls and women up to 40 years). For our study countries, we used the average of the reported campaign coverage rates from the respective WHO regions. We thus assumed a 72% mass vaccination coverage in the Eastern Mediterranean and European regions, 73% in South East Asia and the Western Pacific, 75% in Africa and 76% in the Americas.

BCG vaccination was not modelled explicitly, but was assumed to continue at current levels in both settings due to the known benefits (1).

Transmission model

The model structure is outline in Figure 3. The basic TB natural history framework is shown in Figure 3a, whilst Figure 3b shows the vaccinated and HIV stratification layers.

- TB natural history

Susceptibles are infected at a rate $\lambda = \eta z Prev$ where η is the number of respiratory contacts a year, z the probability of transmission per effective contact rate (0.1) and *Prev* is the prevalence of Infectious TB cases (Figure S3). A proportion p develop active TB, and a proportion of these are infectious (f) or

non-infectious (1 – *f*), while (1 - *p*) become latently infected. Latents are assumed to progress to active TB via reactivation at a rate *v* or via re-infection at a rate λpx, where *x* is the protection provided by latent infection. Of these proportions *f* and (1 - *f*) become infectious or non-infectious, respectively. Infectious and non-infectious cases have TB mortality rates u_i and u_{ni}, respectively, which are higher than the background mortality rate *u*. Non-infectious cases convert to infectious at a rate *w*.

A proportion *CDR* of new infectious active TB cases are detected and started on treatment. This proportion is a factor *e* lower for non-infectious cases. A proportion *CoT* complete treatment and move to a Recovered class. Active TB cases can also naturally cure at a rate *n*. Recovered individuals are assumed to progress to active TB via relapse at a rate *r* or via re-infection at a rate λpx, where *x* is the protection provided by previous infection. Of these *f* and (1 - *f*) become infectious or non-infectious, respectively. Of those who relapse, a proportion *f* becomes infectious.

Multi-drug resistant TB was not included explicitly. Instead the prevalence in each country was used to add an additional number of MDR-TB treatments to the number of standard TB treatments.

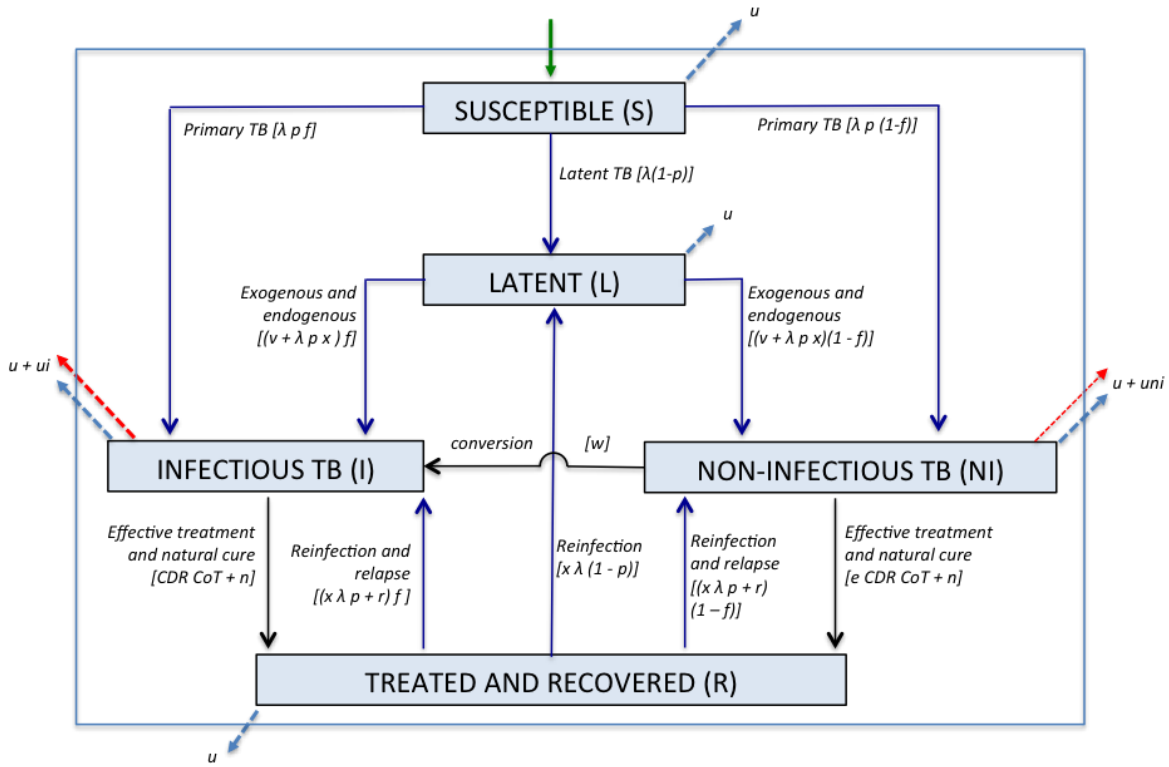

Figure S3a: Model outline with parameters as described in Table S1.

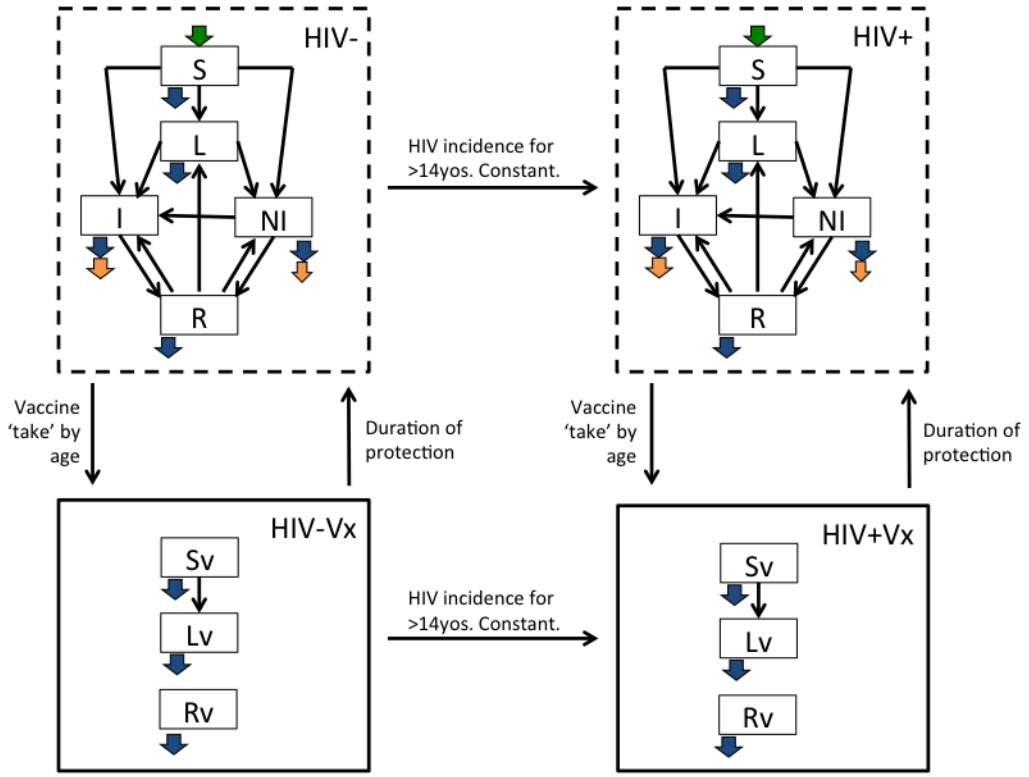

Figure S3b: Model outline with vaccinated and HIV-infected subpopulations. States are labelled with abbreviated versions of those in Figure S3a where S, L, I, NI and R represent susceptible, latent, infectious, non-infectious and recovered respectively. Shaded blue arrows represent mortality, shaded yellow arrows represent TB related mortality and black thin arrows represent transitions between states with descriptions provided as to what governs the transitions.

- Age stratification

Age is stratified into single years with three age-dependent parameters; the proportion of infections that develop active TB (p), the proportion of active TB cases that are infectious (f) and the background mortality rate (u). The first two are assumed to be lower for children (<15yos) than for adults (Table S1). Age structure is not a calibration target but instead an initial country level input. The method of Schenzle was used to capture aging (17) (see Model equations).

- HIV

HIV status is included as a separate stratum (HIV infected or not). HIV specific TB natural history rates were taken from the literature (Table S1). We assume that only those older than 15 years can become infected with HIV. Here HIV positive individuals are those with late stage HIV infection (low CD4 counts, HIV infection stages 3&4 (AIDS)) as has been assumed in previous models (18). This was based on the much higher risk of TB in late stage HIV (19). Under this assumption, instead of averaging over the changing TB disease risk over the whole of HIV infection, we assume that all HIV TB incident cases occur in the late stages. As such, we assumed an average life expectancy of 5 years in this late HIV stage without ART (independent of age of acquisition) (20), and an increase from 5 to 10 years with ART (21, 22).

Those members of the population with HIV have different rates of developing active TB (p_H, v_H, $x_{H,}$ r_H), different proportions of active cases progressing to infectious disease (f_H) and different mortality rates (u_{HA}, u_{iHA} and u_{niHA}). (21, 22)Based on evidence from hepatitis B vaccine studies,

vaccine efficacy is decreased by 40% (10-70%) for those who are HIV positive and ART naïve (ef_H) based on evidence from comparative efficacy of hepatitis B vaccines in PLHIV (23, 24) *and* decreased by 20% (0-60%) for those who are on ART (ef_A).

ART coverage (*art*) for each country is included as a weighted average. It is assumed to affect both the HIV mortality rates (u_{HA}, u_{iH}, u_{niHA}) and the progression parameters for HIV positives (p_H, v_H, x_H, r_H). The additional background mortality for people with HIV is $u_{HA} = \frac{1}{(1-art)LE_{HIV}+artLE_{ART}}$. Similarly, within the weighted average for TB specific mortality rates (u_{iH}, u_{niHA}) the mortality rate if HIV positive with active TB disease but on ART is 75% less than those who are ART naïve. The progression parameters are reduced by 65% in those with HIV on ART, for example decreasing the proportion of (re-)infections becoming active: $p_{HA} = (1 - art)p_H + art_{impact} \times art \times p_H$.

- Vaccination

In the model only those that do not have active TB (Susceptibles, Latents and Recovereds) can be vaccinated (those with active TB would not be vaccinated but instead treated). Vaccination moves people into an 'Immunised' category, with associated altered risk of *Mtb*-related events. The proportion that moves is dependent on the coverage of the population age *j* at time *i* and the efficacy of the vaccine. The model is thus a representation of vaccine 'take' (i.e. all or nothing protection) rather than 'degree' protection. Hence 'efficacy' here means the proportion of those vaccinated in whom the vaccine is 100% effective, e.g. 80% efficacy means that in 80% of those vaccinated the vaccine gave 100% protection, but in 20% it had no effect. Varying coverage by age allows the model to capture both vaccination in standard programmes at certain ages and mass campaigns. Coverage is assumed to be of those receiving both doses of the vaccine and used to decide numbers moving into the 'Immunised' category (Table S3).

At exactly the end of the duration of protection, individuals return to the non-immunised strata. The vaccine is assumed to have the same efficacy on progress to active disease following primary infection, progress to active disease following re-infection of a Latent or Recovered and progress to active disease via endogenous reactivation of a Latent or relapse of a Recovered.

Efficacy of the vaccine is denoted a_I and coverage in year *k* age *j* is denoted $c_I[k,j]$. $\theta[k,j]$ is the product of these two values: $\theta[k,j] = a_I c_I[k,j]$. The proportion of the Susceptible, Recovered and Latent population, $\theta[k,j]$, that move into the Immunised category are then only those in whom the vaccine is completely (100%) efficacious. The vaccine is assumed to prevent active disease but not latent infection. Hence, with the same force of infection as in the non-vaccinated population, vaccinated Susceptibles and vaccinated Recovereds can become latently infected. However, no proportion of these infections progress to active disease during the duration of protection. Due to the reduced efficacy of vaccine take in the HIV positive population a smaller proportion is vaccinated: $\theta_H[k,j] = ef_{HA} a_I c_I[k,j]$. Here ef_{HA} is a weighted average taking into account ART coverage.

(2) Model calibration

Overview: Model calibration was performed for each country to match population size in 2009 and 2050, and TB incidence and TB mortality in both those with and without HIV in 2009 (the latest time point with UNAIDS estimates available at the time of writing). Parameter sets were drawn from the parameter space using random sampling to generate a 1,000 model outputs for each country which lay within the confidence intervals of the estimates for that country for the above listed indicators. All analyses were performed at the level of income group but calibration was performed for each country, so these country level fits were aggregated: the 1,000 fits for each country were added fit by fit to give 1,000 fits for each income group (see "Combining country level outputs for income group results" section below). Hence, the 1,000 income-group level fits reflect the uncertainty in our input natural history parameters and the uncertainty intervals in the WHO estimates to which we fit.

Details:

The 'no new vaccine' setting was calibrated to 6 outputs for each country: population size in 2009 and 2050 (UN Population Division 2010 revision), TB incidence in HIV negatives, TB incidence in HIV positives, TB mortality in HIV negatives (WHO, 2011) and TB mortality in HIV positives (calculated using WHO methodology). Two stages were required for some countries, due to the narrow confidence intervals in the estimates: the first was the basic parameter search (stages 1-5 below), the second used Markov Chain Monte Carlo to more efficiently explore the parameter space (6) if 1,000 fits had not been found after sampling at least 400,000 parameter sets. The results are shown for LIC (Fig. 2) and LMIC&UMIC (Fig. S4).

Birth and mortality rate from 2009 were taken as stable from 1900-2009 (to allow the epidemic to stabilise by 2009). The age structure from 2009 was used to initialise the population in 1900 (UN Population Division 2010 revision). It is assumed that TB is endemic in all countries by 2009. To reflect the uncertainty in natural history parameters, 25 parameters were varied between runs but remained constant over time. These were 21 natural history parameters and four calibration factors (Table S1). The calibration factors have no specific biological definition and were used to help calibrate the model to the estimates of TB burden in 2009 and population size in 2050. They were values which multiplied parameters estimated directly from data (*CDRscale* and *rmort* for case detection rate and background mortality respectively) or from the literature (α and *rmortTB* for the HIV specific progression parameters and TB associated mortality).

The calibration method proceeds as an Approximate Bayesian Computation algorithm (25) as follows

1) 400,000 parameter sets consisting of 21 natural history parameters and four calibration factors were generated using Sobol sequences. These 25 parameters were kept constant over time but varied by fit. These sequences generate a quasi-random, well-distributed set of samples of the entire parameter space. The "randtoolbox" package in the statistical programme *R* (2) was used.
2) A model output was generated using as inputs one of the parameter sets generated above and an initial 1900 population size of 20,000. From each solution, the initial population size in 1900 needed to match the correct 2009 population size could then be calculated using:

   Pop^n size in 1900

   = 20,000 x (Required pop^n size in 2009) / (Outputted pop^n size in 2009)
3) Using this corrected initial population size in 1900, a new model output was generated using the same parameter set. The outputs of TB incidence and mortality stratified by HIV status in 2009 and the population size at 2050 were then compared against the estimates from the WHO. Only three parameters vary over time to reflect improved TB control and were inputs: ART coverage, case detection rate and treatment success proportions. These changes in TB control were the same for each fit.

4) The model outputs generated from this set of parameters were assessed via a "rejection method": outputs were only deemed "to fit" when the outputs for all five indicators fell within the 95% confidence intervals of the estimates from the WHO and UN (disease indicators at 2009 and population size in 2050) and were never negative.
5) Steps 2-4 were repeated until either 1000 runs that fit had been found or at least 400,000 samples had been investigated.
6) If 1000 matching runs (fits) had not been found at this point, a different parameter space exploration was employed: Markov chain Monte Carlo (MCMC). This allows for the parameter space to be searched efficiently without the need for the calculation of a likelihood. The *EasyABC* package in R was modified in order to allow for the summary statistic to be a simple rejection algorithm – did the model output fall within the data estimate limits or not? The fits discovered via the Sobol sequencing were used as the initial parameter sets for the MCMC walk within the ABC algorithm. This was performed until 1,000 fits had been generated.

The figures in the main paper show the median value at each time step for the fitted model outputs, with the 95% range shown in the grey bands. For the income groupings, the median line is the sum of the median fit from each of the member countries, with the 95% range shown in grey bands.

The vaccine interventions were implemented in each country using the model with fitting natural history and calibration factors. Again the median value at each time point from these intervention simulations and the 95% range are presented.

The prior and posterior distributions are shown in Figure S5 for all countries. There is some difference in the fitted parameters between prior and posterior as would be expected. That many posteriors remain uniform reflects that we are, in effect, assuming a step function of a uniform distribution over the confidence intervals from the data and zero outside.

(3) Combining country level outputs for income group results

All results are presented at the income group level. To do this the following steps were used:

1. The 1,000 fits for each country were generated using the calibration method above.
2. All vaccine interventions were implemented in each country separately for all 1,000 fits. From this, for each country, there were 1,000 sets of basic outputs (e.g. total TB cases, total costs, total DALYs) for the baseline ('BCG only') and each vaccine intervention.
3. These 1,000 outputs for each country were used to calculate the impact of each vaccine intervention at the country level (e.g. TB cases averted, Net costs, DALYs averted).
4. These 1,000 outputs were combined to give vaccine impact in each income group (e.g. all of the outputs for the first fits for each country were combined to give the outputs for the first fit for the income group). At this time the cost-effectiveness measures were calculated (e.g. cost per DALY averted) and compared against the mean GNI of the income group to calculate cost-effectiveness. The cost-effective vaccine price was calculated using the mean GNI for the income group and the 1,000 income group outputs.
5. The median of these impacts and the 95% range from the 1,000 aggregated fits at the income group level were generated.

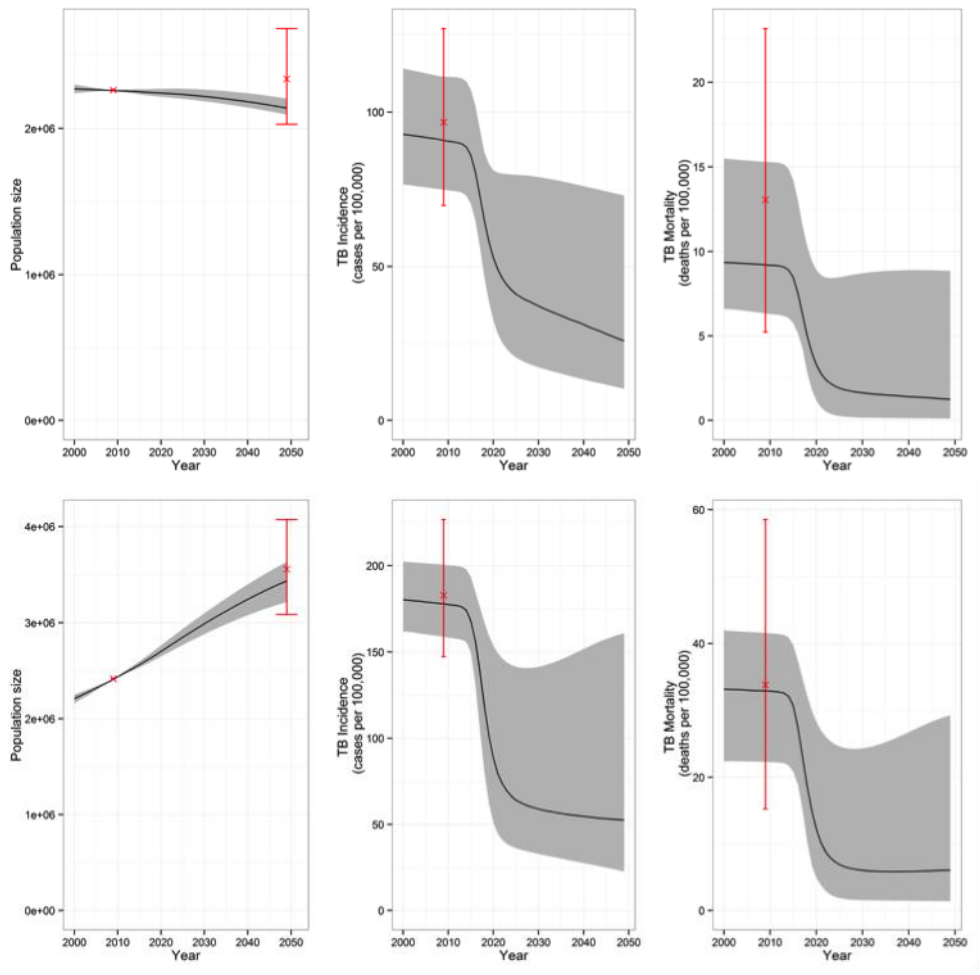

Figure S4: Model calibration for lower-middle- (top) and upper-middle- (bottom) income countries. The median (solid black line) and 95% range (grey cloud) of model fits to UN estimates on population size (/1000) and WHO estimates on total TB incidence and mortality (red, cross and range).

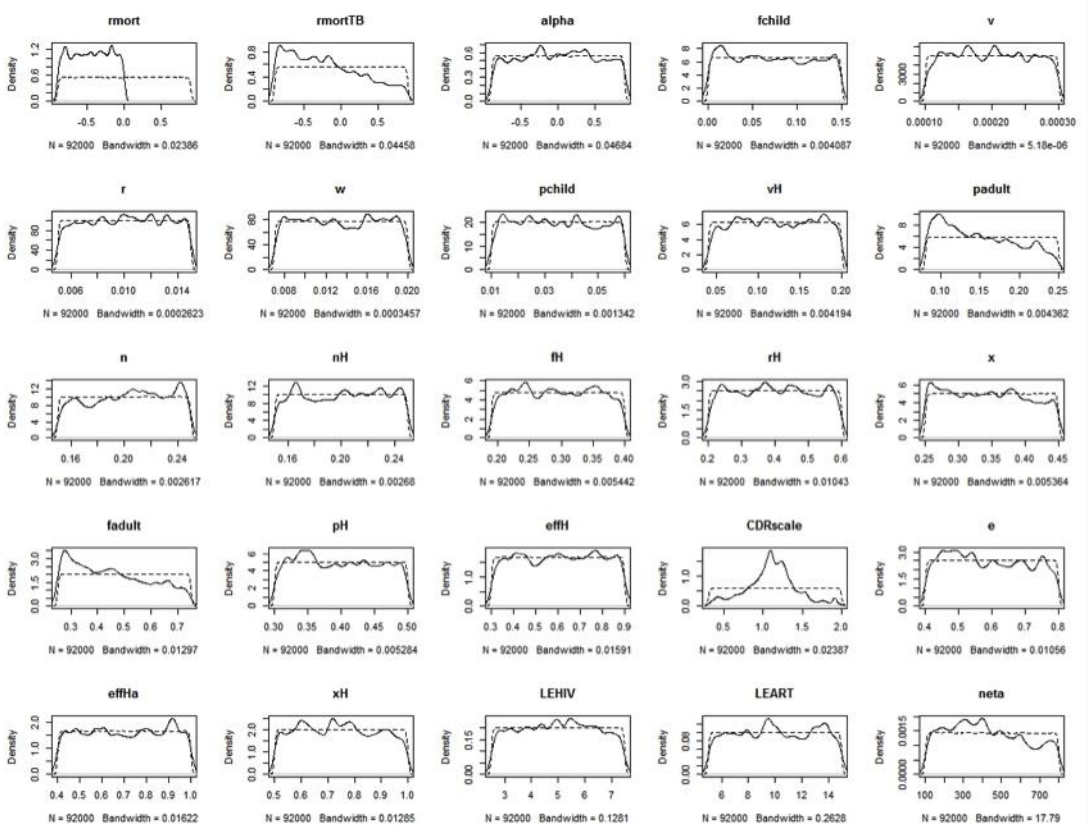

Figure S5: Plot of priors (dashed lines) and posterior (full lines) for all parameters across all three income groups. Few priors are distinct from their posterior, apart from "rmort" (a scaling of mortality rates) and "CDRscale" (a scaling for case detection ratios). For the former, this parameter was usually negative, suggesting that we had to decrease the background mortality rate. For the latter we found that the estimated CDR from the WHO was usually only a slight underestimate of that in our fits (highly peaked posterior just above 1).

(4) Model equations

The equations for the five *Mtb* sub-populations in year *k*, time step *i* and age *j* are shown below. The size of the time step is *dt*. Thus $i = 1$ is the initial time and here $i = \frac{k-(year\ of\ start)}{dt} + 1$. The method of Schenzle (1984) is used to model ageing – at the end of each year all members of the population age by one year. New-borns (births) enter the population as Susceptibles at the start of each year.

The following equations are valid for all time steps except that at the start of the year. Equations for the first time step of the year are given in the Aging section below. Firstly, the equations without vaccine use are given in order to outline the interplay between TB and HIV (Section 1.). Following this the full set of equations for the HIV negative, HIV positive, Vaccinated HIV negative and Vaccinated HIV positive subsets are given (Section 2.). The time step used was 6 months.

<u>1. Without Vaccine</u>

Transmission

$$\lambda[i] = \eta z\left(\frac{I[i] + I_H[i]}{T[i]}\right)$$

where $T[i] = \sum_{j=1}^{j=nage} \begin{bmatrix} S[i,j] + L[i,j] + I[i,j] + NI[i,j] + R[i,j] \\ +S_H[i,j] + L_H[i,j] + I_H[i,j] + NI_H[i,j] + R_H[i,j] \end{bmatrix}$ and *nage* is the number of age classes. Here $\lambda[i]$ is the force of infection. This was converted, for the discrete time formulation, to the cumulative probability which is used in the below formulas.

HIV negative

TB Susceptibles

$$S[i,j] = S[i-1,j] - (u[j] + \lambda[i-1])S[i-1,j]dt - hiv[j]S[i-1,j]dt$$

$hiv[j]$ is zero unless *j* > *14*.

Latent

$$L[i,j] = L[i-1,j] + \lambda[i-1](1-p[j])(S[i-1,j] + xR[i-1,j])dt$$
$$-(v + \lambda[i-1]p[j]x + u[j])L[i-1,j]dt - hiv[j]L[i-1,j]dt$$

New infectious active TB cases

$$new\_I[i,j] = \lambda[i-1]p[j]f[j](S[i-1,j] + xR[i-1,j])dt$$
$$+(v + \lambda[i-1]p[j]x)f[j]L[i-1,j]dt + rf[j]R[i-1,j]dt + wNI[i-1,j]dt$$

New non-infectious active TB cases

$$new\_NI[i,j] = \lambda[i-1]p[j](1-f[j])(S[i-1,j] + xR[i-1,j])dt$$
$$+(v + \lambda[i-1]p[j]x)(1-f[j])L[i-1,j]dt + r(1-f[j])R[i-1,j]dt$$

Infectious active TB cases

$$I[i,j] = I[i-1,j] + (1 - CDR[k] \times CoT[k])new\_I[i,j]dt$$
$$-(n + u[j] + u_i)I[i-1,j]dt - hiv[j]I[i-1,j]dt$$

Non-infectious active TB cases

$$NI[i,j] = NI[i-1,j] + (1 - eCDR[k] \times CoT[k])new\_NI[i-1,j]dt$$
$$-(n + u[j] + u_{ni} + w)NI[i-1,j]dt - hiv[j]NI[i-1,j]dt$$

Recovered

$$R[i,j] = R[i-1,j] + n(I[i-1,j] + NI[i-1,j])dt$$
$$+CDR[k] \times CoT[k](new\_I[i-1,j] + e\ new\_NI[i-1,j])dt$$

$$-(r+\lambda[i-1]x+u[j])R[i-1,j]dt-hiv[j]R[i-1,j]dt$$

where *CDR[k]* is the case detection rate and *CoT[k]* the proportion successfully treated in HIV negatives in year *k*.

HIV positive

TB Susceptibles

$$S_H[i,j] = S_H[i-1,j]-(u[j]+u_{HA}+\lambda[i-1])S_H[i-1,j]dt+hiv[j]S[i-1,j]dt$$

Latent

$$L_H[i,j] = L_H[i-1,j]+(\lambda[i-1](1-p_{HA}[j])(S_H[i-1,j]+x_H R_H[i-1,j])dt$$
$$-(v_H+\lambda[i-1]p_{HA}[j]x_H+u[j]+u_{HA})L_H[i-1,j])dt+hiv[j]L[i-1,j]dt$$

New infectious active TB cases

$$new\_I_H[i,j] = \lambda[i-1]p_{HA}[j]f_{HA}[j](S_H[i-1,j]+x_H R_H[i-1,j])dt$$
$$+(v_H+\lambda[i-1]p_{HA}[j]x_H)f_{HA}[j]L_H[i-1,j]dt$$
$$+rf_{HA}[j]R_H[i-1,j]dt+wNI_H[i-1,j]dt$$

New non-infectious active TB cases

$$new\_NI_H[i,j] = \lambda[i-1]p_{HA}[j](1-f_{HA}[j])(S_H[i-1,j]+x_H R_H[i-1,j])dt$$
$$+(v_H+\lambda[i-1]p_{HA}[j]x_H)(1-f_{HA}[j])L_H[i-1,j]dt$$
$$+r(1-f_{HA}[j])R_H[i-1,j]dt$$

Infectious active TB cases

$$I_H[i,j] = I_H[i-1,j]+(1-CDR_H[k]\times CoT_H[k])new\_I_H[i,j]dt$$
$$-(n+u[j]+u_{HA}+u_{iHA})I_H[i-1,j]dt+hiv[j]I[i-1,j]dt$$

Non-infectious active TB cases

$$NI_H[i,j] = NI_H[i-1,j]$$
$$+(1-eCDR_H[k]\times CoT_H[k])new\_NI_H[i-1,j]dt$$
$$-(n+u[j]+u_{HA}+u_{niHA}+w)NI_H[i-1,j]dt+hiv[j]NI[i-1,j]dt$$

Recovered

$$R_H[i,j] = R_H[i-1,j]+n(I_H[i-1,j]+NI_H[i-1,j])dt$$
$$+CDR_H[k]\times CoT_H[k](new\_I_H[i-1,j]+e\ new\_NI_H[i-1,j])dt$$
$$-(r+\lambda[i-1]x_H+u[j]+u_{HA})R_H[i-1,j]dt+hiv[j]R[i-1,j]dt$$

<u>2. With Vaccine</u>

Transmission

$$\lambda[i] = \eta z\left(\frac{I[i]+I_H[i]}{T[i]}\right)$$

where $T[i]=\sum_{j=1}^{j=nage}\begin{bmatrix} S[i,j]+L[i,j]+I[i,j]+NI[i,j]+R[i,j] \\ +S_H[i,j]+L_H[i,j]+I_H[i,j]+NI_H[i,j]+R_H[i,j] \\ +S_V[i,j]+L_V[i,j]+R_V[i,j] \\ +S_{VH}[i,j]+L_{VH}[i,j]+R_{VH}[i,j]\end{bmatrix}$ and *nage* is the number of age classes. Here $\lambda[i]$ is the force of infection. This was converted for the discrete time formulation, to the cumulative probability which is used in the below formulas.

<u>For time steps not the start of the year</u>

HIV strata

HIV negatives

TB Susceptibles

$$S[i,j] = S[i-1,j]-(u[j]+\lambda[i-1]+\theta[i,j])S[i-1,j]dt-hiv[j]S[i-1,j]dt$$

where $\theta[i,j]$ is the coverage of effective vaccine in year k at time step i to those aged j. For time steps not at the start of the year, this is only non-zero for the midpoint of the year and for those aged 1 ($j = 1$).

Latent

$$L[i,j] = L[i-1,j] + (\lambda[i-1](1-p[j])(S[i-1,j] + xR[i-1,j])dt$$
$$-(v + \lambda[i-1]p[j]x + u[j])L[i-1,j])dt$$
$$-hiv[j]L[i-1,j]dt - \theta[i,j]L[i-1,j]dt$$

New infectious active TB cases

$$new\_I[i,j] = \lambda[i-1]p[j]f[j](S[i-1,j] + xR[i-1,j])dt$$
$$+(v + \lambda[i-1]p[j]x)f[j]L[i-1,j]dt$$
$$+rf[j]R[i-1,j]dt + wNI[i-1,j]dt$$

New non-infectious active TB cases

$$new\_NI[i,j] = \lambda[i-1]p[j](1-f[j])(S[i-1,j] + xR[i-1,j])dt$$
$$+(v + \lambda[i-1]p[j]x)(1-f[j])L[i-1,j]dt + r(1-f[j])R[i-1,j]dt$$

Infectious active TB cases

$$I[i,j] = I[i-1,j] + (1 - CDR[k] \times CoT[k])new\_I[i,j]dt$$
$$-(n + u[j] + u_i)I[i-1,j]dt - hiv[j]I[i-1,j]dt$$

Non-infectious active TB cases

$$NI[i,j] = NI[i-1,j] + (1 - eCDR[k] \times CoT[k])new\_NI[i-1,j]dt$$
$$-(n + u[j] + u_{ni} + w)NI[i-1,j]dt - hiv[j]NI[i-1,j]dt$$

Recovered

$$R[i,j] = R[i-1,j] + n(I[i-1,j] + NI[i-1,j])dt$$
$$+CDR[k] \times CoT[k](new\_I[i-1,j] + e\ new\_NI[i-1,j])dt$$
$$-(r + \lambda[i-1]x + u[j])R[i-1,j]dt - hiv[j]R[i-1,j]dt - \theta[i,j]R[i-1,j]dt$$

HIV positives

TB Susceptibles

$$S_H[i,j] = S_H[i-1,j] - (u[j] + u_{HA} + \lambda[i-1])S_H[i-1,j]dt + hiv[j]S[i-1,j]dt$$

The only vaccine applied not at the start of a year is the infant vaccine for those aged 6months. It is assumed that only adults(>15yos) can become HIV positive, therefore there is no vaccine coverage for HIV positives during the year.

Latent

$$L_H[i,j] = L_H[i-1,j] + (\lambda[i-1](1-p_{HA}[j])(S_H[i-1,j] + x_H R_H[i-1,j])dt$$
$$-(v_H + \lambda[i-1]p_{HA}[j]x_H + u[j] + u_{HA})L_H[i-1,j])dt + hiv[j]L[i-1,j]dt$$

New infectious active TB cases

$$new\_I_H[i,j] = \lambda[i-1]p_{HA}[j]f_{HA}[j](S_H[i-1,j] + x_H R_H[i-1,j])dt$$
$$+(v_H + \lambda[i-1]p_{HA}[j]x_H)f_{HA}[j]L_H[i-1,j]dt$$
$$+rf_{HA}[j]R_H[i-1,j]dt + wNI_H[i-1,j]dt$$

New non-infectious active TB cases

$$new_{NI_H[i,j]} = \lambda[i-1]p_{HA}[j](1-f_{HA}[j])(S_H[i-1,j] + x_H R_H[i-1,j])dt$$
$$+(v_H + \lambda[i-1]p_{HA}[j]x_H)(1-f_{HA}[j])L_H[i-1,j]dt$$
$$+r(1-f_{HA}[j])R_H[i-1,j]dt$$

Infectious active TB cases

$$I_H[i,j] = I_H[i-1,j] + (1 - CDR_H[k] \times CoT_H[k])new\_I_H[i,j]dt$$
$$-(n + u[j] + u_{HA} + u_{iHA})I_H[i-1,j]dt + hiv[j]I[i-1,j]dt$$

Non-infectious active TB cases

$$NI_H[i,j] = NI_H[i-1,j] + (1 - eCDR_H[k] \times CoT_H[k])new\_NI_H[i-1,j]dt$$
$$-(n + u[j] + u_{HA} + u_{niHA} + w)NI_H[i-1,j]dt + hiv[j]NI[i-1,j]dt$$

Recovered

$$R_H[i,j] = R_H[i-1,j] + n(I_H[i-1,j] + NI_H[i-1,j])dt$$
$$+CDR_H[k] \times CoT_H[k](new\_I_H[i-1,j] + e\ new\_NI_H[i-1,j])dt$$
$$-(r + \lambda[i-1]x_H + u[j] + u_{HA})R_H[i-1,j]dt + hiv[j]R[i-1,j]dt$$

Vaccine strata

Vaccinated HIV negatives

TB Susceptibles

$$S_V[i,j] = S_V[i-1,j] + \theta[i,j]S[i-1,j] - \lambda[i-1]S_V[i-1,j]dt$$
$$-u[j]S_V[i-1,j]dt - d[i,j]S_V[i-1,j]\ - hiv[j]S_V[i-1,j]dt$$

Here $d[i,j]$ is the death risk at time step *i* and age *j*. This is only non-zero for the midpoint of the year and for those aged half a year plus duration of vaccine protection. The vaccinated terms are not multiplied by *dt* as they only occur at set time steps in the year.

Latent

$$L_V[i,j] = L_V[i-1,j] + \theta[i,j]L[i-1,j] + \lambda[i-1](S_V[i-1,j] + R_V[i-1,j])dt$$
$$-u[j]L_V[i-1,j]dt - d[i,j]L_V[i-1,j] - hiv[j]L_V[i-1,j]dt$$

Recovereds

$$R_V[i,j] = R_V[i-1,j] + \theta[i,j]R[i-1,j] - \lambda[i-1]R_V[i-1,j]dt$$
$$-u[j]R_V[i-1,j]dt - d[i,j]R_V[i-1,j]\ - hiv[j]R_V[i-1,j]dt$$

Vaccinated HIV positives

TB Susceptibles

$$S_{VH}[i,j] = S_{VH}[i-1,j] \text{-} \lambda[i-1]S_{VH}[i-1,j]dt$$
$$-(u[j] + u_{HA})S_{VH}[i-1,j]dt - d[i,j]S_{VH}[i-1,j]\ + hiv[j]S_V[i-1,j]dt$$

Latent

$$L_{VH}[i,j] = L_{VH}[i-1,j]$$
$$+\lambda[i-1](S_{VH}[i-1,j] + R_{VH}[i-1,j])dt$$
$$-(u[j] + u_{HA})L_{VH}[i-1,j]dt$$
$$-d[i,j]L_{VH}[i-1,j]$$
$$+hiv[j]L_V[i-1,j]dt$$

Recovereds

$$R_{VH}[i,j] = R_{VH}[i-1,j] - \lambda[i-1]R_{VH}[i-1,j]dt$$
$$-(u[j] + u_{HA})R_{VH}[i-1,j]dt - d[i,j]R_{VH}[i-1,j]\ + hiv[j]R_V[i-1,j]dt$$

Aging

If *i* is the first time point of a year *k*, then the updated values are functions of those aged one year younger in the previous time step in the method of Schenzle (Schenzle, 1984).

The key equations at the start of the year are those for Susceptibles as the number of births, *B[k]*, in year *k* are all assumed susceptible and HIV negative. Vaccination of these new borns is assumed to occur at the same time i.e. only at the start of the year.

HIV negatives

TB Susceptibles

$$S[i,j] = S[i-1,j-1] - (u[j] + \lambda[i-1])S[i-1,j-1]dt$$
$$-\theta[k-1,j-1]S[i-1,j-1]$$
$$+d[k-1,j-1](1-\theta[k-1,j-1])S_V[i-1,j-1]$$
$$-hiv[j-1]S[i-1,j-1]dt$$

HIV positives

TB Susceptibles

$$S_H[i,j] = S_H[i-1,j-1] - (u[j-1] + u_{HA} + \lambda[i-1])S_H[i-1,j-1]dt$$
$$-\theta_H[k-1,j-1]S_H[i-1,j-1]$$
$$+d[k-1,j-1](1-\theta_H[k-1,j-1])S_{VH}[i-1,j-1]$$
$$+hiv[j-1]S[i-1,j-1]dt$$

Vaccinated HIV negatives

TB Susceptibles

$$S_V[i,j-1] = S_V[i-1,j-1] + \theta[k-1,j-1]S[i-1,j-1]$$
$$-\lambda[i-1]S_V[i-1,j-1]dt - u[j-1]S_V[i-1,j-1]dt$$
$$-d[k-1,j-1](1-\theta_H[k-1,j-1])S_V[i-1,j-1]$$
$$-hiv[j-1]S_V[i-1,j-1]dt$$

Vaccinated HIV positives

TB Susceptibles

$$S_{VH}[i,j-1] = S_{VH}[i-1,j-1] + \theta[k-1,j-1]\square_H[i-1,j-1]$$
$$-\lambda[i-1]S_{VH}[i-1,j-1]dt - (u[j-1] + u_{HA})S_{VH}[i-1,j-1]dt$$
$$-d[k-1,j-1](1-\theta_H[k-1,j-1])S_{VH}[i-1,j-1]$$
$$+hiv[j-1]S_V[i-1,j-1]dt$$

Further equations for the other sub-populations are as show above, but are dependent not only the last time step but the lower age. For example, the equation for HIV negative Latents becomes:

Latent

$$L[i,j] = L[i-1,j-1]$$
$$+(\lambda[i-1](1-p[j-1])(S[i-1,j-1] + xR[i-1,j-1])dt$$
$$-(v + \lambda[i-1]p[j-1]x + u[j-1])L[i-1,j-1])dt$$
$$-hiv[j-1]L[i-1,j-1]dt$$
$$-\theta[k-1,j-1]L[i-1,j-1]$$

(5) Natural history and vaccine cost parameters

Table S1: Parameter descriptions, additional notes, proposed values and references. The parameters of the model are shown for year *k* or time step *i* and age *j*. All risks are shown per year (unless otherwise stated) and applied per time step (*dt*). Proposed values for parameters used in the sampling are for illustration purposes only.

	Symbol	Description	Notes	Proposed value (ranges for sensitivity)	References
Births	$B[k]$	Number of births in year *k*		Taken from estimates	UN Population Division (2010 revision) (3)
Transmission	$\lambda[i]$	*Mtb* transmission risk in time step *i*		Calculated per time step	
	η	Number of respiratory contacts in a year	Varies by country.	Calibrated by country to match TB incidence Range sampled: (200-800) Initial values taken from (26).	
	z	Probability of transmission per respiratory contact between an Infectious and Susceptible		0.1	(26)
Progression	$p[j]$; $p_H[j]$;	Proportion of (re-)infected Susceptible, Latents or Recovereds which develop active TB; For HIV infecteds;	Varies by age (NB those under 15 cannot be HIV positive). (27)	$p[j < 15] = 0.02$ (0.01-0.06); $p[j \geq 15] = 0.15$ (0.08 – 0.25)	Child level calibrated to percentage of TB in children. (18, 26, 28-35)
				$.p_H[j < 15] = 0$; $p_H[j \geq 15] = 0.405$ (0.3-0.5)	
	$p_{HA}[j]$	Proportion (re-)infected which develop active TB	Weighted average to include ART coverage. ART decreases the	$p_{HA} = (1 - art)p_H + art_{impact}(art)p_H$	This is varied to calibrate TB incidence and mortality in HIV infecteds.

		from the PLHIV class	proportion progressing to active by 65% (27).		
	α	Calibration factor		Calibrated to match TB incidence and mortality in HIV positives. Range sampled: (-1,1) If α <0: $p_H=\alpha^* p_H$; $v_H=\alpha^* v_H$; $r_H=\alpha^* r_H$; If α>0: $p_H=\alpha (1-p_H)+p_H$; $v_H=\alpha (1-v_H)+v_H$; $r_H=\alpha (1-r_H)+r_H$;	
	x; x_H;	Protection from developing active TB due to being latently infected; For HIV infecteds;	*(1-x)* is the value for the level of protection afforded (e.g. here 65% in HIV negatives)	x = 0.35 (0.25 – 0.45)	(18, 31-33, 36)
				x_H = 1 (0.5 – 1);	Assumed (no data).
	x_{HA}	Protection from developing active TB due to being latently infected for the PLHIV class.	Weighted average to include ART coverage	$x_{HA} =(1 - art)x_H + art_{impact}(art)x_H$	
	v; v_H;	Risk of reactivation among latent infections; For HIV infecteds;		v = 1.13 x 10^{-4} (1-3 x 10^{-4})	(18, 31, 33, 37-39)
				v_H = 0.17 (0.04 – 0.2);	
	v_{HA}	Risk of reactivation among latent infections for the PLHIV class	Weighted average to include ART coverage	$v_{HA} =(1 - art)v_H + art_{impact}(art)v_H$	
Infectious TB	$f[j]$; $f_H[j]$;	Proportion of new active cases which	Varies by age. (NB those younger than	$f[j < 15] = 0.1(0-0.15)$; $f[j \geq 15] = 0.5 (0.25-0.75)$;	(18, 30, 36, 40)

		directly become infectious; For HIV infecteds; With ART coverage.	15 cannot get HIV)	$f_H[j < 15] = 0;$ $f_H[j \geq 15] = 0.3$ (0.19 – 0.4);	(41-48)
	w	Non-infectious to infectious TB risk		0.015 (0.007 – 0.02)	(18, 29)
Mortality	$u[j];$	Background death risk at age j	Varies by age.	Varies by country	Taken from UN Population Division (2010 revision) (3)
	u_{HA}	Additional background death risk for HIV infecteds		$u_{HA} = [(1\text{-}art)LE_{HIV} + artLE_{ART}]^{-1}$	
	$rmort$	Calibration factor		Calibrated to match population size in 2050. Range sampled: (-1,1) If ($rmort < 0$): $u=(1+rmort)\,u$ If ($rmort \geq 0$): $u=(1-u)$rmort + u	
	u_i; u_{iHA}	Death risk for infectious untreated TB; For HIV infecteds	ART is assumed to reduce active TB mortality by 75%.	Calibrated to match TB mortality via $rmortTB$ (initially $u_i = 0.6$, $u_{iH} = 0.9$)	(49)
				Calibrated to match TB mortality via $rmortTB$. (initially u_{iHA} = (1-art) 0.9 + art*(0.25)*0.9)	(50, 51)
	u_{ni}; u_{niHA}	Death risk for non-infectious untreated TB; For HIV infecteds		Calibrated to match TB mortality via $rmortTB$. (Initially $u_{ni} = 0.21$, $u_{niH} = 0.3$)	(18, 26, 52, 53)
				Calibrated to match TB mortality via $rmortTB$. (Iniitially u_{niHA} = 1-art) 0.3	(54-60)

				+ art*(0.25)*0.3)	
	rmortTB	Calibration factor		Calibrated to match TB mortality. Range sampled: (-1,1) f (*rmortTB* < 0): $u_i=(1+rmortTB)u_i$, $u_{ni}=(1+rmortTB)u_{ni}$ If (*rmortTB* ≥0): $u_i=(1-u_i)rmortTB + u_i$, $u_{ni}=(1-u_{ni})rmortTB + u_{ni}$	
Natural cure and relapse	*n;* n_H	Annual risk of natural cure for TB cases; For HIV infecteds		0.2 (0.15 – 0.25)	(18)
	r; r_H;	Annual risk of relapse from Recovereds to active TB; For HIV infecteds		r = 0.01 (0.005-0.015); r_H = 0.4 (0.2-0.6)*;*	(61)
	r_{HA}	Annual risk of relapse for PLHIV class.	Weighted average to include ART coverage	$r_{HA} =(1 - art)r_H +$ $art_{impact}(art)r_H$	
Treatment	*CDR[k];* $CDR_H[k]$	Proportion of new active TB cases detected and started on treatment in year *k;* For HIV infecteds		Varies by country and over time.	(4)
	CDRscale	Calibration factor		Calibrated to match TB incidence and mortality. Range sampled: (0.5, 2) $CDR=CDRscale*CDR;\ CDR_H=CDRscale*CDR_H$	
	CoT[k]; $CoT_H[k]$	Proportion of treated cases which are successfully treated (cured or complete treatment) in year *k*; For HIV infecteds		Varies by country, HIV status and over time.	(4)

	e	Relative case detection rate of non-infectious cases		0.6 (0.4 – 0.8)	Assumed.
HIV	*hiv[j]*	Proportion of the HIV negative population that become infected with HIV at age *j*	Only those older than 14yos can become infected.	Taken from data source	(6)
	art	Proportion of the population receiving ART		Country dependent.	Taken as the ART coverage in 2009 (6) rising half the difference between this and 100% by 2020 via a sigmoidal function.
	LE_{HIV}	Average duration of HIV infection before death if ART naïve	Used to calculate the additional component of background mortality for HIV positives	5 (2.5-7.5)	
	LE_{ART}	Average duration of HIV infection on ART before death		10 (5-15)	ART halves the additional mortality rate from acquisition of HIV.
	art_{impact}	Reduction in proportion of (re-)infected Susceptible, Latents or Recovereds which develop active TB for HIV infecteds on ART	Used in several progression parameters ((re-)infection, reactivation, relapse, latent protection)	0.35	(27)
Vaccine	*c[k,j];* $c_0[k]$	Coverage of vaccine to those aged *j* at year *k*; For Newborns		Different coverage levels at different times and for different ages can be included.	To be decided.
	a_I	Efficacy in preventing active disease	Vaccine dependent.	50% / 60% / 80%	Assumed.

	ef_H; ef_{HA}	Relative lower efficacy of vaccine in those with HIV; On ART		ef_H = 0.6 (0.3-0.9); ef_{HA} = 0.8 (0.4-1)			Taken from hepatitis B vaccine data (23, 24).
	$\theta[k,j]$; $\theta_H[k]$	Proportion of Susceptibles, Latents and Recovereds aged *j* that move to the vaccine strata in year *k*; For HIV infecteds		Product of coverage and efficacy.			
	D	Duration of vaccine efficacy	Vaccine dependent.	5yrs / 10yrs / lifetime			Assumed
Costs				**LIC**	**LMIC**	**UMIC**	Assumed
	Vaccine price	Price per single dose of vaccine	Tiered	$ 1.50	$ 5	$ 10	
	Delivery costs	With DTP3		$ 0.59	$ 0.86	$ 1.18	(62-64)
		In schools		$ 1.30	$ 1.95	$ 2.60	
		In mass campaigns		$ 0.86	$ 1.29	$ 1.72	
	Mean GNI			$ 563	$ 2,250	$ 7,149	(9)

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(6) **Countries excluded from the analysis and why**

Several countries were excluded from the analysis for one of two reasons: either a lack of sufficient information on the epidemiology or demography for a country (e.g. TB incidence or population size) or an inability of our methods to determine a model fit. The latter was usually due to these countries having extremely narrow confidence intervals on their TB mortality estimates in 2009 or population size in 2050.

Table S2: Excluded countries

Income group	**Country***	**Reason for exclusion**
Low-	Comoros	Lack of sufficient TB incidence estimates from WHO
	Korea, DPR	*No fit*
	Haiti	*No fit*
Lower-Middle-	Albania	Lack of sufficient TB incidence estimates from WHO
	Belize	No notified cases and outcome estimates from WHO
	Cape Verde	No notified cases and outcome estimates from WHO
	Kiribati	No population size predictions in 2050 from UN.
	Kosovo	No birth estimates from UN
	Marshall Islands	No population size predictions in 2050 from UN.
	Micronesia, Fed. Sts.	Lack of sufficient TB incidence estimates from WHO
	Mongolia	Lack of sufficient TB incidence estimates by HIV status from WHO
	Samoa	Lack of sufficient TB incidence estimates from WHO
	São Tomé & Principe	Lack of sufficient TB incidence estimates by HIV status from WHO
	Solomon Islands	Lack of sufficient TB incidence estimates from WHO
	South Sudan	No population estimates from UN
	Syrian Arab Republic	Lack of sufficient TB incidence estimates from WHO
	Timor-Leste	No notified cases and outcome estimates from WHO
	Tonga	Lack of sufficient TB incidence estimates by HIV status from WHO
	West Bank & Gaza	No population estimates from UN
	Bolivia	*No fit*
	Cote d'Ivoire	*No fit*
	Cuba	*No fit*
	Guatemala	*No fit*
	Iraq	*No fit*
	Lao, PDR	*No fit*
	Moldova	*No fit*
	Vanuatu	*No fit*
	Yemen	*No fit*
Upper-Middle-	American Samoa	No population size predictions in 2050 from UN.
	Antigua and Barbuda	No population size predictions in 2050 from UN.
	Bosnia & Herzegovina	Lack of sufficient TB incidence estimates from WHO
	Dominica	No population size predictions in 2050 from UN.

	Jordan	Lack of sufficient TB incidence estimates by HIV status from WHO
	Libya	No notified cases and outcome estimates from WHO
	Macedonia, FYR	Lack of sufficient TB incidence estimates from WHO
	Montenegro	Lack of sufficient TB incidence estimates by HIV status from WHO
	Palau	No population size predictions in 2050 from UN.
	Seychelles	No birth or population size predictions in 2050 from UN.
	Suriname	No notified cases and outcome estimates from WHO
	Turkmenistan	Lack of sufficient TB incidence estimates from WHO
	Tuvalu	No population size predictions in 2050 from UN.
	Argentina	*No fit*
	Azerbaijan	*No fit*
	Costa Rica	*No fit*
	Grenada	*No fit*
	Iran	*No fit*
	Maldives	*No fit*
	Mauritius	*No fit*
	St. Lucia	*No fit*
	St. Vincent & the Grenadines	*No fit*
	Venezuela	*No fit*

592 * Countries excluded from the initial low- and middle-income list: 30 due to a lack of
593 estimates and 21 due to an inability to find a fit (shown in italics).
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(7) Country level parameters

Table S3: Country level parameter values.

	ART cov. (%) †		HIV	Case detection rate †		Treatment success†		VACCINE COVERAGE (%)			GNI => Income group				
Country*	**2009**	**2020**	**Incidence**	**2009**	**2020**	**2009**	**2020**	**DTP3 (6mos)**	**School attendance (10yos)**	**Mass camp.**	**2009**	**2010**	**2011**	**Income group**	**% MDR**
Afghanistan	0	0	0	44	72	86	93	66	44	72	370	420	470	LIC	3.4
Algeria	7	54	0.01	70	85	91	95	95	94	75	4470	4390	4470	UMIC	1.4
Angola	12	56	0.21	75	87	43	71	86	27	75	3590	3660	3830	LMIC	1.8
**Argentina*	42	71	0.05	68	84	42	71	93	96	71				UMIC	2.2
Armenia	11	56	0.01	74	87	75	87	95	91	68	3050	3200	3360	LMIC	9.4
**Azerbaijan*	4	52	0.01	52	76	62	81	74	64	68	4800	5380	5290	UMIC	22
Bangladesh	19	59	0.005	49	74	91	95	96	80	69	640	700	780	LIC	1.4
Belarus	12	56	0.03	78	89	73	86	98	95	85	5590	5990	5830	UMIC	32
Benin	32	66	0.1	65	82	88	94	85	63	75	770	770	780	LIC	0.5
Bhutan	11	56	0.02	72	86	91	95	95	68	69	1820	2000	2130	LMIC	2.1
**Bolivia*	11	56	0.02	65	82	84	92	82	82	71	1640	1810	2020	LMIC	1.2
Botswana	55	77	1.56	77	88	74	87	96	86	75	6270	6750	7470	UMIC	2.5
Brazil	73	86	0.013	86	93	67	83	96	94	71	8150	9540	10720	UMIC	0.91
Bulgaria	9	54	0.01	86	93	85	92	95	93	85	6080	6320	6640	UMIC	2
Burkina Faso	30	65	0.12	50	75	77	88	91	50	75	520	560	580	LIC	1.8
Burundi	13	56	0.33	59	79	86	93	96	72	75	210	230	250	LIC	3.1
Cambodia	98	99	0.05	62	81	93	96	94	81	73	700	760	820	LIC	1.4
Cameroon	15	58	0.53	48	74	77	88	66	76	75	1200	1190	1210	LMIC	3.1
Central African Republic	15	57	0.17	43	71	46	73	54	38	75	450	470	480	LIC	0.44
Chad	19	60	0.34	51	75	72	86	22	28	75	650	710	720	LIC	1.8
Chile	35	67	0.04	75	87	65	82	94	88	71	9980	10750	12280	UMIC	0.69

	ART coverage (%) †			Case detection rate†		Treatment success†		VACCINE COVERAGE (%)			GNI => Income group				
Country*	**2009**	**2020**	**HIV Incidence**	**2009**	**2020**	**2009**	**2020**	**DTP3 (6mos)**	**School attendance (10yos)**	**Mass camp.**	**2009**	**2010**	**2011**	**Income group**	**% MDR**
China	19	59	0.01	90	95	93	96	99	99	73	3620	4240	4940	UMIC	5.7
Colombia	13	57	0.05	70	85	75	87	85	85	71	5050	5480	6070	UMIC	1.5
Congo	12	56	0.28	63	81	78	89	90	58	75	90	180	190	LIC	3.1
Congo D.R.	9	54	0.155	53	76	87	93	70	59	75	1980	2240	2250	LMIC	3.1
**Costa Rica*	40	70	0.03	62	81	57	78	85	83	71	6200	6860	7640	UMIC	1.5
**Cote d'Ivoire*	23	62	0.11	55	77	77	88	62	59	75	1160	1170	1090	LMIC	2.5
**Cuba*	82	91	0.01	69	84	89	94	96	97	71				LMIC	0.96
Djibouti	8	54	0.25	70	85	78	89	87	62	72	1270			LMIC	1.8
Dominican Republic	30	65	0.09	62	81	61	80	84	83	71	4690	5030	5240	UMIC	6.6
Ecuador	18	59	0.04	48	74	71	85	99	96	71	3630	3850	4200	UMIC	4.9
Egypt	2	51	0.005	65	82	90	95	96	94	72	2160	2420	2600	LMIC	3.4
El Salvador	33	67	0.08	92	96	90	95	89	90	71	3310	3370	3480	LMIC	0.33
Eritrea	24	62	0.08	55	77	86	93	99	70	94	290	340	430	LIC	1.8
Ethiopia	37	68	0.062	66	83	81	90	51	45	75	330	360	370	LIC	1.6
Fiji	11	56	0.01	56	78	83	91	99	89	73	3890	3610	3720	LMIC	0
Gabon	25	63	0.43	84	92	91	95	45	55	75	7620	7680	8080	UMIC	3.1
Gambia	6	53	0.2	41	70	64	82	96	64	75	560	570	500	LIC	0.48
Georgia	29	65	0.01	48	74	88	94	94	85	68	2540	2680	2860	LMIC	11
Ghana	14	57	0.15	82	91	74	87	91	73	75	1190	1250	1410	LMIC	1.8
**Grenada*	0	0	0	68	84	83	91	94	92	88	7090	7130	7350	UMIC	2.1
**Guatemala*	20	60	0.08	120	110	60	80	85	77	71	2660	2740	2870	LMIC	3
Guinea	25	63	0.1	33	66	81	90	59	37	75	380	390	430	LIC	0.56
Guinea-Bissau	16	58	0.21	46	73	79	89	76	50	75	560	570	600	LIC	1.8
Guyana	60	80	0.12	64	82	66	83	93	94	71	2640	2900		LMIC	2.1

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	ART coverage (%) †		HIV	Case detection rate†		Treatment success†		VACCINE COVERAGE (%)			GNI => Income group				
Country*	**2009**	**2020**	**Incidence**	**2009**	**2020**	**2009**	**2020**	**DTP3 (6mos)**	**School attendance (10yos)**	**Mass camp.**	**2009**	**2010**	**2011**	**Income group**	**% MDR**
**Haiti*	27	64	0.15	91	95	61	80	59	40	71	670	650	700	LIC	2.1
Honduras	23	62	0.08	NA	NA	77	88	98	80	71	1780	1860	1980	LMIC	1.8
India	17	58	0.03	68	84	83	91	72	66	69	1150	1270	1420	LMIC	2.1
Indonesia	6	53	0.02	59	79	86	93	63	77	69	2160	2500	2940	LMIC	1.9
**Iran*	2	51	0.02	65	82	89	94	99	93	72	4520			UMIC	5
**Iraq*	0	0	0	71	85	82	91	77	65	72	2310	2380	2640	LMIC	3.4
Jamaica	30	65	0.13	66	83	89	94	99	96	71				UMIC	2.1
Kazakhstan	12	56	0.01	93	96	84	92	99	97	68	6780	7500	8260	UMIC	30
Kenya	28	64	0.53	78	89	66	83	88	68	75	780	810	820	LIC	3.1
**Korea, DPR*	0	0	0	91	95	89	94	94	64	91				LIC	2.1
Kyrgyzstan	3	51	0.03	72	86	86	93	96	91	68	860	840	900	LIC	26
**Lao, PDR*	21	60	0.02	27	63	93	96	78	64	73	900	1010	1130	LMIC	4.9
Lebanon	15	58	0.01	92	96	85	92	81	77	72	7850	8580	9140	UMIC	1.1
Lesotho	24	62	2.58	90	95	66	83	83	77	75	1080	1110	1210	LMIC	0.91
Liberia	11	55	0.15	54	77	86	93	49	32	75	240	260	330	LIC	1.8
Madagascar	1	51	0.02	46	73	80	90	89	60	75	420	430	430	LIC	0.49
Malawi	28	64	0.95	65	82	85	92	97	84	75	330	350	360	LIC	0.42
Malaysia	13	57	0.05	75	87	72	86	99	93	73	7550	8090	8770	UMIC	0.1
**Maldives*	3	52	0.005	82	91	40	70	96	94	69	5070	5440	5720	UMIC	2.1
Mali	31	66	0.1	70	85	79	89	72	42	75	560	600	610	LIC	1.8
Mauritania	12	56	0.07	24	62	60	80	75	45	75	1030	1010	1030	LMIC	1.8
**Mauritius*	9	55	0.1	41	70	88	94	98	94	75	7260	7780	8040	UMIC	1
Mexico	34	67	0.03	63	81	76	88	97	94	71	8670	8910	9420	UMIC	2.4
**Moldova*	13	56	0.04	71	85	58	79	93	79	85	1570	1820	1980	LMIC	19

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	ART coverage (%) †			Case detection rate†		Treatment success†		VACCINE COVERAGE (%)			GNI => Income group				
Country*	**2009**	**2020**	**HIV Incidence**	**2009**	**2020**	**2009**	**2020**	**DTP3 (6mos)**	**School attendance (10yos)**	**Mass camp.**	**2009**	**2010**	**2011**	**Income group**	**% MDR**
Morocco	15	58	0.01	88	94	85	92	99	89	72	2770	2850	2970	LMIC	0.48
Mozambique	14	57	1.19	35	67	85	92	76	63	75	430	440	460	LIC	3.5
Myanmar	13	56	0.06	69	84	83	91	99	50	69				LIC	4.2
Namibia	46	73	0.43	54	77	79	89	82	79	75	3970	4180	4700	UMIC	3.8
Nepal	5	53	0.04	73	86	90	95	92	40	69	440	490	540	LIC	2.9
Nicaragua	18	59	0.02	90	95	84	92	98	81	71	1380	1410	1510	LMIC	0.63
Niger	13	56	0.08	56	78	78	89	75	34	75	340	360	360	LIC	1.8
Nigeria	12	56	0.38	44	72	84	92	47	49	75	1160	1250	1280	LMIC	3.1
Pakistan	1	51	0.01	67	83	90	95	80	42	72	990	1050	1120	LMIC	3.4
Panama	27	64	0.09	94	97	75	87	87	94	71	6570	7000	7470	UMIC	2.1
Papua New Guinea	22	61	0.09	52	76	66	83	61	55	73	1190	1300	1480	LMIC	4.9
Paraguay	21	61	0.03	79	89	73	86	90	84	71	2230	2720	3020	LMIC	0.31
Peru	24	62	0.04	98	99	80	90	91	91	71	4190	4630	5150	UMIC	5.3
Philippines	18	59	0.005	57	78	85	92	80	79	73	1870	2060	2210	LMIC	4
Romania	66	83	0.01	83	91	80	90	89	89	85	8250	7950	8140	UMIC	2.8
Russia	10	55	0.1	78	89	63	81	97	85	68	9290	9900	10650	UMIC	20
Rwanda	53	76	0.18	62	81	79	89	97	76	75	480	520	570	LIC	3.9
**Saint Lucia*	0	0	0	69	84	45	72	97	91	88	6760	6680	6820	UMIC	2.1
**St. Vincent&the Grenadines*	0	0	0	34	67	0	50	95	95	88	6260	5990	6070	UMIC	2.1
Senegal	23	62	0.09	69	84	80	90	83	47	75	1070	1080	1070	LMIC	2.1
Serbia	16	58	0.01	89	94	85	92	91	93	85	5730	5630	5690	UMIC	0.49

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	ART coverage (%) †		HIV	Case detection rate†		Treatment success†		VACCINE COVERAGE (%)			GNI => Income group				
Country*	**2009**	**2020**	**Incidence**	**2009**	**2020**	**2009**	**2020**	**DTP3 (6mos)**	**School attendance (10yos)**	**Mass camp.**	**2009**	**2010**	**2011**	**Income group**	**% MDR**
Serbia	16	58	0.01	89	94	85	92	91	93	85	5730	5630	5690	UMIC	0.49
Sierra Leone	8	54	0.14	31	65	80	90	84	67	75	430	440	460	LIC	0.85
Somalia	2	51	0.07	43	71	63	81	41	16	72				LIC	5.2
South Africa	20	60	1.49	75	87	67	83	72	57	75	5730	6090	6960	UMIC	1.8
Sri Lanka	4	52	0.005	68	84	86	93	99	87	69	1970	2260	2580	LMIC	0.18
Sudan	2	51	0.11	50	75	75	87	93	55	72	1190	1280	1310	LMIC	1.8
Swaziland	31	65	2.66	68	84	65	82	91	80	75	3010	3050	3470	LMIC	7.7
Tajikistan	5	52	0.02	48	74	84	92	96	92	68	750	810	870	LIC	13
Tanzania	18	59	0.45	77	88	87	93	90	72	75	500	530	540	LIC	1.1
Thailand	44	72	0.13	71	85	83	91	99	97	91	3730	4150	4440	UMIC	1.7
Togo	18	59	0.27	69	84	82	91	81	77	75	520	550	570	LIC	1.8
Tunisia	14	57	0.005	78	89	83	91	98	94	72	4100	4150	4020	LMIC	3.4
Turkey	5	53	0.005	86	93	88	94	97	87	68	9060	9890	10410	UMIC	0.93
Uganda	22	61	0.74	57	78	64	82	82	61	75	470	500	510	LIC	1.4
Ukraine	6	53	0.11	76	88	54	77	50	87	85	2840	2990	3130	LMIC	16
Uruguay	31	65	0.05	96	98	76	88	95	96	71	8640	10290	11860	UMIC	0.24
Uzbekistan	11	56	0.01	45	72	84	92	99	99	68	1130	1300	1510	LMIC	23
**Vanuatu*	0	0	0	80	90	93	96	68	61	73	2520	2580	2730	LMIC	0
**Venezuela*	0	0	0	68	84	83	91	78	79	71	10230	11630	11820	UMIC	0.52
Viet Nam	19	59	0.04	55	77	92	96	95	89	73	1030	1160	1270	LMIC	2.7
**Yemen*	0	0	0	67	83	87	93	81	66	72	1070	1160	1070	LMIC	1.7
Zambia	37	68	1.17	73	86	90	95	81	75	75	1070	1110	1160	LMIC	1.8
Zimbabwe	24	62	0.84	52	76	75	87	99	82	75	380	500	660	LIC	1.9

*Those countries removed from the final analysis due to an inability to find a fit are shown in italics. †Methods for determining the level at 2020 are given in the text (Modelling methods in full).

(8) Vaccine impact in LMIC and UMIC, and results with productivity costs

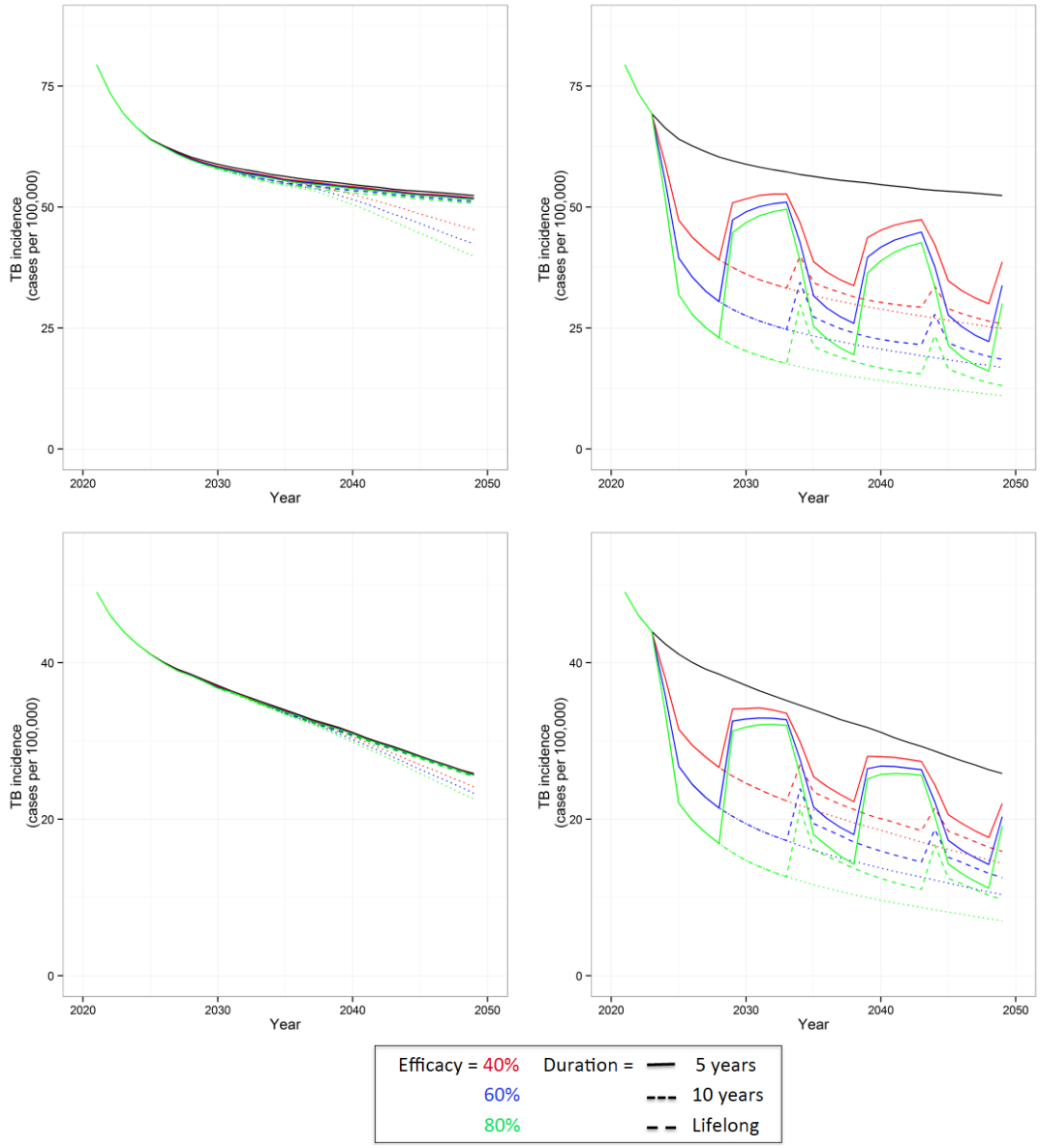

Figure S6: A vaccine targeted at infants (left) has a smaller impact on TB disease incidence than one targeted at adolescents/adults (right). Shown here is the median TB disease incidence of the calibrated runs for LMIC (top) and UMIC (bottom) (black line). The different colours represent different example vaccine efficacies (red, blue, green), whilst the line types represent example vaccine durations of protection. The 'waves' within the adolescent/adult incidence figure are due to mass campaigns.

Table S4: Impact of introduction of a new TB vaccine across 2024-2050 with societal perspective: Percentage reduction in tuberculosis (TB) cases, Cost per DALY averted and cost-effective (CE) vaccine price, by income group, vaccine age target group, vaccine duration of protection and vaccine efficacy.

		LIC (GNI = $563)			**LMIC** (GNI = $2,250)			**UMIC** (GNI = $ 7,149)			
Without new vaccine [median (95% range)]											
Total cases (millions)		32 (23-44)			46 (30-87)			19 (11-32)			
Total deaths (millions)		4.2 (2.2-7.1)			5.0 (2.0-13.5)			0.9 (0.3-3.5)			
With new vaccine [median (95% range)]											
		Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$10,000s)*		CE vaccine price (US$)†
			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective	
Infant													
Dur.	Eff.												
5 yr	40%	1.0 (0.6-1.6)	4.72 (1.78-12.77)	4.66 (1.79-13.01)	NA	0.6 (0.3-1.3)	33.11 (9.94-91.32)	33.98 (8.50-127.71)	NA	0.3 (0.1-0.7)	54.42 (5.84-232.15)	53.41 (5.94-238.90)	NA
	60%	1.5 (0.9-2.4)	3.09 (1.17-8.39)	3.09 (1.17-8.63)	NA	0.9 (0.4-2.0)	21.55 (6.60-60.68)	22.04 (54.45-84.41)	0.11 (NA-1.55)	0.4 (0.1-1.1)	34.87 (3.76-150.75)	33.52 (3.69-158.41)	0.24 (NA-3.24)
	80%	1.9 (1.2-3.2)	2.28 (0.87-6.24)	2.19 (0.82-6.24)	0.07 (NA-0.86)	1.2 (0.6-2.7)	15.82 (4.63-45.06)	16.13 (3.98-62.66)	0.42 (NA-2.40)	0.5 (0.2-1.4)	25.39 (2.58-110.06)	23.60 (2.28-117.03)	0.66 (NA-4.71)
10 yr	40%	1.8 (1.1-2.9)	2.61 (0.98-7.11)	2.55 (0.97-7.35)	NA	1.1 (0.5-2.4)	18.24 (5.32-51.85)	18.33 (4.54-71.68)	0.25 (NA-1.97)	0.5 (0.2-1.3)	28.63 (3.08-128.89)	26.95 (3.02-133.87)	0.42 (NA-4.33)
	60%	2.7 (1.6-4.3)	1.69 (0.63-4.60)	1.62 (0.57-4.7)	0.28 (NA-1.29)	1.7 (0.8-3.6)	11.62 (3.47-34.52)	11.89 (2.50-46.72)	0.82 (NA-3.26)	0.7 (0.3-1.9)	18.11 (1.67-80.91)	16.55 (1.46-84.04)	1.25 (NA-6.84)
	80%	3.5 (2.1-5.7)	1.22 (0.44-3.50)	1.13 (0.39-3.36)	0.54 (NA-1.97)	2.3 (1.1-4.8)	8.38 (2.52-25.45)	8.40 (1.73-34.55)	1.36 (0.06-4.50)	0.9 (0.4-2.6)	12.34 (1.06-59.97)	11.39 (0.18-60.43)	2.06 (NA-9.14)
Lifelong	40%	6.2 (4.1-8.3)	0.65 (0.26-1.87)	0.56 (0.20-1.67)	1.26 (0.25-3.03)	3.9 (2.1-6.2)	5.12 (1.31-18.63)	4.47 (1.02-17.26)	2.39 (0.37-7.76)	1.6 (0.6-3.1)	5.38 (0.42-32.15)	4.66 (CS-31.37)	3.53 (0.23-11.75)
	60%	8.9 (5.9-11.9)	0.40 (0.15-1.20)	0.30 (0.07-1.02)	2.07 (0.61-4.47)	5.7 (3.1-9.0)	2.99 (0.68-11.45)	2.55 (0.37-10.77)	3.97 (0.89-11.27)	2.3 (0.9-4.6)	2.75 (CS-20.33)	1.81 (CS-18.24)	5.81 (0.90-18.82)
	80%	11.5 (7.6-15.2)	0.30 (0.08-0.83)	0.16 (CS-0.70)	2.81 (1.01-5.82)	7.4 (4.0-11.7)	2.03 (0.24-8.61)	1.62 (CS -7.52)	5.40 (1.49-15.06)	3.1 (1.2-6)	1.36 (CS-13.99)	0.71 (CS-12.64)	8.15 (1.48-23.58)
Adolescent/Adult													
Dur.	Eff.												
5 yr	40%	23.9 (18.8-29.1)	0.63 (0.30-1.38)	0.50 (0.23-1.24)	1.30 (0.39-2.89)	24.3 (18.3-32)	3.50 (1.48-9.17)	3.71 (0.93-11.88)	3.45 (1.13-7.1)	17.5 (11.2-25.8)	2.45 (CS-11.61)	1.46 (CS-9.45)	6.97 (2.39-15.87)
	60%	33.1 (26.3-39.7)	0.38 (0.15-0.88)	0.26 (0.04-0.73)	2.18 (0.85-4.27)	33.9 (26.0-43.4)	2.05 (0.79-5.75)	2.04 (0.21-7.21)	5.36 (2.29-9.94)	25.0 (16.3-36.1)	0.40 (CS-5.70)	CS (CS-3.85)	10.90 (4.47-22.22)
	80%	40.7 (32.8-48.2)	0.26 (0.08-0.65)	0.14 (CS-0.45)	2.88 (1.30-5.37)	41.9 (33.1-52.9)	1.28 (0.27-3.95)	1.11 (CS-4.70)	7.08 (3.31-12.33)	31.9 (21.1-44.9)	CS (CS--3.28)	CS (CS-1.56)	14.69 (6.10-28.89)
10 yr	40%	39.6 (32.7-46.4)	0.28 (0.09-0.69)	0.16 (CS-0.49)	2.73 (1.20-5.19)	39.6 (31.6-49.4)	1.53 (0.47-4.48)	1.39 (CS-5.32)	6.44 (3.01-11.58)	30.4 (21.3-41.0)	CS (CS -3.37)	CS (CS-2.48)	13.18 (5.62-25.48)
	60%	52.1 (44.1-59.5)	0.15 (CS-0.39)	0.03 (CS-0.23)	3.98 (2.05-7.07)	52.8 (44.0-63.4)	0.72 (CS-2.54)	0.44 (CS-2.70)	9.04 (4.58-15.87)	42.4 (30.8-54.9)	CS (CS -1.10)	CS (CS-0.16)	19.95 (9.25-37.04)
	80%	61.8 (53.5-69.0)	0.07 (CS-0.24)	CS (CS-0.10)	5.03 (2.75-8.48)	63.5 (54.9-73.5)	0.26 (CS-1.59)	CS (CS-1.52)	11.52 (6.20-19.48)	53.0 (39.7-66.2)	CS (CS-0.28)	CS (CS-CS)	25.78 (12.14-47.90)
Lifelong	40%	44.1 (38.4-49.9)	0 (CS-0.13)	CS (CS-0.08)	7.39 (3.93-12.54)	42.1 (34.6-50.9)	0.14 (CS-1.49)	CS (CS-0.71)	13.25 (6.19-28.43)	34.4 (28.6-43.2)	CS (CS-CS)	CS (CS-CS)	30.38 (13.54-55.94)
	60%	58.5 (52.6-64.3)	CS (CS-0.05)	CS (CS-CS)	10.10 (5.67-16.47)	56.6 (48.7-65.6)	CS (CS-0.48)	CS (CS-CS)	18.31 (9.12-39.20)	48.5 (41.5-57.8)	CS (CS-CS)	CS (CS-CS)	41.95 (20.91-82.04)
	80%	70.0 (64.4-75.0)	CS (CS-CS)	CS (CS-CS)	12.22 (7.00-19.82)	68.3 (61.0-76.2)	CS (CS-0.05)	CS (CS-CS)	22.56 (11.23-44.06)	61.0 (53.5-69.7)	CS (CS-CS)	CS (CS-CS)	54.49 (26.16-97.53)

* Discounting included. Societal perspective includes productivity costs. CS: cost-saving (i.e. negative cost per DALY, the intervention was dominant).
†Discounting included. NA indicates that a negative vaccine price is cost-effective

(9) Sensitivity and uncertainty analysis

PRCC analysis

Partial rank correlation coefficients (PRCCs) were used to investigate the relative influence of individual parameters on the model outcomes (18, 65-67). We used the parameters from each of the model fits to calculate PRCCs. The outcome was the percentage of TB cases in HIV negatives averted by 2050 by a vaccine with 60% efficacy and 10 year duration of protection (the mid-range vaccine profile) targeted at adolescent/adults or infants. The parameters with the greatest influence (PRCC > 0.5 in the targeting adolescents/adults strategy or targeting infants strategy) and with medium influence in both strategies (PRCC > 0.1 in both targeting adolescents/adults strategy and targeting infants strategy) are shown in Figure S7.

This shows that α, the parameter governing HIV-progression, *CDRscale* (the parameter used to multiply the CDR from the data), *padult* and *pchild* (the proportion of infections that progress to active disease in adults and children respectively) are important. All parameters influence (increase/decrease) the percentage of TB cases averted as would be expected. For example, increasing the *CDRscale* reduces the number of cases in the population (as more are found and treated) and hence the % averted will be lower. Thus the correlation between *CDRscale* and percentage of cases averted is negative (Figure S7).

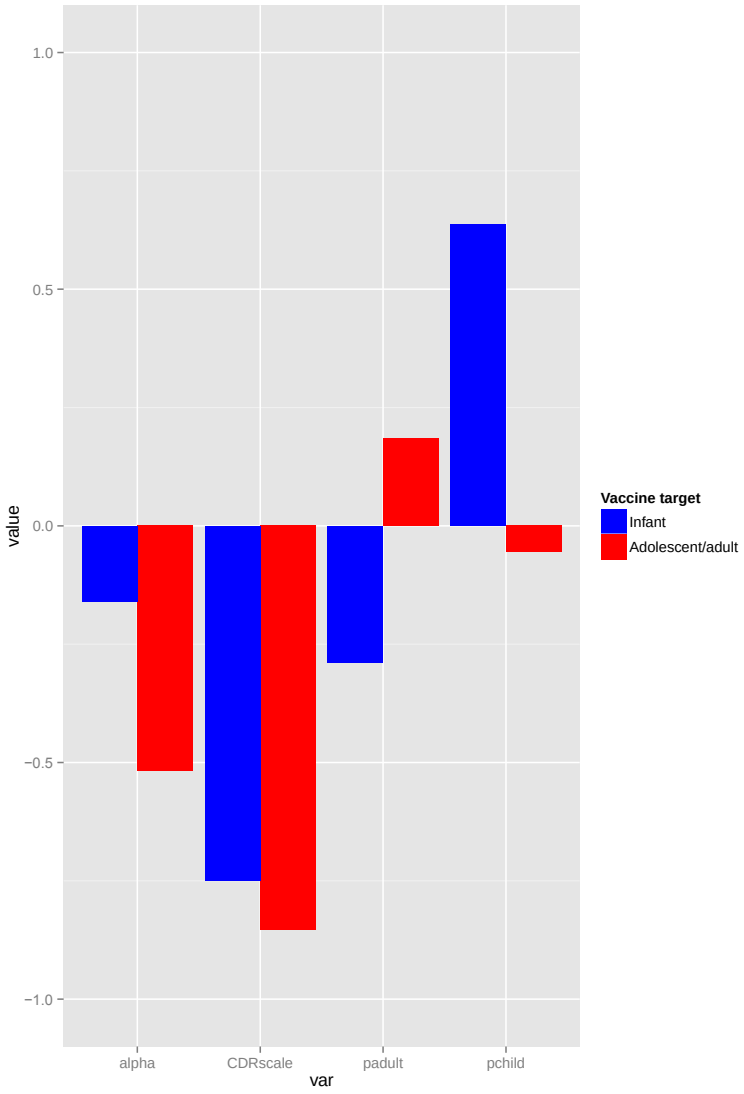

Figure S7: Partial rank correlation coefficients for the parameters with the greatest influence on the percentage of cases averted at 2050 (PRCC > 0.1) for a vaccine with 60% efficacy and 10 year duration of protection targeted at infants (blue) or adolescent/adults (red).

Scenario 1: Less optimistic TB control scale-up

In the main analysis, we include an optimistic scale-up of TB control, halving the difference between current levels in a country and 100%. In this analysis, we consider a less dramatic scale-up, increasing the current levels in a country by 25% of the difference between current levels of 100% coverage.

Results

With the decreased scale-up in TB control, there are more TB cases and deaths over the 2024-2050 time period than in the main analysis (Figure S8). The vaccines thus have a greater impact (Figure S9). As in the main analysis, a new TB vaccine targeted at infants was predicted to avert less than 12% of TB cases, compared to up to 67% when targeted at adolescent/adults.

With a larger TB burden in the absence of a new TB vaccine, the vaccines are predicted to avert a higher percentage of cases and thus be more cost-effective. When targeting infants, with our tiered pricing structure and with the lower TB control scale-up, all life-long duration of protection vaccine profiles are cost-effective in all three income-groups (Table S5). In UMIC, the higher efficacy

vaccine profiles become cost-saving. Moreover, in LIC, a 10 year duration of protection vaccine with 80% efficacy could be cost-effective at an estimate cost per DALY averted of $420 ($190-$820).

All vaccine profiles targeted at adolescent/adults with the reduced, non-conservative scale-up in TB control are estimated to be cost-effective. For all income groups, vaccines with duration of protection of at least 10 years and/or efficacy greater than 60% are estimated to be cost-saving. In UMIC, all vaccine profiles are cost-saving.

With the inclusion of productivity costs, more profiles are considered to be cost-saving, with an increasing number of infant targeted profiles becoming cost-saving. Similarly, higher vaccine prices were cost-effective when the vaccine profile was targeted at adolescent/adults. These were over double the levels in the optimistic TB control scale-up.

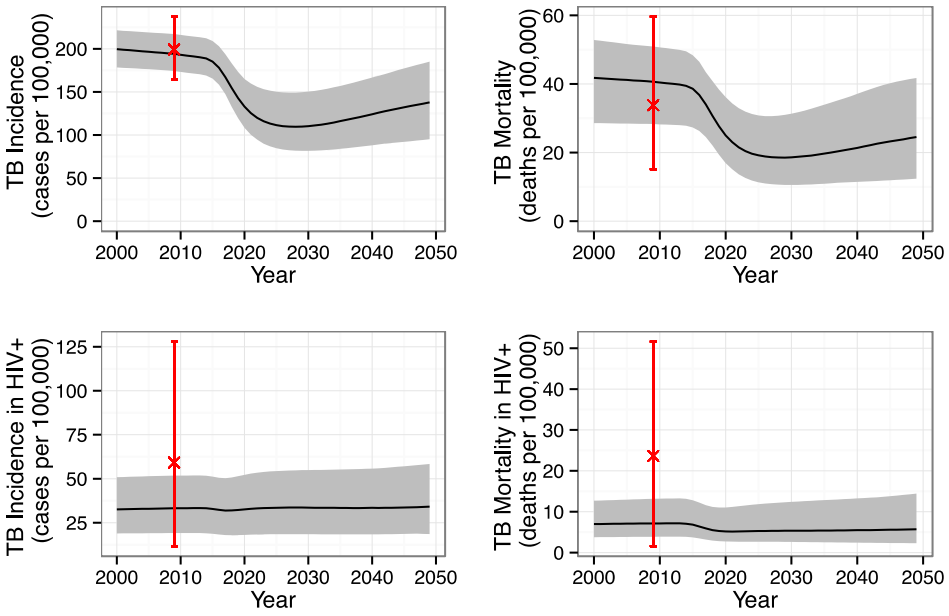

Figure S8: TB burden and vaccine impact for LICs in the less optimistic TB control scenario. Top figures show calibration and prediction of TB incidence (left) and mortality (right) for those without HIV (top two graphs), and those with HIV (bottom two graphs).

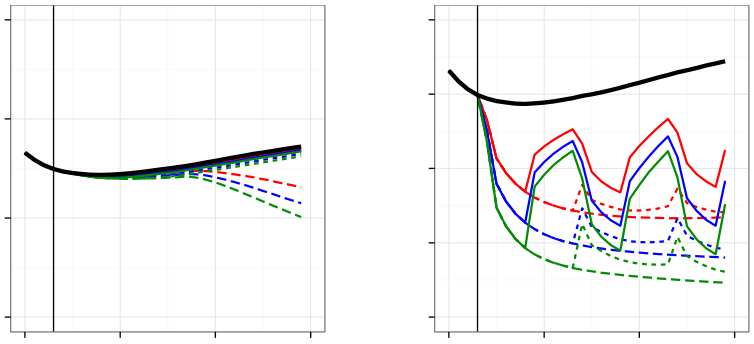

Figure S9: Impact of vaccines on TB incidence in LICs in the less optimistic TB control scenario. The impact of vaccines targeted at infants (left) is smaller than the impact of adolescent/adult targeted vaccines (right).

Table S5: Impact of introduction of a new TB vaccine across 2024-2050: Percentage reduction in tuberculosis (TB) cases, Cost per DALY averted and cost-effective (CE) vaccine price, by income group, vaccine age target group, vaccine duration of protection and vaccine efficacy in Scenario 1: Less optimistic TB control scale-up. Differences in cost-effectiveness conclusions to main analysis are shown in bold.

		LIC (GNI = $563)			**LMIC** (GNI = $2,250)			**UMIC** (GNI = $ 7,149)			
Without new vaccine [median (95% range)]											
Total cases (millions)		51 (42-61)			85 (60-118)			29 (20-41)			
Total deaths (millions)		8.7 (6.0-11.7)			12.1 (7.6-20.7)			2.4 (1.3-4.9)			
With new vaccine [median (95% range)]											
		Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$10,000s)*		CE vaccine price (US$)†
			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective	
Infant													
Dur.	Eff.												
5 yr	40%	1.3 (0.9-1.8)	1.84 (0.97-3.46)	1.76 (0.91-3.35)	0.18 (NA-0.73)	0.9 (0.5-1.6)	10.93 (4.17-25.41)	10.53 (3.98-24.60)	0.79 (NA-2.63)	0.5 (0.2-0.9)	12.34 (2.99-33.65)	11.48 (2.59-32.23)	1.51 (0.01-4.80)
	60%	1.9 (1.4-2.7)	1.18 (0.62-2.25)	1.10 (0.56-2.13)	0.55 (0.09-1.32)	1.3 (0.8-2.4)	6.90 (2.53-16.53)	6.51 (2.30-15.92)	1.58 (0.41-4.49)	0.7 (0.4-1.3)	7.07 (1.60-21.06)	6.17 (0.90-20.16)	2.86 (0.58-7.58)
	80%	2.5 (1.8-3.6)	0.85 (0.44-1.61)	0.76 (0.38-1.51)	0.91 (0.31-1.92)	1.8 (1.0-3.2)	4.94 (1.70-12.37)	4.51 (1.45-11.57)	2.42 (0.79-6.05)	0.9 (0.5-1.7)	4.66 (0.52-14.64)	3.79 (CS-13.35)	4.22 (1.10-10.91)
10 yr	40%	2.3 (1.7-3.3)	0.98 (0.50-1.89)	0.90 (0.44-1.79)	0.73 (0.19-1.66)	1.6 (1.0-3.0)	5.75 (2.12-14.01)	5.30 (1.81-13.38)	2.00 (0.61-5.29)	0.8 (0.5-1.6)	5.55 (0.86-17.01)	4.71 (CS-15.84)	3.61 (0.90-9.53)
	60%	3.5 (2.5-4.9)	0.61 (0.30-1.15)	**0.54 (0.23-1.05)**	1.36 (0.58-2.69)	2.5 (1.5-4.4)	3.47 (1.16-8.74)	3.06 (0.84-8.08)	3.46 (1.32-8.25)	1.3 (0.7-2.4)	2.75 (CS-10.20)	1.95 (CS-8.84)	5.84 (1.93-13.53)
	80%	4.6 (3.3-6.5)	**0.42 (0.19-0.82)**	**0.33 (0.12-0.72)**	2.00 (0.97-3.71)	3.3 (1.9-5.8)	2.33 (0.66-6.06)	**1.93 (0.30-5.62)**	4.86 (2.02-11.50)	1.7 (0.9-3.1)	1.40 (CS-6.89)	**0.67 (CS-5.88)**	8.23 (2.85-19.97)
Lifelong	40%	8.3 (6.9-9.7)	**0.17 (0.78-0.34)**	**0.09 (CS-0.23)**	3.84 (2.30-5.75)	5.8 (4.5-7.7)	**0.99 (0.21-2.48)**	**0.58 (CS-1.89)**	8.64 (4.71-15.41)	2.8 (2.1-4.1)	0.94 (CS-1.78)	**CS (CS-1.21)**	13.83 (6.91-24.14)
	60%	11.9 (10-13.7)	0.07 (CS-0.18)	CS (CS-0.08)	5.80 (3.56-8.38)	8.5 (6.6-11.1)	0.35 (CS-1.22)	CS (CS-0.75)	12.80 (7.29-22.59)	4.2 (3.2-6.0)	**CS (CS-0.73)**	**CS (CS-0.28)**	20.81 (10.04-37.22)
	80%	15.2 (12.8-17.5)	0.02 (CS-0.10)	CS (CS-0.02)	7.58 (4.85-10.97)	10.9 (8.5-14.2)	0.06 (CS-0.74)	CS (CS-0.32)	16.88 (9.78-29.61)	5.4 (4.2-7.9)	**CS (CS-0.15)**	CS (CS-CS)	27.66 (14.01-49.46)
Adolescent/Adult													
Dur.	Eff.												
5 yr	40%	30.1 (26.5-33.8)	**0.17 (0.08-0.30)**	0.01 (CS-0.02)	4.14 (2.66-5.85)	31.4 (27.6-36.0)	**0.87 (0.15-1.87)**	**0.44 (CS-1.33)**	9.22 (5.72-14.69)	24.4 (17.9-31.2)	**CS (CS-0.72)**	**CS (CS-0.22)**	17.96 (10.06-30.18)
	60%	40.9 (36.4-45.5)	0.07 (CS-0.17)	CS (CS-0.07)	5.97 (3.89-8.30)	42.8 (37.9-48.1)	0.33 (CS-1.03)	CS (CS-0.57)	12.99 (8.23-20.90)	33.8 (25.2-42.4)	CS (CS-CS)	CS (CS-CS)	25.68 (14.24-42.67)
	80%	49.6 (44.6-54.4)	0.03 (CS-0.10)	CS (CS-0.00)	7.46 (5.07-10.30)	51.9 (46.5-57.6)	0.05 (CS-0.60)	CS (CS-0.18)	16.28 (10.4-25.37)	41.9 (31.7-51.7)	CS (CS-CS)	CS (CS-CS)	32.19 (18.79-52.15)
10 yr	40%	48.0 (43.4-52.4)	0.04 (CS-0.11)	CS (CS-0.03)	7.19 (4.80-9.84)	49.1 (44.3-54.5)	0.17 (CS-0.72)	CS (CS-0.26)	15.16 (9.79-23.26)	39.6 (31.3-47.7)	CS (CS-CS)	CS (CS-CS)	30.71 (17.01-50.08)
	60%	61.3 (56.4-65.8)	CS (CS-0.00)	CS (CS-CS)	9.60 (6.65-12.99)	63.1 (58.1-68.2)	CS (CS-0.29)	CS (CS-CS)	20.3 (13.2-30.53)	53.0 (42.8-62.0)	CS (CS-CS)	CS (CS-CS)	41.66 (23.43-68.54)
	80%	70.8 (66.1-74.7)	CS (CS -0.00)	CS (CS-CS)	11.46 (8.04-15.26)	73.1 (68.5-77.7)	CS (CS-0.11)	CS (CS-CS)	23.74 (15.82-35.82)	63.5 (52.1-72.6)	CS (CS-CS)	CS (CS-CS)	51.10 (30.15-86.00)
Lifelong	40%	51.3 (47.7-55.2)	CS (CS-CS)	CS (CS-CS)	16.78 (11.80-22.37)	50.9 (46.6-56.0)	CS (CS-CS)	CS (CS-CS)	33.68 (22.46-51.21)	43.1 (37.3-49.9)	CS (CS-CS)	CS (CS-CS)	64.37 (37.08-100.27)
	60%	66.0 (62.5-69.7)	CS (CS-CS)	CS (CS-CS)	21.81 (15.52-29.20)	65.6 (61.4-70.2)	CS (CS-CS)	CS (CS-CS)	43.79 (29.08-65.39)	57.7 (51.6-64.4)	CS (CS-CS)	CS (CS-CS)	87.72 (52.77-135.30)
	80%	76.7 (73.6-79.6)	CS (CS-CS)	CS (CS-CS)	25.63 (18.49-33.80)	76.3 (72.9-79.9)	CS (CS-CS)	CS (CS-CS)	51.27 (34.41-75.18)	69.5 (63.9-75.3)	CS (CS-CS)	CS (CS-CS)	106.94 (62.35-165.4)

Scenario 2: Reduced HIV incidence scenario

In the main analysis, HIV incidence remains constant at the 2009 level until 2050. In this scenario analysis, we reduced HIV incidence by 50%, at the same time and in the same way, as optimistic ART scale-up. This 50% reduction is in the middle of the range of impact found from modelling increased ART coverage (8) and in line with the reduction in discordant couples seen in (68).

Results

With the optimistic scale-up in TB control, and a 50% reduction in HIV incidence, the TB burden between 2024 and 2050 was low even with no vaccine introduction (Figure S10). The impact of the introduction of different vaccine profiles (Figure S11), was thus lower than in the main analysis with no HIV incidence reduction.

In terms of cost-effectiveness, from the health sector perspective, the results were similar to those with constant HIV incidence although a minority of vaccine profiles were no longer cost-effective (Table S6). When targeted at infants, only in LICs is the vaccine profile with the highest efficacy and lifelong duration of protection cost-effective. In LMICs and UMICs, no infant vaccine profiles considered were deemed cost-effective. Meanwhile, vaccines targeted at adolescent/adults could be cost-effective if duration of protection is greater than 5 years, or duration of protection is 5 years and efficacy is greater than 80%. This is similar to the main analysis. When including productivity costs, a similar pattern was seen. Comparable vaccine prices were cost-effective with lower HIV incidence.

Thus despite there being fewer PLHIV, in whom the vaccine is less effective, with a lowered HIV incidence there is an overall lower burden of TB and hence a new TB vaccine would have the potential to avert fewer cases and thus be slightly less cost-effective in general. The main result remains, however, that a new TB vaccine targeted at adolescent/adults would be more cost-effective than one targeted at infants.

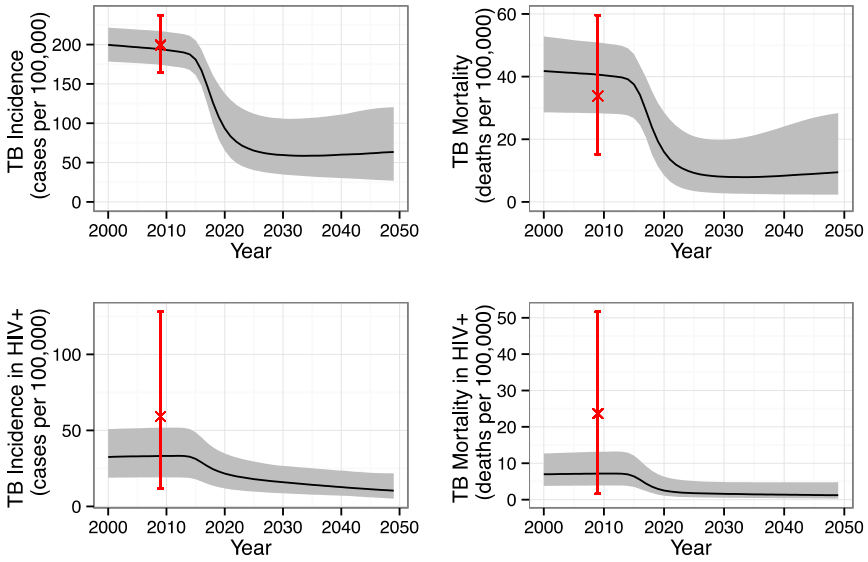

Figure S10: TB burden and vaccine impact for LICs in the reduced HIV incidence scenario. Top figures show calibration and prediction of TB incidence (left) and mortality (right) for those without HIV (top two graphs), and those with HIV (bottom two graphs).

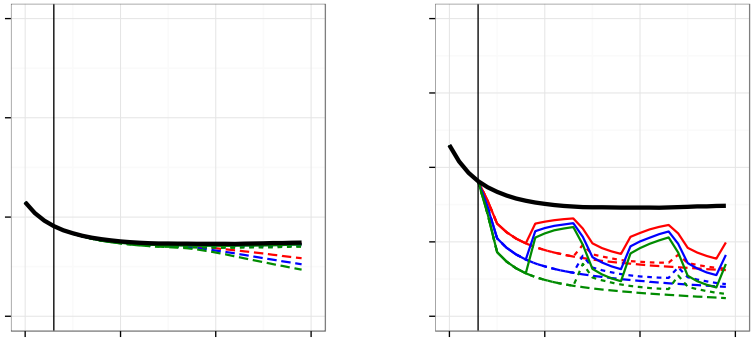

Figure S11: Impact of vaccines on TB incidence in LICs in the reduced HIV incidence scenario. The impact of vaccines targeted at infants (left) is smaller than the impact of adolescent/adult targeted vaccines (right).

Table S6: Impact of introduction of a new TB vaccine across 2024-2050: Percentage reduction in tuberculosis (TB) cases, Cost per DALY averted and cost-effective (CE) vaccine price, by income group, vaccine age target group, vaccine duration of protection and vaccine efficacy in Scenario 2: reduced HIV incidence scenario. Differences in cost-effectiveness conclusions to main analysis are shown in bold.

		LIC	(GNI = $563)			**LMIC**	(GNI = $2,250)			**UMIC**	(GNI = $ 7,149)		
Without new vaccine [median (95% range)]													
Total cases (millions)		25 (17-34)				41 (26-80)				15 (10-25)			
Total deaths (millions)		3.4 (1.8-6.0)				4.4 (1.7-12.4)				0.7 (0.3-2.2)			
With new vaccine [median (95% range)]													
		Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$1000s)*		CE vaccine price (US$)†	Reduction in cases (%)	Cost per DALY averted (US$10,000s)*		CE vaccine price (US$)†
			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective			Health sector perspective	Societal perspective	
Infant													
Dur.	Eff.												
5 yr	40%	0.2 (0-1.3)	5.79 (2.15-16.78)	5.69 (2.09-16.59)	-0.30 (-0.46-0.03)	0.5 (0-1.7)	39.45 (9.51-15.70)	38.94 (9.20-15.62)	-0.33 (-0.68-0.83)	0.1 (0-0.2)	69.11 (9.59-279.43)	67.89 (9.12-276.96)	-0.37 (-0.93-1.56)
	60%	0.3 (0-1.9)	3.81 (1.40-11.19)	3.71 (1.34-11.04)	-0.17 (-0.40-0.35)	0.7 (0.1-2.6)	26.07 (6.20-104.21)	25.58 (5.91-10.35)	-0.07 (-0.6-1.67)	0.1 (0-0.2)	44.54 (6.15-186.18)	42.93 (5.88-184.60)	0.03 (-0.81-2.68)
	80%	0.4 (0-2.6)	2.81 (1.04-8.28)	2.72 (0.97-8.10)	-0.04 (-0.36-0.65)	0.9 (0.1-3.5)	19.27 (4.51-77.97)	18.76 (4.27-77.18)	0.19 (-0.52-2.49)	0.1 (0-0.3)	32.83 (4.25-137.08)	31.17 (3.67-136.27)	0.42 (-0.75-4.15)
10 yr	40%	0.4 (0-2.4)	3.24 (1.17-9.48)	3.14 (1.13-9.24)	-0.10 (-0.37-0.50)	0.8 (0.1-3)	22.10 (5.35-88.98)	21.51 (5.10-87.94)	0.05 (-0.56-2.01)	0.1 (0-0.3)	37.35 (5.18-157.00)	36.12 (4.64-154.91)	0.18 (-0.77-3.59)
	60%	0.6 (0-3.6)	2.12 (0.76-6.22)	2.02 (0.72-6.08)	0.11 (-0.28-1.01)	1.3 (0.1-4.5)	14.23 (3.22-58.39)	13.71 (3.05-57.67)	0.52 (-0.43-3.46)	0.2 (0-0.4)	23.84 (2.88-103.78)	22.46 (2.27-101.98)	0.84 (-0.62-5.55)
	80%	0.7 (0-4.8)	1.55 (0.55-4.70)	1.45 (0.49-4.53)	0.34 (-0.19-1.51)	1.7 (0.2-6)	10.39 (2.37-43.43)	9.80 (2.08-42.59)	0.97 (-0.3-4.81)	0.2 (0-0.6)	16.29 (1.66-75.81)	15.10 (0.99-73.47)	1.52 (-0.45-7.6)
Lifelong	40%	1.3 (0.1-7)	0.86 (0.33-2.55)	0.75 (0.28-2.36)	0.90 (0.07-2.55)	2.9 (0.4-7.5)	6.10 (1.53-25.07)	5.55 (1.18-23.90)	1.97 (0.12-6.98)	0.4 (0.1-1.2)	8.39 (0.88-43.16)	7.41 (0.09-40.83)	2.7 (-0.01-9.48)
	60%	2 (0.1-10.1)	0.53 (0.20-1.61)	0.43 (0.13-1.40)	1.57 (0.38-3.86)	4.2 (0.7-10.9)	3.71 (0.84-16.28)	**3.22 (0.43-15.44)**	3.31 (0.51-10.34)	0.6 (0.2-1.8)	4.53 (CS-27.52)	3.52 (CS-26.30)	4.54 (0.64-14.1)
	80%	2.6 (0.1-12.8)	0.37 (0.12-1.16)	0.28 (0.04-0.95)	2.14 (0.67-5.00)	5.6 (0.9-14.1)	**2.61 (0.39-11.84)**	2.06 (CS-10.91)	4.49 (1.02-13.35)	0.8 (0.3-2.3)	2.52 (CS-19.48)	**1.62 (CS-17.77)**	6.31 (1.06-19.81)
Adolescent/Adult													
Dur.	Eff.												
5 yr	40%	12.2 (5.2-32.3)	0.76 (0.34-1.78)	**0.64 (0.27-1.56)**	1.02 (0.14-2.56)	10 (5.1-19.9)	4.91 (1.42-15.38)	4.28 (1.11-14.21)	2.47 (0.48-7.2)	17.3 (15-20.9)	3.34 (CS-13.16)	1.86 (CS-11.53)	6.3 (2.06-14.47)
	60%	17.8 (7.8-43.4)	0.49 (0.21-1.15)	0.36 (0.12-0.96)	1.72 (0.58-3.73)	14.6 (7.6-27.9)	**2.97 (0.70-9.81)**	**2.33 (0.22-8.67)**	4.02 (1.25-10.43)	25.4 (22.3-30.2)	0.83 (CS-6.83)	CS (CS-5.05)	9.8 (3.92-20.51)
	80%	22.9 (10.3-51.9)	0.35 (0.12-0.85)	0.22 (0.01-0.64)	2.33 (0.94-4.73)	18.8 (10-34.8)	2.08 (0.37-7.21)	1.45 (CS-6.05)	5.29 (1.94-12.81)	33.2 (29.5-38.7)	CS (CS-3. 80)	CS (CS-2.29)	13.03 (5.67-26.3)
10 yr	40%	23.5 (12.5-49.7)	0.37 (0.16-0.92)	0.25 (0.06-0.71)	2.19 (0.83-4.41)	20.9 (12.9-35.2)	2.41 (0.52-8.11)	1.72 (0.03-7.04)	4.77 (1.7-11.91)	30 (26.6-34.2)	0.99 (CS-4.59)	CS (CS-2.91)	11.57 (4.99-23.58)
	60%	33.3 (18.6-62.7)	0.229 (0.05-0.58)	0.10 (CS-0.40)	3.16 (1.43-6.04)	29.6 (19.1-47.1)	1.36 (CS-4.72)	0.64 (CS-3.45)	6.78 (3.04-15.81)	43.7 (39.4-48.2)	CS (CS-1.73)	CS (CS-0.60)	17.78 (7.85-33.95)
	80%	42.2 (24.5-72.5)	0.14 (CS-0.41)	0.02 (CS-0.21)	3.93 (1.96-7.15)	37.4 (25.1-56.5)	0.77 (CS-3.21)	0.09 (CS-2.02)	8.55 (4.08-18.56)	56.5 (51.9-60.5)	CS (CS-0.55)	CS (CS-CS)	22.57 (10.69-42.28)
Lifelong	40%	30 (20.4-52.7)	0.06 (CS-0.25)	CS (CS-0.09)	5.68 (2.78-10.55)	30.8 (22-42.1)	0.29 (CS-2.14)	CS (CS-1.10)	11.42 (5.18-26.2)	31.2 (28.4-35.4)	CS (CS-0.06)	CS (CS-CS)	26.33 (12.32-50.08)
	60%	42.9 (30.3-66.7)	CS (CS-0.09)	CS (CS-CS)	7.74 (4.18-13.43)	43.9 (32.5-56.7)	CS (CS-0.78)	CS (CS-0.06)	15.78 (7.7-33.82)	45.4 (42-49.9)	CS (CS-CS)	CS (CS-CS)	37.22 (18.9-69.81)
	80%	54.6 (40-76.6)	CS (CS-0.04)	CS (CS-CS)	9.39 (5.21-15.57)	56.1 (42.8-68.8)	CS (CS-0.23)	CS (CS-CS)	19.09 (9.73-39.71)	58.9 (55.1-62.7)	CS (CS-CS)	CS (CS-CS)	48.42 (23.69-86.54)

(10) Cost-effective vaccine price calculations

Our secondary outcome was the vaccine price that set the costs per DALY to be equal to the mean Gross National Income per capita across each income group (Low- (LIC), Lower-middle (LMIC) and Upper-middle- (UMIC)). This price is referred to as the cost-effective vaccine price. This is calculated via a series of equations laid out below for non-discounted prices.

Costs per DALY averted

= (Net costs) / (# DALYs averted)

= (Vaccine costs – Treatment costs averted) / (# DALYs averted) (1)

The vaccine costs are compromised of the number of vaccines administered and the price of each vaccine. The price of each vaccine is composed of four parts – the price of the dose (Vxd), the number of doses (2), the price of each delivery (D) and the amount of vaccine wastage (5%).

Cost of vaccine p = 2 x Vxd_p x (1/(1-0.05)) + 2 x D_p (2)

Substituting (2) into (1), letting N_p be the number of vaccines of type p given, gives (3).

Costs per DALY averted

$$= \frac{(N_p\,(2 \times Vxd_p \times (1/(1-0.05)) + 2 \times D_p) - \text{Treatment costs averted})}{(\#\ \text{DALYs averted})} \quad (3)$$

To be cost-effective, the costs per DALY averted must equal the mean GNI for the income group, which when included in (3), with some rearrangement gives (4), the final formula.

$$\text{Mean GNI} = \frac{(N_p\,(2 \times Vxd_p \times (1/(1-0.05)) + 2 \times D_p) - \text{Treatment costs averted})}{(\#\ \text{DALYs averted})} \quad (3)$$

Mean GNI x # DALYs averted = $(2N_p\,(Vxd_p \times (1/(0.95)) + D_p) - \text{Treatment costs averted})$

$$\frac{\text{Mean GNI} \times \#\ \text{DALYs averted} + \text{Treatment costs averted}}{2\,N_p} = (Vxd_p \times (1/(0.95)) + D_i)$$

$$\frac{0.95(\text{Mean GNI} \times \#\ \text{DALYs averted} + \text{Treatment costs averted})}{2\,N_p} = Vxd_p + (0.95)\,D_p$$

$$Vxd_p = 0.475\left(\frac{\text{Mean GNI} \times \#\ \text{DALYs averted} + \text{Treatment costs averted} - 2 \times N_p \times D_p)}{N_p}\right) \quad (4)$$

With discounting

To include discounting, the # DALYS averted and the treatment costs averted can be discounted independently. Formula (3) then becomes (5) with a discount rate of dr (3%).

Costs per DALY averted = Mean GNI

$$= \sum_{t=1}^{n} N_p(t)/(1+dr)^t \times \frac{(2 \times Vxd_p \times (1/(1-0.05)) + 2 \times D_p) - \text{Disc. Treatment costs av.})}{(\text{Disc. \# DALYs averted})} \quad (5)$$

Here $\sum_{t=1}^{n} N_p(t)/(1+dr)^t = \frac{(\text{No. } Vx_p \text{ at t=1})}{(1+dr)^0} + \frac{(\text{No. } Vx_p \text{ at t=2})}{(1+dr)^1} + \frac{(\text{No. } Vx_p \text{ at t=3})}{(1+dr)^2} + \ldots = d\mathbf{N}_p$

where $t = 1$ is 2024 and n = 2050-2024.

Discounting reduces the cost of giving a vaccine in the future, both in terms of delivery costs and dose price. Note that as the vaccine price remains constant, the discounted vaccine costs can be calculated by only discounting the number of vaccines given. The discounted number of vaccines of type p given is $d\mathbf{N}_p$. This changes (5) to (6), an equivalent of (3).

Costs per DALY averted =

Mean GNI = $\frac{(d\mathbf{N_p} \times (2 \times Vxd_p \times (1/(1-0.05)) + 2 \times D_p) - \text{Disc. Treatment costs av.})}{\text{(Disc. \# DALYs averted)}}$ (6)

Rearranging gives an equivalent but discounted Vx price (7).

$$Vxd_p = 0.475 \frac{(\text{Mean GNI} \times \text{\# DALYs averted} + \text{Treatment costs averted} - 2 \times dN_p \times D_p)}{\mathbf{dN_p}} \quad (7)$$

(11) DALY calculations

Disability Adjusted Life Years (DALYS) were calculated by summing the number of Years of Life Lost (YLL) and Years Lost due to Disability (YLD). Each of these was calculated using the formulas given by the Global Burden of Disease (GBD) project (69). The inputs from the model are number of TB deaths, average age of death and number of TB cases in those with and without HIV. A 3 % discounting rate was used for the discounted values. No age weighting was used (i.e. K = 0 in the GBD formula).

For the YLL, the life expectancy at age of death was calculated by subtracting the average age of death due to TB from the life expectancy for each country in that year. The total YLL was then the sum over all years of the product of the life expectancy at age of death and the number of TB deaths in each year.

For the YLD, the disability weights for TB disease in HIV negatives (0.331) and HIV positives (0.399) was used and multiplied by the length of time disabled (set at 5 months) (70) and the number of TB cases in each HIV category.

The total number of DALYS was then the sum of the above two values. We present both discounted and non-discounted values in Table S4.

(12) TB vaccine prices and delivery costs assumptions

The price of new TB vaccines will not be known until they are on the market. Tiered pricing, where low-income countries are charged less for vaccines than middle- and high-income countries, has been common practice in the past decades (71). The GAVI Alliance has been able to obtain relatively favourable vaccine prices for LICs and LMICs. GAVI vaccine prices per dose for rotavirus, pneumococcal, Human Papilloma virus and meningococcal A are approximately $4, $5, $4.50 and $0.60, respectively (72). Prices for non-GAVI eligible countries are generally not publicly available. A study on *Haemophilus influenzae* type B vaccines showed that prices in UMICs were approximately 3 times higher than GAVI prices (73). Our assumed TB prices per dose for the three income groups are seen in Table S7. These prices are varied in our vaccine price sensitivity analysis (what price makes the vaccine cost-effective?).

A number of studies have been undertaken on the costs of vaccine delivery in LICs and LMICs, but we could not identify studies from UMICs. We assumed that delivery costs in UMICs were 50% higher than in LICs, and costs in LMICs were in between these estimates. Delivery costs in routine services were based on studies from Ethiopia and Vietnam. Costs in schools were derived from a study on delivery of human papillomavirus vaccination to school-girls in Peru, Uganda and Viet Nam. Campaign delivery costs were taken from a literature review on this topic by Gandhi and Lydon (74).

Table S7: Assumed TB vaccine prices and delivery costs

	LIC	**LMIC**	**UMIC**	**References**
Vaccine price per dose	$ 1.50	$ 5.00	$ 10.00	Assumption
Delivery costs per dose:				
Routine delivery alongside BCG and DTP at birth and six months	$ 0.59	$ 0.86	$ 1.18	(62, 75)
In schools	$ 1.30	$ 1.95	$ 2.60	(76)
In mass campaigns	$ 0.86	$ 1.29	$ 1.72	(63, 74)

(13) Treatment costs

Introduction

The study objective was to estimate treatment costs per patient with TB and MDR-TB for the 91 low- and middle-income countries (LMICs) included in the cost-effectiveness analysis. Other studies have shown correlation between treatment costs and Gross National Income (GNI) per capita (73, 77). We undertook a systematic literature review to retrieve country-specific treatment cost estimates and used these data points to construct a regression equation with GNI as the independent variable.

These costs were used to multiply the number of treatment cases in order to generate the total costs spend on treatment. This minus the cost of vaccine delivery and dosage gave the net cost.

Systematic literature review

A literature review was conducted to determine mean treatment costs per patient with TB and MDR-TB. Five databases were searched; EMBASE, Medline, National Health Service Economic Evaluation Database, Cost-effectiveness Registry, and Pan American Journal of Public Health. The search period was from January 1990 until April 2013. Search terms were a combination of "tuberculosis", "multidrug resistant tuberculosis", "cost", and "treatment". Full details of the search methods, papers included, data abstraction and quality assessment will be described in a paper by Laurence *et al*. (78).

Seventy one studies on TB and sixteen studies on MDR-TB treatment costs were included in the literature review. For TB and MDR-TB, 45 and 15 countries were represented, respectively. Data were available from nine high-income countries (HICs), 12 UMICs, 12 LMICs and 13 LICs. Costs were converted to 2012 US$ values, using consumer price indices (imf.org/external/data.htm) and average annual exchange rates (oanda.com/currency/historical-rates/). For countries with more than one study available, we chose to use the estimate we considered of highest quality (according to the criteria that will be described in Laurence *et al.* (78)). For studies that compared the costs of more than one treatment strategy, we selected the intervention considered most likely to be the current standard practice in the respective country. Only half of the papers reported productivity costs and since widely different methods were used for estimating these, productivity costs were not abstracted The estimates are seen in Tables S8 and S9.

852 **Table S8. Estimates of TB treatment costs derived from the literature review (n=45) (2012 US$)**

Country	GNI per capita	Costs per patient	Country	GNI per capita	Costs per patient
Sierra Leone	340	32	Indonesia	2,940	520
Malawi	360	228	Ukraine	3,130	1276
Ethiopia	370	68	Ecuador	4,200	484
Uganda	510	339	Thailand	4,440	456
Nepal	540	108	China	4,940	436
Tanzania	540	77	Dominican Rep.	5,240	148
Burkina Faso	570	105	Colombia	6,070	948
Zimbabwe	660	43	South Africa	6,960	1,061
Haiti	700	1,937	Botswana	7,470	2,887
Bangladesh	780	93	Malaysia	8,770	1,211
Cambodia	820	621	Mexico	9,420	5,187
Kenya	820	64	Brazil	10,720	985
Tajikistan	870	464	Russia	10,730	6,307
Pakistan	1,120	166	Latvia	12,350	16,008
Zambia	1,160	13	Taiwan	19,980	1,062
Vietnam	1,270	165	New Zealand	29,140	14,666
Nigeria	1,280	120	Spain	30,890	9,633
Sudan	1,310	307	Italy	35,290	26,226
India	1,410	242	United	37,840	12,642
Ghana	1,410	145	Canada	45,560	11,478
Philippines	2,210	286	United States	48,620	17,086
Egypt	2,600	229	Australia	49,130	9,210
Syrian Arab Rep.	2,750	210			

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854 **Table S9. Estimates of MDR treatment costs derived from the literature review (n=15) (2012**
855 **US$)**

Country	GNI per capita	Costs per patient
Cambodia	820	1,556
Philippines	2,210	8,094
Ecuador	4,200	1,412
Thailand	4,440	4,550
China	4,940	1,708
Peru	5,150	4,419
South Africa	6,960	15,349
Botswana	7,470	5,417
Brazil	10,720	5,954
Russia	10,730	28,863
Latvia	12,350	54,873
Estonia	15,260	16,222
South Korea	20,870	20,379
United Kingdom	37,840	125,584
United States	48,620	202,953

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Regression analysis

Methods

TB treatment costs in the 91 LMICs were estimated using regression models informed by the data in Tables S9 and S10. Ordinary least squares (OLS) methods have been criticised in relation to cost analysis because they produce biased estimates when applied to non-normally distributed dependent variables (such as costs, which are usually right skewed) and are sensitive to outliers, especially in small datasets (79, 80). Transforming costs towards normality, for example by using a logarithmic scale, also has several limitations, arguably the most important being that inferences about log cost apply more readily to the geometric mean of costs, instead of to the arithmetic mean, which is of interest to economists. Generalised linear models (GLMs) have been advocated in cost analysis as they address some of the above problems associated with OLS. GLMs can also easily incorporate appropriate distributional assumptions, such as modelling cost data using a log-normal or Gamma distribution (80).

A GLM with a Gamma distribution and a log link was used to model TB treatment cost per case. The natural logarithm of GNI per capita was used as a single predictor of TB treatment costs per patient. The regression model was, thus, specified as:

$$\text{Log}(\overline{\text{cost}}) = \beta_0 + \beta_1 * \log(\text{GNI per capita}), \text{ cost} \sim \text{Gamma}$$

Where:

$\overline{\text{cost}}$ = Expected value of treatment cost per patient

The GLM regression model was run separately for TB (n=45 countries) and MDR-TB (n=15 countries) samples and then used to predict TB treatment costs in the 91 LMICs based on their GNI values. 95% confidence intervals were calculated for the predicted point estimates of costs:

$$L_{95} = \exp(\widehat{\text{cost}} - 1.96*SE), \quad U_{95} = \exp(\widehat{\text{cost}} + 1.96*SE)$$

Where:

L_{95}, U_{95} = Lower and upper 95% confidence limit, respectively;

$\widehat{\text{cost}}$ = Predicted value of treatment cost;

SE = Standard error.

Analyses were performed using R 3.0.1 statistical software.

Results

The results of the two regressions are shown in Table S10. Predicted values for the 91 countries are presented in Table S11. Observed and predicted costs (with 95% CIs) for DOTS and MDR-TB are depicted graphically in Figures S12 and S13, respectively.

Table S10. Results of the generalised linear regression models

	TB (n=46)		**MDR-TB (n=15)**	
	Estimate	**p-value**	**Estimate (SE)**	**p-value**
Intercept	-1.013 (1.128)	0.374	-0.785 (1.775)	0.666
Log(GNI per capita)	0.986 (0.138)	<0.001	1.156 (0.196)	<0.001
Null deviance (df)	150.61 (44)		33.17 (14)	
Residual deviance (df)	47.03 (43)		9.12 (13)	
AIC	720.25		321.7	

Table S11. Predicted treatment costs per patient used in the cost-effectiveness analysis (2012 US$)

		TB			MDR-TB		
	GNI per capita	**Predicted costs**	**Lower 95%**	**Upper 95%**	**Predicted costs**	**Lower 95%**	**Upper 95%**
Congo, Dem. Rep.	190	64	27	152	196	44	872
Somalia	200	68	29	158	208	48	908
Burundi	250	84	38	186	270	67	1,082
Liberia	330	111	53	230	372	103	1,347
Malawi	360	121	59	246	411	117	1,443
Niger	360	121	59	246	411	117	1,443
Ethiopia	370	124	61	251	424	122	1,474
Eritrea	430	144	73	282	505	153	1,660
Guinea	430	144	73	282	505	153	1,660
Madagascar	430	144	73	282	505	153	1,660
Mozambique	460	153	79	297	546	170	1,752
Sierra Leone	460	153	79	297	546	170	1,752
Afghanistan	470	157	81	302	559	176	1,782
Central African Rep.	480	160	84	307	573	181	1,812
Gambia	500	167	88	316	601	193	1,872
Uganda	510	170	90	321	615	199	1,901
Nepal	540	180	96	336	657	217	1,990
Tanzania	540	180	96	336	657	217	1,990
Rwanda	570	190	103	350	699	235	2,077
Togo	570	190	103	350	699	235	2,077
Burkina Faso	580	193	105	355	713	242	2,106
Guinea-Bissau	600	199	109	365	742	254	2,164
Mali	610	203	111	370	756	261	2,193
Zimbabwe	660	219	122	393	828	294	2,335
Haiti	700	232	131	412	886	321	2,448
Chad	720	239	135	422	916	335	2,504
Bangladesh	780	258	148	449	1,005	378	2,670
Benin	780	258	148	449	1,005	378	2,670
Myanmar	800	265	153	459	1,034	393	2,725
Cambodia	820	271	157	468	1,064	408	2,779
Kenya	820	271	157	468	1,064	408	2,779
Tajikistan	870	288	169	491	1,140	446	2,915
Kyrgyzstan	900	297	175	504	1,185	469	2,996
Mauritania	1,030	340	205	563	1,385	574	3,341
Senegal	1,070	353	214	581	1,448	608	3,446
Pakistan	1,120	369	225	604	1,510	642	3,550
Zambia	1,160	382	235	622	1,542	660	3,602
Cameroon	1,210	398	246	644	1,589	686	3,680
Lesotho	1,210	398	246	644	1,669	731	3,809

		TB			MDR-TB		
	GNI per capita	**Predicted costs**	**Lower 95%**	**Upper 95%**	**Predicted costs**	**Lower 95%**	**Upper 95%**
Djibouti	1,270	418	260	671	1,765	786	3,963
Vietnam	1,270	418	260	671	1,669	731	3,809
Nigeria	1,280	421	262	676	1,765	786	3,963
Ghana	1,410	463	292	734	1,781	795	3,989
India	1,420	466	294	738	1,829	823	4,065
Papua New Guinea	1,480	486	308	765	1,991	918	4,318
Nicaragua	1,510	495	315	778	2,106	987	4,495
Uzbekistan	1,510	495	315	778	2,008	928	4,344
Honduras	1,980	647	423	990	2,156	1,017	4,570
Bhutan	2,130	695	457	1,058	2,948	1,517	5,731
Philippines	2,210	721	475	1,094	3,017	1,562	5,828
Congo, Rep.	2,250	734	484	1,113	3,208	1,688	6,096
Sri Lanka	2,580	840	558	1,265	3,348	1,781	6,291
Egypt	2,600	847	562	1,275	3,418	1,829	6,388
Georgia	2,860	930	619	1,397	4,111	2,305	7,333
Guatemala	2,870	933	621	1,401	4,274	2,419	7,551
Guyana	2,900	943	628	1,416	4,310	2,444	7,600
Indonesia	2,940	956	637	1,435	4,510	2,586	7,866
Morocco	2,970	965	643	1,449	4,510	2,586	7,866
Paraguay	3,020	981	654	1,473	4,528	2,599	7,890
Ukraine	3,130	1,016	677	1,525	4,583	2,638	7,963
Jamaica	3,300	1,071	714	1,607	4,656	2,690	8,060
Armenia	3,360	1,090	726	1,636	4,711	2,729	8,133
Swaziland	3,470	1,125	749	1,690	4,803	2,794	8,254
El Salvador	3,480	1,128	751	1,695	5,006	2,940	8,522
Fiji	3,720	1,205	801	1,813	5,061	2,980	8,595
Angola	3,830	1,240	824	1,867	5,321	3,168	8,937
Tunisia	4,020	1,301	863	1,962	5,433	3,250	9,083
Ecuador	4,200	1,358	899	2,053	5,639	3,400	9,353
Thailand	4,440	1,435	947	2,175	5,658	3,414	9,378
Algeria	4,470	1,444	952	2,191	6,111	3,746	9,969
Namibia	4,700	1,518	998	2,309	6,321	3,901	10,242
China	4,940	1,594	1,044	2,434	6,608	4,113	10,616
Peru	5,150	1,661	1,084	2,545	6,685	4,170	10,716
Dominican Rep.	5,240	1,690	1,101	2,592	7,381	4,687	11,624
Azerbaijan	5,290	1,705	1,111	2,619	7,498	4,774	11,777
Serbia	5,690	1,833	1,185	2,833	7,655	4,890	11,981
Belarus	5,830	1,877	1,211	2,909	8,166	5,270	12,652
Colombia	6,070	1,953	1,255	3,040	8,205	5,300	12,704
Bulgaria	6,640	2,134	1,357	3,355	8,482	5,506	13,069
South Africa	6,960	2,235	1,414	3,535	8,941	5,845	13,675
Botswana	7,470	2,397	1,502	3,825	9,523	6,275	14,451

		TB			MDR-TB		
	GNI per capita	**Predicted costs**	**Lower 95%**	**Upper 95%**	**Predicted costs**	**Lower 95%**	**Upper 95%**
Panama	7,470	2,397	1,502	3,825	9,181	6,023	13,995
Gabon	8,080	2,590	1,605	4,178	10,272	6,826	15,460
Romania	8,140	2,609	1,615	4,213	10,763	7,183	16,127
Kazakhstan	8,260	2,647	1,635	4,283	10,763	7,183	16,127
Malaysia	8,770	2,808	1,719	4,585	11,939	8,030	17,751
Lebanon	9,140	2,924	1,780	4,806	12,314	8,297	18,276
Mexico	9,420	3,013	1,825	4,974	12,607	8,504	18,689
Turkey	10,410	3,325	1,981	5,580	12,984	8,770	19,224
Russia	10,650	3,400	2,018	5,728	13,427	9,079	19,857
Brazil	10,720	3,422	2,029	5,772	13,681	9,255	20,222
Uruguay	11,860	3,781	2,203	6,490	14,041	9,504	20,744
Chile	12,280	3,913	2,266	6,759	14,894	10,086	21,995

Figure S12. Observed (n=45) and predicted TB treatment costs (2012 US$)

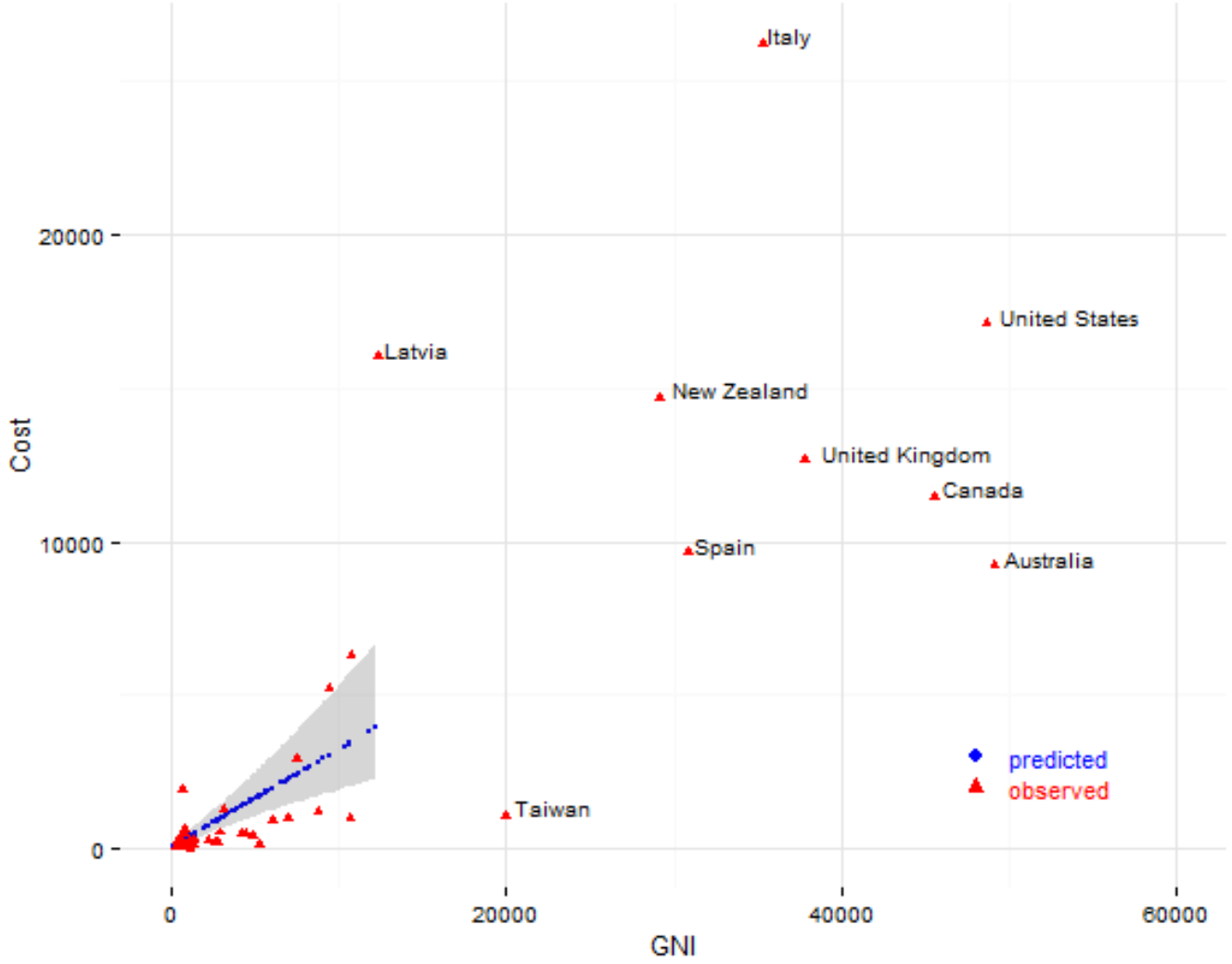
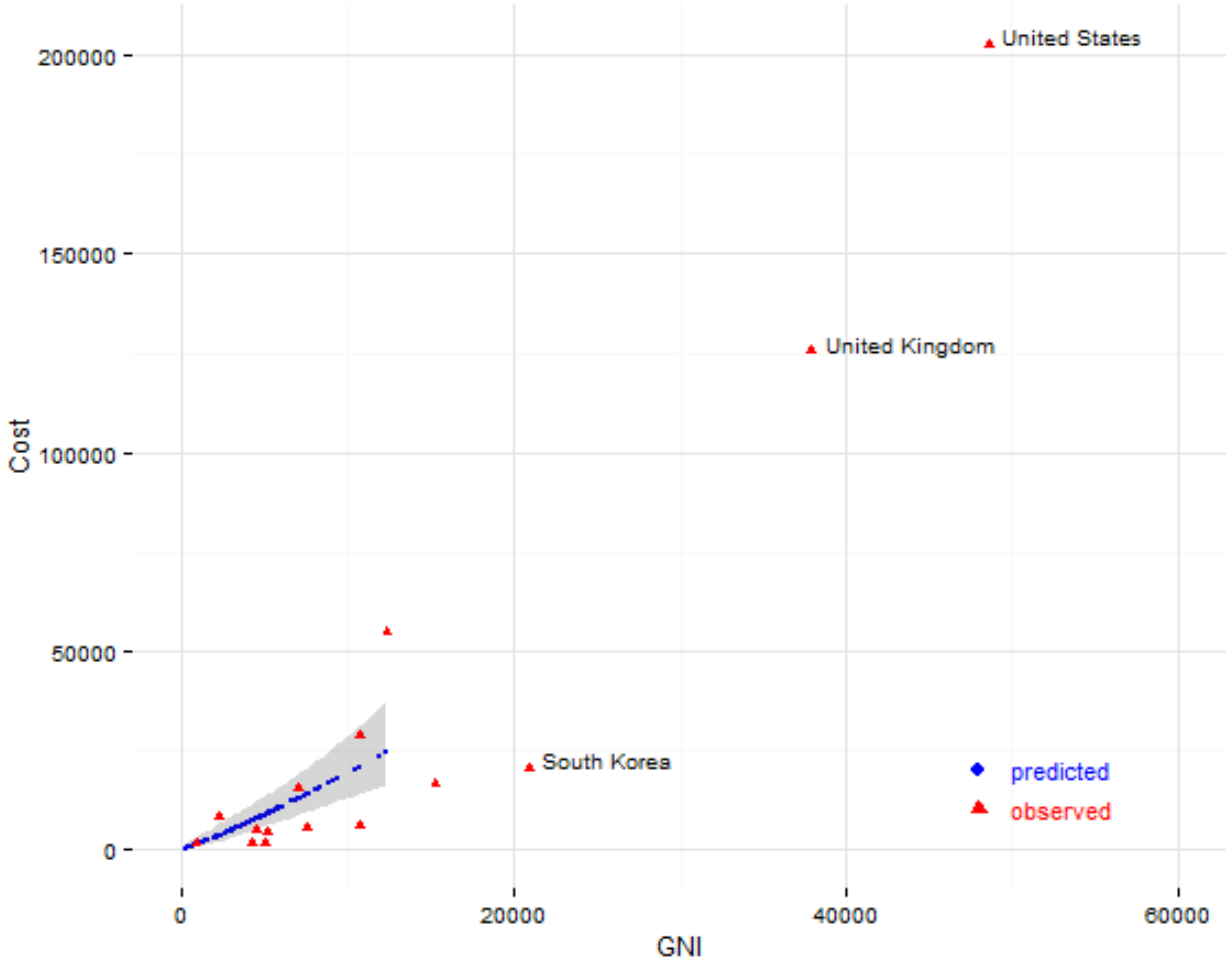


Figure S13. Observed (n=15) and predicted TB-MDR treatment costs per patient (2012 US$)



(14) Productivity costs

Productivity costs associated with TB morbidity were included in a scenario analysis in the cost-effectiveness analysis. We assumed that TB and MDR-TB patients would lose two and six months of productive time due to illness, respectively (81, 82). We did not include productivity costs due to mortality. We used the human capital method for valuing the potential production not performed due to TB morbidity (83). In this approach, either the average, the minimum wage or average earnings in the respective country is used for valuing productive time.

Data

The database of the International Labour Organization (ILOSTAT, www.ilo.org/ilostat) was used to obtain data on the average, nominal monthly earnings. These were estimated as average earnings across all economic sectors. The earnings included gross remuneration in kind and in cash received on a regular basis by employees, inclusive of annual vacation, paid leave and holidays.

2011 monthly earnings were obtained in local currency and converted to US$ using the average exchange rate for 2011. When 2011 data were not available, the most recent estimate was used and adjusted for inflation to the 2011 value. For some countries, monthly earnings were not available, and hourly, daily, weekly or annual earnings were given. In such instances, the following assumptions were used to derive monthly rates: eight working hours/day, five working days/week and 22 working days/calendar month. Income data were available for 36 countries in the ILO database (Table S12).

Table S12. Yearly earnings and GNI per capita for 36 countries (2011 US$)

Country	Earnings	GNI per capita
Ethiopia	879	370
Madagascar	4012	430
Tajikistan	653	870
Kyrgyzstan	1728	880
Uzbekistan	858	1510
Philippines	2265	2210
Sri Lanka	1602	2580
Georgia	4311	2860
Guyana	5539	2900
Indonesia	1784	2940
Paraguay	4441	3020
Ukraine	4492	3130
Armenia	3386	3360
El Salvador	3505	3480
Egypt	3590	4200
Ecuador	5434	4200
China	4885	4940
Azerbaijan	4824	5290
Serbia	9507	5690
Belarus	3156	5830
Colombia	5467	6070

Country	Earnings	GNI per capita
Bulgaria	4891	6530
Dominican Rep.	3852	7030
Panama	7280	7470
Botswana	8198	7470
Romania	7044	7910
Kazakhstan	6087	8260
Mexico	5279	9420
Brazil	9664	10720
Russia	9296	10730
Uruguay	13460	11860
Chile	13425	12280
Latvia	11376	12350
United Kingdom	48015	37840
Canada	46305	45560
United States	39948	48620

Regression analysis

An OLS regression model was run with the available average earnings data as dependent variable and GNI per capita as the independent variable. The regression was equation was used to predict monthly earnings for the 91 LMICs considered in the cost-effectiveness analysis. The regression model was:

Monthly earnings = $\beta_0 + \beta_1$*GNI per capita

Results

The results of the regression model are presented in Table S13. The model used for prediction was:
Earnings = 11.726 + 0.081 * GNI per capita

Predicted monthly earnings for the 91 countries are presented in Table S14.

Table S13. Results of the earnings OLS regression model

	Estimate (SE)	p-value
Intercept	11.726 (49.825)	0.815
GNI per capita	0.081 (0.004)	<0.001
Adjusted R-squared	0.94	

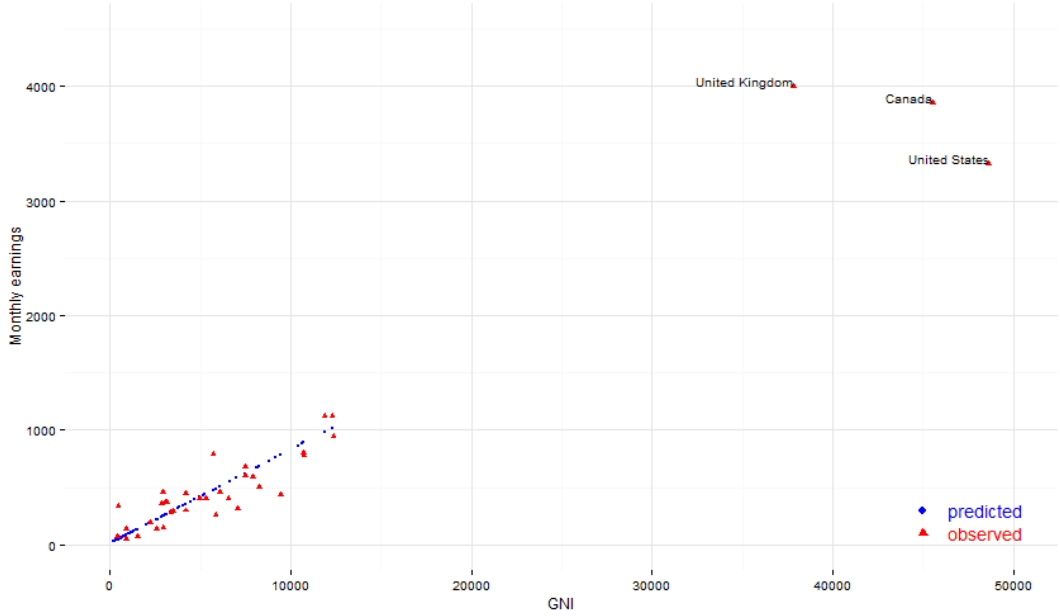
Table S14. Predicted average monthly earnings (2011 US$)

Country	GNI per capita	Earnings	Country	GNI per capita	Earnings
Congo, Dem. Rep.	190	27	Honduras	1980	174
Somalia	200	28	Bhutan	2130	186
Burundi	250	32	Philippines	2210	193
Liberia	330	39	Congo, Rep.	2250	196
Malawi	360	41	Sri Lanka	2580	223
Niger	360	41	Egypt	2600	225

Ethiopia	370	42	Georgia	2860	246
Eritrea	430	47	Guyana	2900	249
Guinea	430	47	Indonesia	2940	252
Madagascar	430	47	Morocco	2970	255
Mozambique	460	49	Paraguay	3020	259
Sierra Leone	460	49	Ukraine	3130	268
Afghanistan	470	50	Jamaica	3300	282
Central African Republic	480	51	Armenia	3360	287
Gambia	500	53	Swaziland	3470	296
Uganda	510	53	El Salvador	3480	297
Nepal	540	56	Fiji	3720	316
Tanzania	540	56	Angola	3830	325
Rwanda	570	58	Tunisia	4020	341
Togo	570	58	Ecuador	4200	356
Burkina Faso	580	59	Thailand	4440	375
Guinea-Bissau	600	61	Algeria	4470	378
Mali	610	62	Namibia	4700	397
Zimbabwe	660	66	China	4940	416
Chad	720	71	Peru	5150	433
Bangladesh	780	76	Argentina	5170	435
Benin	780	76	Dominican Republic	5240	441
Myanmar	800	77	Serbia	5690	478
Cambodia	820	79	Belarus	5830	489
Kenya	820	79	Colombia	6070	509
Tajikistan	870	83	Bulgaria	6640	555
Kyrgyzstan	900	85	South Africa	6960	582
Mauritania	1030	96	Panama	7470	623
Senegal	1070	99	Botswana	7470	623
Pakistan	1120	103	Gabon	8080	673
Zambia	1160	107	Romania	8140	678
Cameroon	1210	111	Kazakhstan	8260	688
Lesotho	1210	111	Malaysia	8770	730
Vietnam	1270	116	Lebanon	9140	760
Djibouti	1270	116	Mexico	9420	783
Nigeria	1280	117	Turkey	10410	864
Ghana	1410	127	Russia	10650	884
India	1420	128	Brazil	10720	889
Papua New Guinea	1480	133	Uruguay	11860	983
Uzbekistan	1510	135	Chile	12280	1017
Nicaragua	1510	135			

Observed and predicted earnings are depicted in Figure S14.

Figure S14. Observed (n=36) and predicted monthly earnings (2011 US$)



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