Table of Contents

1 MODEL STRUCTURE AND PARAMETERISATION ........................................................................ 5

2 MODEL EQUATIONS ............................................................................................................. 5

2.1 TIME STEPS NOT THE FIRST TIME STEP OF THE YEAR ................................................. 6

2.1.1 Unvaccinated (non-first time step) ............................................................................. 6

2.1.2 Vaccinated (non-first time step) ................................................................................. 7

2.2 FIRST TIME STEP OF THE YEAR (AGEING AND VACCINE DELIVERY/WANING) .......... 9

2.2.1 Unvaccinated (first time step of the year) .................................................................... 9

2.2.2 Vaccinated (first time step of the year) ....................................................................... 11

3 MODEL PARAMETERS AND DATA SOURCES ...................................................................... 14

3.1 NATURAL HISTORY (BIOLOGICAL) PARAMETERS .......................................................... 14

3.1.1 Age-related impact on TB natural history ................................................................. 14

3.1.2 HIV-related impact on TB natural history ............................................................... 14

3.2 DEMOGRAPHIC AND HIV INCIDENCE PARAMETERS ............................................... 20

3.2.1 Births and deaths ...................................................................................................... 20

3.2.2 HIV incidence ......................................................................................................... 22

3.3 SOCIAL MIXING PARAMETERS ....................................................................................... 23

3.4 TB AND HIV CONTROL MEASURES ............................................................................ 24

3.4.1 BCG ......................................................................................................................... 24

3.4.2 Case detection rate and treatment success ............................................................... 24

3.4.3 Antiretroviral therapy .............................................................................................. 25

3.4.4 Private sector delivery of care ................................................................................... 25

4 CALIBRATION METHODOLOGY ....................................................................................... 28

4.1 EPIDEMIOLOGICAL CALIBRATION TARGETS ............................................................. 28

4.1.1 China ....................................................................................................................... 28

4.1.2 South Africa ............................................................................................................ 29

4.1.3 India ........................................................................................................................ 30

4.2 EPIDEMIOLOGICAL CALIBRATION ............................................................................. 32

4.3 CALIBRATED MODEL .................................................................................................... 32

4.3.1 China ....................................................................................................................... 32

4.3.2 South Africa ............................................................................................................ 35

4.3.3 India ........................................................................................................................ 39

5 VACCINATION ................................................................................................................ 43

5.1 VACCINE EFFICACY ................................................................................................... 43

5.1.1 Vaccine efficacies for prevention of infection versus disease .................................. 43

5.1.2 Host infection status for efficacy (pre-versus post-infection) .................................. 44

5.1.3 Duration of protection and waning .......................................................................... 44

5.2 VACCINE IMPLEMENTATION AND COVERAGE ....................................................... 44

6 OUTCOME ESTIMATION .................................................................................................. 47

7 SUPPORTING EPIDEMIOLOGICAL DATA AND INFORMATION ....................................... 47

7.1 NEW TRANSMISSION VERSUS REACTIVATION/RELAPSE ......................................... 47

7.2 PREVALENCE OF LTBI BY AGE ................................................................................ 48

8 SUPPORTING VACCINE DATA AND INFORMATION ...................................................... 50

8.1 UNCERTAINTY RANGES ............................................................................................... 50

8.1.1 China ....................................................................................................................... 50

8.1.2 South Africa ............................................................................................................ 51

8.1.3 India ........................................................................................................................ 52

8.2 CASES AVOIDED .......................................................................................................... 52

8.2.1 China ....................................................................................................................... 52

8.2.2 South Africa ............................................................................................................ 53

8.2.3 India ........................................................................................................................ 54

8.3 MORTALITY IMPACT ................................................................................................... 55
1 Model structure and parameterisation

We developed an age-stratified population-level compartmental deterministic transmission model, calibrated to the TB epidemics in China, India and South Africa in R.(47)

As described in the main text, the model includes five TB natural history states: susceptible, latent, bacteriologically-positive active disease, bacteriologically-negative active disease, and recovered from disease. All of these compartments were represented by an unvaccinated and a vaccinated stratum (Figure 1A), and age was modelled in single years from 0-100 years. In the South Africa model, due to the high HIV co-infection proportion (60%),(4, 48) each natural history state was modelled with an HIV-positive and HIV-negative stratum. An HIV infected state was not explicitly included in the India or China model, as HIV coinfection in patients with TB was very low in these countries (3% and 1%, respectively).(1)

Background mortality ($u$) was age-specific and occurred in all infection states. In South Africa, background mortality ($u$) was all non-AIDS deaths, and AIDS mortality ($u_{HIV}$) only occurred in HIV-positive populations. Infection occurred at rate $\lambda$, of which a proportion ($p$) experienced fast progression directly to primary disease. The remainder of those infected ($1-p$) entered latency. Latently infected individuals could develop active disease through ‘slow progression’ of the existing infection ($v$) or ‘fast progression’ upon reinfection ($lp$). Some protection against development of disease was assumed to be provided by the immune response to existing or past infection, so reinfection events in latent and recovered populations were proportionally reduced by $x$. For all new active cases, regardless of whether fast or slow progressors, a proportion ($f$) developed bacteriologically positive active disease, and the remainder ($1-f$) developed bacteriologically-negative disease. Detection (parameterised as the case detection ratio, CDR) and effective treatment (CoT) of active cases moved new cases directly to the recovered state. CDR was scaled down by factor $e$ for bacteriologically-negative disease, as these cases were considered less likely to be detected. The undetected cases entered the relevant active disease state and became prevalent cases. Prevalent cases could be removed by natural cure ($n$) to the recovered state, TB death ($u/u_{HIV}$ differing for infectious versus non-infectious, respectively), or all-cause mortality ($u$), and by AIDS-related mortality in HIV-positive populations in the South Africa model ($u_{HIV}$). Individuals with bacteriologically negative disease could convert to infectious disease at rate $w$, at which point there was another opportunity for case detection at the bacteriologically-positive disease case detection rate. The population in the recovered state could be re-infected at rate $2x$ to develop primary active disease ($p$) or enter the latent pool ($1-p$). Reactivation/relapse ($r$) to one of the active disease states was also possible from the recovered state, at a higher rate than reactivation from the latent state. In the South Africa model, HIV infection could occur in any TB natural history state, and incident HIV in 0-4 year olds was assumed to occur at birth by mother to child transmission.

The impact of vaccination was implemented in the vaccinated stratum as described in section 5 below. As vaccine was modelled as “leaky”, all infection and disease states existed in the vaccinated stratum. All vaccinated individuals move to the vaccinated stratum, where the relevant natural history parameters for progression to infection and/or disease were reduced proportionally based upon the vaccine efficacy.

Full model equations are provided in section 2 below. In addition to the full model equations and information provided in this appendix, model code and data are made available for download at this link:10.5281/zenodo.4003442.

2 Model equations

The series of difference equations comprising the vaccinated and unvaccinated model strata, and time steps at the beginning of the year and later in the year are provided in this section. The first set of equations is valid for all time steps except that at the start of the year. Equations for the first time step of the year are provided in the second section, as this is the step in which the population is aged, and could be vaccinated or protection wane. Equations for both the HIV-positive and HIV-negative strata are provided. The ‘HIV-negative stratum’ represented ‘all TB’ in the China and India models and therefore the HIV-positive stratum was not employed; whereas in South Africa, HIV coinfection was explicitly modelled, so HIV incidence rates ($hiv$) were non-zero and both the HIV-negative and -positive strata were employed.

Given $i=1$ was the first time step in the model, successive time steps were given by $i = \frac{k-(year \ of \ start)}{dt} + 1$. The size of the time step was $dt$, which in this research was selected as 0.5 years as a balance between sufficient granularity and computing time/capacity. Life span was limited to no more than 100 years. Following the methodology of Schenzle (1984),(49) ageing was implemented in the model on an annual basis by transitioning.
the population in a given sub-population of age \( j \), to the same sub-population of age \( j+1 \) at the very end of each year. New-borns (births) entered the population as susceptibles at the start of each year.

The equations for the five \( M.tb \) sub-populations (susceptible, latently infected, infectious active disease, non-infectious active disease, and recovered) in year \( k \), time step \( i \) and age \( j \) are provided for HIV-negative and HIV-positive populations.

For the baseline scenario of no vaccination, \( \theta_{Sd}, \theta_{Rd}, \theta_{SH}, \theta_{LH}, \theta_{RH} \) and \( d \) were set to zero. In the vaccine scenarios later in this section, vaccination was delivered by setting the relevant theta to a non-zero value equal to vaccine coverage for the appropriate age groups during the first time step of each vaccination year.

**Transmission**

\[
\lambda(i,j) = \eta_{calc} \sum_{y=nygrp}^{y=nygrp} \eta[m,y] z \left( l[i,y] + l_v[i,j] + IH[i,y] + IH_v[i,j] \right) / T[i,y]
\]

Where

\[
T[i,y] = \sum_{y=jmin}^{jmax} \left[ S[i,j] + L[i,j] + l[i,j] + NI[i,j] + R[i,j] + S_V[i,j] + L_V[i,j] + l_V[i,j] + \right.
\]

\[
\]

\[
NIH_V[i,j] + RH_V[i,j].
\]

\( nygrp \) was the number of contact age groups, \( m \) was the age group of the individual exposed to infection (including \( j \) ), \( y \) was age group of contacts, \( \eta[m,y] \) was number of respiratory contacts of age group \( m \) with contacts of age group \( y \), \( \eta_{calc} \) was the calibration factor for model fitting, \( z \) was the probability of transmission per respiratory contact between an infectious active case and a susceptible person (which is later scaled for protection afforded by latent infection), and \( jmin \) and \( jmax \) were the lower and upper bounds of age classes within a contact age group (\( y \)).

### 2.1 Time steps not the first time step of the year

#### 2.1.1 Unvaccinated (non-first time step)

\( CDR[k,j] \) was the case detection rate (proportion) for year \( k \) in age \( j \), and \( CoT[k] \) was the proportion of detected cases that were treated successfully in a given year.

**HIV-negative susceptible**

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

**HIV-negative latent**

\[
L[i,j] = L[i-1,j] + \lambda[i-1,j](1-p[j])(S[i-1,j] + xL[i-1,j])dt -
\]

\[
(\nu[j] + \lambda[i-1,j]p[j])x + u[j])L[i-1,j]dt - hiv[k-1,j]L[i-1,j]
\]

**HIV-negative new infectious active TB cases**

\[
new_{I[i,j]} = \lambda[i-1,j]p[j]f[j](S[i-1,j] + xL[i-1,j] + xR[i-1,j])dt + \nu[j]f[j]L[i-1,j]dt
\]

\[
+ r[j]f[j]R[i-1,j]dt + wNI[i-1,j]dt
\]

**HIV-negative new non-infectious active TB cases**

\[
new_{NI[i,j]} = \lambda[i-1,j]p[j](1-f[j])(S[i-1,j] + xL[i-1,j] + xR[i-1,j])dt
\]

\[
+ \nu[j](1-f[j])L[i-1,j]dt + r[j](1-f[j])R[i-1,j]dt
\]

**HIV-negative infectious active TB cases**

\[
i[i,j] = I[i-1,j] + (1 - CDR[k,j] \times CoT[k])new_{I[i,j]} - (n[j] + u[j] + u[j])I[i-1,j]dt
\]

\[
- hiv[k-1,j]I[i-1,j]
\]
**HIV-negative non-infectious active TB cases**

\[ NI[i,j] = NI[i - 1,j] + (1 - CDR[k,j] \times CoT[k] \times e) \text{new}_{NI[i,j]} - (n[j] + u[j] + uni[j] + w)NI[i - 1,j]dt - hint[k - 1,j]NI[i - 1,j] \]

**HIV-negative recovered**

\[ R[i,j] = R[i - 1,j] + n[j](l[i - 1,j] + NI[i - 1,j])dt + (CDR[k,j] \times CoT[k])(new_{R}[i,j] + e \times new_{NI}[i,j]) - (r[j] + \lambda[i - 1,j]u[j])R[i - 1,j]dt - hint[k - 1,j]R[i - 1,j] \]

**HIV-positive susceptible**

\[ SH[i,j] = SH[i - 1,j] - (u[j] + uH[j] + \lambda[i - 1,j])SH[i - 1,j]dt + hint[k - 1,j]S[i - 1,j] \]

**HIV-positive latent**

\[ LH[i,j] = LH[i - 1,j] + \lambda[i - 1,j](1 - pHa[j])SH[i - 1,j] + (xHa \times RH[i - 1,j])dt - (uHa[j] + \lambda[i - 1,j]pHa[j]xHa + u[j] + uH[j])LH[i - 1,j]dt + hint[k - 1,j]L[i - 1,j] \]

**HIV-positive new infectious active TB cases**

\[ new_{IH[i,j]} = \lambda[i - 1,j]pHa[j]fH[j](SH[i - 1,j] + (xHa \times LH[i - 1,j]) + (xHa \times RH[i - 1,j])dt + vHa[j]fH[j]H[i - 1,j]dt + RHa[j]fH[j]RH[i - 1,j]dt + wNI[i - 1,j]dt \]

**HIV-positive new non-infectious active TB cases**

\[ new_{NIH[i,j]} = \lambda[i - 1,j]pHa[j](1 - fH[j])(SH[i - 1,j] + (xHa \times LH[i - 1,j]) + (xHa \times RH[i - 1,j])dt + vHa[j](1 - fH[j])LH[i - 1,j]dt + RHa[j](1 - fH[j])RH[i - 1,j]dt \]

**HIV-positive infectious active TB cases**

\[ IH[i,j] = IH[i - 1,j] + (1 - CDR[k,j] \times CoT[k])\text{new}_{IH[i,j]} - (nH[j] + u[j] + uH[j] + uniHa[j] + w)IH[i - 1,j]dt + hint[k - 1,j]H[i - 1,j] \]

**HIV-positive non-infectious active TB cases**

\[ NIH[i,j] = NIH[i - 1,j] + (1 - CDR[k,j] \times CoT[k] \times e)\text{new}_{NIH[i,j]} - (nH[j] + u[j] + uH[j] + uniHa[j] + w)NIH[i - 1,j]dt + hint[k - 1,j]NIH[i - 1,j] \]

**HIV-positive recovered**

\[ RH[i,j] = RH[i - 1,j] + nH[j](IH[i - 1,j] + NIH[i - 1,j])dt + (CDR[k,j] \times CoT[k])(\text{new}_{IH[i,j]} + e \times \text{new}_{NIH[i,j]}) - (RHa[j] + \lambda[i - 1,j]xHa + u[j] + uH[j])RH[i - 1,j]dt + hint[k - 1,j]R[i - 1,j] \]

### 2.1.2 Vaccinated (non-first time step)

Vaccination and waning only occurred at first time step of year, so in the middle of the year the only transitions for vaccinated populations were between states within the vaccinated stratum, and, for South Africa, from the HIV-negative to HIV-positive stratum. Vaccine efficacy was modelled as ‘leaky’, therefore those in vaccinated categories could be infected and develop disease during all time steps, but with reduced rates of development of infection or disease due to vaccine effects. The parameters affected by vaccination depended upon the vaccine type. Prevention of infection vaccines with vaccine efficacy (effI) reduced infection rates (\( \lambda \)) by 1-effI. Vaccine efficacy against disease (effD) was applied in the same manner to development of disease parameters, which were the proportion developing primary active disease (p), and risk of reactivation from the latent (r) and recovered (R) classes. In the South African model, in scenarios where HIV co-infection reduced the efficacy of the vaccine, the vaccine efficacy parameters (effI and effD) for HIV positive vaccinated states were multiplied by the relative efficacy in HIV positive populations (VEH).

For vaccines only efficacious when delivered pre-infection (PRI), \( \theta_L \) and \( \theta_R \) were zero. For vaccines only efficacious when delivered post-infection (PSI), \( \theta_S \) was zero, therefore \( S_v \) remained at zero.
HIV-negative vaccinated susceptibles
\[ S_v[i, j] = S_v[i - 1, j] - (u[j] + (1 - eff I)Λ[i - 1, j])S_v[i - 1, j]dt - hiv[k - 1, j]S_v[i - 1, j] \]

HIV-negative vaccinated latent
\[ L_v[i, j] = L_v[i - 1, j] + (1 - eff I)Λ[i - 1, j](1 - (1 - eff D)p[j])S_v[i - 1, j] + xR_v[i - 1, j]dt \]
\[-(1 - eff D)v[j] + (1 - eff I)Λ[i - 1, j]x + u[j]L_v[i - 1, j]dt \]
\[-hiv[k - 1, j]L_v[i - 1, j] \]

HIV-negative vaccinated new infectious active TB cases
\[ \text{new } L_v[i, j] = (1 - eff I)Λ[i - 1, j](1 - eff D)p[j]f[j]S_v[i - 1, j] + xL_v[i - 1, j] + xR_v[i - 1, j]dt \]
\[ + (1 - eff D)v[j]L_v[i - 1, j]dt + (1 - eff D)r[j]f[j]R_v[i - 1, j]dt \]
\[ + wNI_v[i - 1, j]dt \]

HIV-negative vaccinated new non-infectious active TB cases
\[ \text{new } N_l_v[i, j] = (1 - eff I)Λ[i - 1, j](1 - eff D)p[j](1 - f[j])S_v[i - 1, j] + xL_v[i - 1, j] + xR_v[i - 1, j]dt \]
\[ + (1 - eff D)v[j](1 - f[j])L_v[i - 1, j]dt + (1 - eff D)r[j](1 - f[j])R_v[i - 1, j]dt \]

HIV-negative vaccinated infectious active TB cases
\[ l_v[i, j] = l_v[i - 1, j] + (1 - CDR[k, j] \times CoT[k])\text{new } l_v[i, j] \]
\[-(n[j] + u[j] + u[n][j])l_v[i - 1, j]dt - hiv[k - 1, j]l_v[i - 1, j] \]

HIV-negative vaccinated non-infectious active TB cases
\[ N_l_v[i, j] = N_l_v[i - 1, j] + (1 - CDR[k, j] \times CoT[k] \times e)\text{new } N_l_v[i, j] \]

HIV-negative vaccinated recovered
\[ R_v[i, j] = R_v[i - 1, j] + n[j]l_v[i - 1, j] + N_l_v[i - 1, j]dt \]
\[ + (CDR[k, j] \times CoT[k])(\text{new } l_v[i, j] + e \times \text{new } N_l_v[i, j]) \]
\[-((1 - eff D)r[j] + (1 - eff I)Λ[i - 1, j]x + u[j])R_v[i - 1, j]dt - hiv[k - 1, j]R_v[i - 1, j] \]

HIV-positive vaccinated susceptible
\[ S_vH[i, j] = S_vH[i - 1, j] - (u[j] + u[H]) + (1 - eff I \times VEH)Λ[i - 1, j]S_vH[i - 1, j]dt \]
\[ + hiv[k - 1, j]S_v[i - 1, j] \]

HIV-positive vaccinated latent
\[ L_vH[i, j] = L_vH[i - 1, j] + (1 - eff I \times VEH)Λ[i - 1, j] \]
\[ + (1 - eff D \times VEH)p[H][j](S_vH[i - 1, j] \]
\[ + xHaR_vH[i - 1, j]dt \]
\[-((1 - eff D \times VEH)v[H][j]) \]
\[ + (1 - eff I \times VEH)Λ[i - 1, j] \]
\[ + (1 - eff D \times VEH)p[H][j]xHa + u[j] + u[H][j])L_vH[i - 1, j]dt \]
\[-hiv[k - 1, j]L_vH[i - 1, j] \]

HIV-positive vaccinated new infectious active TB cases
\[ \text{new } L_vH[i, j] = (1 - eff I \times VEH)Λ[i - 1, j] \]
\[ + (1 - eff D \times VEH)p[H][j]f[H][j](S_vH[i - 1, j] \]
\[ + xHaL_vH[i - 1, j] + xHaR_vH[i - 1, j]dt \]
\[ + (1 - eff D \times VEH)v[H][j]f[H][j]L_vH[i - 1, j]dt \]
\[ + (1 - eff D \times VEH)r[H][j]R_vH[i - 1, j]dt + wNI_vH[i - 1, j]dt \]
HIV-positive vaccinated new non-infectious active TB cases

\[ \text{new}_{NI}V[i,j] = (1 - efff \times VEH)\lambda[i-1,j](1 - effD \times VEH)\phi Ha[j](1 - fH[j])S_V[i-1,j] + xHaLV[i-1,j] + xHa\phi R_V[i-1,j]dt \]

HIV-positive vaccinated infectious active TB cases

\[ I_V[i,j] = I_V[i-1,j] + (1 - CDR[k,j] \times CoT[k])\text{new}_{I_V}[i,j] \]

\[ - (nH[i,j] + uH[i,j] + uH[a])I_V[i-1,j]dt + hiv[k-1,j]I_V[i-1,j] \]

HIV-positive vaccinated non-infectious active TB cases

\[ N_{IV}[i,j] = N_{IV}[i-1,j] + (1 - CDR[k,j] \times CoT[k] \times e)\text{new}_{N_{IV}}[i,j] \]

\[ - (nH[i,j] + uH[i,j] + uniHa[j] + w)N_{IV}[i-1,j]dt + hiv[k-1,j]N_{IV}[i-1,j] \]

HIV-positive vaccinated recovered

\[ R_V[i,j] = R_V[i-1,j] + nH[i,j]I_V[i-1,j] + N_{IV}[i-1,j]dt \]

\[ + (CDR[k,j] \times CoT[k])(\text{new}_{I_V}[i,j] + e \times \text{new}_{N_{IV}}[i,j]) - \left( (1 - efff \times VEH)\phi Ha[j](1 - fH[j])S_V[i-1,j] + xHa\phi R_V[i-1,j]dt + hiv[k-1,j]R_V[i-1,j] \right) \]

2.2 First time step of the year (ageing and vaccine delivery/wareing)

Ageing was implemented using the method of Schenzle (1984). In the first time step (i) of any given year, the updated values for populations of age j were functions of those aged one year younger (j-1) in the previous time step (i-1).

New-borns (births) entered the population as susceptibles at the start of each year. In China and India, in year k (B[k]) entered the unvaccinated HIV-negative susceptible population in the first time step of the year. In the South Africa model, due to mother-to-child transmission of HIV, a proportion of births (BH[k]) entered the unvaccinated susceptible population in the HIV positive stratum in the first time step of the year (see sections 3.2.1 and 3.2.2 for detail). All remaining births for South Africa in year k (B[k]) entered the unvaccinated HIV-negative susceptible population in the first time step of the year.

Vaccination (Θ) and end of duration of protection (d) were assumed to occur in the first time step of a given year. As the vaccine was modelled as ‘leaky’, all those receiving vaccine were moved to the vaccinated stratum, thus \( θ_a[j,k] \) was equal to percentage coverage for age group j of infection state a in year k. Here, \( d[i,j] \) is the risk of ending vaccine protection at time step i and age j. The vaccinated terms are not multiplied by \( dt \) as they only occur at set time steps in the year.

Therapeutic vaccination was not considered, so transition from unvaccinated to vaccinated strata was only possible for the susceptible, latent and recovered populations (\( θ_5, θ_4 \) and \( θ_3 \), respectively). \( θ_2 \) was equal to vaccine coverage in the given age group and year. Individuals departed the vaccinated stratum either through all-cause mortality (u), AIDS mortality (uH) or reaching the end of the duration of protection and returning to the unvaccinated stratum at rate d.

2.2.1 Unvaccinated (first time step of the year)

If \( j=1 \):

\[ SH[i,1] = BH, S[i,1] = B - BH \]

HIV-negative susceptible

If \( j \neq 1 \):

\[ S[i,j] = S[i-1,j-1] - (u[j-1] + λ[i-1,j-1])S[i-1,j]dt - θ_5[k,j]S[i-1,j-1] + d[k,j](1 - θ_3[k,j])S_V[i-1,j-1] - hiv[k-1,j]S[i-1,j] \]
The provided text appears to be a mathematical formulation related to the dynamics of HIV infection, possibly in the context of a mathematical model. The text includes differential equations and various parameters such as $L[i,j]$, $new_{I[i,j]}$, $new_{NI[i,j]}$, $I[i,j]$, $NI[i,j]$, $R[i,j]$, $SH[i,j]$, $LH[i,j]$, $new_{IH[i,j]}$, and $new_{NIH[i,j]}$. Each of these equations and variables seems to represent different states or transitions in a model of HIV infection, possibly within a population or a specific group of individuals. The equations likely involve parameters such as population sizes, infection rates, and recovery rates, among other factors. The text is dense and requires a clear understanding of the context and the variables involved to interpret correctly.
HIV- positive infectious active TB cases

\[ IH[i,j] = IH[i-1,j-1] + (1 - CDR[k,j] \times CoT[k])new_{NIH[i,j]} \]
\[ - (nH[j-1] + u[j-1] + uH[j-1] + uIMH[j-1])IH[i-1,j-1]dt + d[k,j]l[iH][i-1,j] \]
\[ + hv[k-1,j][i-1,j] \]

HIV- positive non-infectious active TB cases

\[ NIH[i,j] = NIH[i-1,j-1] + (1 - CDR[k,j] \times CoT[k] \times e)new_{NIH[i,j]} \]
\[ + d[k,j]NIH[i-1,j-1] + hv[k-1,j]NIH[i-1,j] \]

HIV- positive recovered

\[ RH[i,j] = RH[i-1,j-1] + nH[j-1](IH[i-1,j-1] + NIH[i-1,j-1])dt \]
\[ + (CDR[k,j] \times CoT[k])\left(new_{NIH[i,j]} + e \times new_{NIH[i,j]}\right) \]
\[ - (rH[j-1] + \lambda[i-1,j-1]xH[j] + u[j-1] + uH[j-1])RH[i-1,j-1]dt \]
\[ - \theta RH[k,j]RH[i-1,j-1] + d[k,j](1 - \theta RH[k,j])RH[i-1,j-1] + hv[k-1,j]RH[i-1,j] \]

2.2.2 Vaccinated (first step of the year)

Mechanism of action (pre- vs post-infection vaccine) was altered by changing values of \( \theta_S, \theta_\nu, \theta_R, \theta_{SH}, \theta_{LH} \) or \( \theta_{RH} \).

When modelling a pre-infection vaccine, only \( \theta_S \) and \( \theta_{SH} \) contained non-zero values, therefore vaccination in the other populations could only arise from infection and development of disease from vaccinated susceptibles. Conversely, the post-infection vaccine contained non-zero values for \( \theta_\nu, \theta_{LH} \) and \( \theta_{RH} \). Post-infection vaccines were assumed not to work in susceptible populations as they were not primed by previous infection. For those vaccines efficacious both pre- and post-infection, the vaccine was delivered to all groups that did not have active disease (i.e. non-zero and equal numbers for all theta values). Transitions between the vaccinated and unvaccinated active disease classes were unidirectional, only occurring upon waning of protection. In the South Africa model, in the main vaccine scenarios, efficacy (\( eff/D \)) and coverage (\( theta \)) were assumed to be the same in HIV positive and HIV negative groups. In some scenarios lower efficacy (\( VEH \)) or coverage of vaccination in HIV positive populations was explored.

HIV-negative vaccinated susceptible

\[ S_\nu[i,j] = S_\nu[i-1,j-1] - (u[j-1] + (1 - effI)\lambda[i-1,j-1])S_\nu[i-1,j-1]dt \]
\[ + \theta_S[k,j]S[i-1,j-1] - d[k,j](1 - \theta_S[k,j])S[i-1,j-1] + hv[k-1,j]S[i-1,j] \]

HIV-negative vaccinated latent

\[ L_\nu[i,j] = L_\nu[i-1,j-1] \]
\[ + (1 - effI)\lambda[i-1,j-1](1 - (1 - effD)p[j-1])S_\nu[i-1,j-1] \]
\[ + xR_\nu[i-1,j-1]dt \]
\[ - ((1 - effD)v[j-1] + (1 - effI)\lambda[i-1,j-1]) \times (1 - effD)p[j-1]x + u[j-1])L_\nu[i-1,j-1]dt + \theta_L[k,j]L[i-1,j-1] \]
\[ - d[k,j](1 - \theta_L[k,j])L_\nu[i-1,j-1]dt + hv[k-1,j]L_\nu[i-1,j] \]

HIV-negative new vaccinated infectious active TB cases

\[ new_{L_\nu[i,j]} = (1 - effI)\lambda[i-1,j-1](1 - effD)p[j-1]f[j-1]L_\nu[i-1,j-1] \]
\[ + xR_\nu[i-1,j-1]dt + (1 - effD)v[j-1]f[j-1]L_\nu[i-1,j-1]dt \]
\[ + (1 - effD)r[j-1]f[j-1]R_\nu[i-1,j-1]dt + wNI_\nu[i-1,j-1]dt \]

HIV-negative new vaccinated non-infectious active TB cases

\[ new_{NI_\nu[i,j]} = (1 - effI)\lambda[i-1,j-1](1 - effD)p[j-1]f[j-1] \]
\[ - f[j-1])S_\nu[i-1,j-1] + xL_\nu[i-1,j-1] + xR_\nu[i-1,j-1]dt \]
\[ + (1 - effD)v[j-1](1 - f[j-1])L_\nu[i-1,j-1]dt + (1 - effD)r[j-1](1 \]
\[ - f[j-1])R_\nu[i-1,j-1]dt \]

11
HIV-negative vaccinated infectious active TB cases
\[ I_V[i,j] = I_V[i-1,j-1] + (1 - CDR[k,j] \times CoT[k])new_I_V[i,j] \]
\[ - (n[j-1] + u[j-1] + u[i(j-1)])I_V[i-1,j-1]dt - d[k,j]I_V[i,j] \]
\[ - hiv[k-1,j]I_V[i-1,j] \]

HIV-negative vaccinated non-infectious active TB cases
\[ Nl_V[i,j] = Nl_V[i-1,j-1] + (1 - CDR[k,j] \times CoT[k] \times e)new_Nl_V[i,j] \]
\[ - hiv[k-1,j]Nl_V[i-1,j] \]

HIV-negative vaccinated recovered
\[ R_v[i,j] = R_v[i-1,j-1] + n[j-1]I_V[i-1,j-1] + Nl_V[i-1,j-1]dt \]
\[ + (CDR[k,j] \times CoT[k] \times e)new_R_v[i,j] \]
\[ - ((1 - eff_D)r[j-1] + (1 - eff_I)\alpha[i-1,j-1]\lambda[i-1,j-1])x + u[j-1])R_v[i-1,j-1]dt \]
\[ + \theta_{br}[k,j]R[i-1,j-1] - d[k,j](1 - \theta_{br}[k,j])R_v[i-1,j-1] - hiv[k-1,j]R_v[i-1,j] \]

HIV-positive vaccinated susceptible
\[ S_h_V[i,j] = S_h_V[i-1,j-1] \]
\[ - (u[j-1] + uH[j-1] + (1 - eff_H)VEH)S_h_V[i-1,j-1]dt \]
\[ + \theta_{sh}[k,j]S_h_V[i,j-1] - d[k,j](1 - \theta_{sh}[k,j])S_h_V[i-1,j-1] + hiv[k-1,j]S_h_V[i-1,j] \]

HIV-positive vaccinated latent
\[ L_h_V[i,j] = L_h_V[i-1,j-1] \]
\[ + (1 - eff_I \times VEH)\alpha[i-1,j-1](1 - (1 - eff_D \times VEH)pH_a[j-1])*S_h_V[i-1,j-1] \]
\[ + xHaRH_V[i-1,j-1]dt \]
\[ - (1 - eff_D \times VEH)vHa[j-1]*L_h_V[i-1,j-1] \]
\[ + (1 - eff_I \times VEH)\alpha[i-1,j-1] \times (1 - eff_D \times VEH)pH_a[j-1]xHa + u[j-1] \]
\[ + uH[j-1]*L_h_V[i,j-1]dt + \theta_{lh}[k,j]L_h_V[i-1,j-1] \]
\[ - d[k,j](1 - \theta_{lh}[k,j])L_h_V[i-1,j-1] + hiv[k-1,j]L_h_V[i-1,j] \]

HIV-positive new vaccinated infectious active TB cases
\[ new_h_{I_H_V}[i,j] = (1 - eff_I \times VEH)\alpha[i-1,j-1] \times (1 - eff_D \times VEH)pH_a[j-1]*fH[j-1]*S_h_V[i-1,j-1] \]
\[ + xHaL_H_V[i-1,j-1] + xHaRH_V[i-1,j-1]dt \]
\[ + (1 - eff_D \times VEH)vHa[j-1]*fH[j-1]*L_H_V[i-1,j-1]dt \]
\[ + (1 - eff_D \times VEH)rHa[j-1]*fH[j-1]*R_H_V[i-1,j-1]dt + wNIH_V[i-1,j-1]dt \]

HIV-positive new vaccinated non-infectious active TB cases
\[ new_NI_H_V[i,j] = (1 - eff_I \times VEH)\alpha[i-1,j-1] \times (1 - eff_D \times VEH)pH_a[j-1]*fH[j-1]*S_h_V[i-1,j-1] \]
\[ + xHaL_H_V[i-1,j-1] + xHaRH_V[i-1,j-1]dt \]
\[ + (1 - eff_D \times VEH)vHa[j-1]*fH[j-1]*L_H_V[i-1,j-1]dt \]
\[ + (1 - eff_D \times VEH)rHa[j-1]*fH[j-1]*R_H_V[i-1,j-1]dt + wNIH_V[i-1,j-1]dt \]

HIV-positive new vaccinated infectious active TB cases
\[ I_H_V[i,j] = I_H_V[i-1,j-1] + (1 - CDR[k,j] \times CoT[k])new_I_H_V[i,j] \]
\[ - (nH[j-1] + u[j-1] + uH[j-1] + uHa[j-1])I_H_V[i-1,j-1]dt \]
\[ - d[k,j]I_H_V[i-1,j-1] + hiv[k-1,j]I_H_V[i-1,j] \]

HIV-positive new vaccinated non-infectious active TB cases
\[ N_I_H_V[i,j] = N_I_H_V[i-1,j-1] + (1 - CDR[k,j] \times CoT[k] \times e)new_N_I_H_V[i,j] \]
\[ - d[k,j]NIH_V[i-1,j-1] + hiv[k-1,j]NIH_V[i-1,j] \]
HIV- positive vaccinated recovered

\[ RH_V[i, j] = RH_V[i - 1, j - 1] + nH[j - 1](IH_V[i - 1, j - 1] + NIH_V[i - 1, j - 1])dt \\
+ (CDR[k, j] \times \text{CoT}[k])(\text{new}_{IH_V}[i, j] + e \times \text{new}_{NIH_V}[i, j]) \\
- \left( (1 - e_{effD} \times \text{VEH})rHa[j - 1] + (1 - e_{effI} \times \text{VEH})\lambda[i - 1, j - 1]xHa + u[j - 1] + \\
uH[j - 1])RH_V[i - 1, j - 1]dt + \theta_{RH}[k, j]RH_V[i - 1, j - 1] - d[k, j](1 - \theta_{RH}[k, j])RH_V[i - 1, j - 1] + hiv[k - 1, j]RH_V[i - 1, j] \]
3 Model parameters and data sources

Justification of selection and sources for natural history, demographic, social mixing, and TB and HIV control parameters are provided in this section.

3.1 Natural history (biological) parameters

3.1.1 Age-related impact on TB natural history

Parameter ranges for calibration were based upon available literature (see references in Table 1 and Table 3).

Parameters considered invariant by age or with insufficient data demonstrating age variability, such as protection from active disease due to latent infection (x) and conversion from non-infectious to infectious active case (w), were modelled with the same value for all ages based on estimates from the literature. The ranges sampled from during calibration were in-line with values applied in Knight et al. and historical literature.\(^{(71,72)}\)

However, age-related differences in immunity, such as immune immaturity in children and immunosenescence in the elderly, are believed to influence the course of infection and disease.\(^{(50)}\) Therefore, to improve the modelled epidemiology, parameters with an epidemiological or biological basis for age-based differences were calibrated separately for the relevant age groups. These were the proportion progressing directly to active disease (p), proportion developing infectious disease (f), risk of reactivation of latent infection or relapse of recovered disease (v and r), and an age-wise calibration factor for TB mortality rate (uiscale). The age groups with calibrated parameters were children (0-14 years), and adults (≥15 years). Given availability of age-stratified data for calibration of the China model, the adult age group was also stratified, for the China model only, to separate the elderly (≥65 years) age group to account for immunosenescence.\(^{(50)}\) To smooth the transition between adult and elderly parameters for v, r and n, older adults (55-64 years) took the mean of the younger adults (15-54 years) and elderly (≥65 years) calibrated values.

Data were available to inform most parameter ranges for calibration. However, where data to inform elderly parameter ranges for calibration were unavailable, based upon recent publications and expert opinion the HIV-positive parameter ranges were considered a reasonable proxy for the upper bound of immunosenescence in old age.\(^{(51)}\) For example, where the HIV-positive parameter was higher than the HIV-negative parameter, the lower bound of the HIV-negative adult parameter provided the lower elderly bound, and the upper bound of the elderly parameter for fitting was approximated as either the upper or lower bound of the parameter range in HIV positive populations (see Table 1).

Two further sets of parameters were employed for calibration of the two TB mortality rates (u and u0). First, TB mortality was scaled by calibration factor rmortTB (increased if rmortTB greater than zero, and reduced if less than zero). Secondly, TB mortality was scaled by age with age-specific calibration factors for children and adults (uiscaleC and uiscaleA) in all three country models, and also for the elderly in China (uiscaleE).

3.1.2 HIV-related impact on TB natural history

Immunosenesence as a consequence of HIV infection is known to impact natural history parameters for TB disease.\(^{(52)}\) This was accounted for by differentiating the TB natural history parameters in the HIV-positive stratum in the model calibrated to South Africa data. The HIV positive stratum was not included for the India and China models, as adult HIV prevalence was less than 0.5% in both countries, and TB-HIV coinfection proportion was very low, at 3% and 1%, respectively.\(^{(1, 26)}\)

In model calibration, the age-specific and HIV-specific values for a given parameter were sampled independently. Where data or biological plausibility were suggestive of an age-wise relationship between parameters, constraints were set to ensure only parameter sets adhering to those relationships were retained. Details of these constraints can be found in Table 1. A parameter (alpha) was employed for calibration of the HIV-related parameters.

TB progression parameters were parameterised separately for HIV-positive (versus HIV-negative) states, such as proportion rapidly progressing to active disease (pH), proportion progressing to infectious disease (fH), protection from progression due to current or previous infection (xH), rate of progression to active disease from latency (vH) and recovered (rH) states, and TB mortality (rmortTBH).

14
Primary progression parameters for HIV positive populations \((p_H)\) were mostly based upon studies of nosocomial outbreaks in HIV-positive populations.\(^{53, 54}\) The parameter for TB reactivation in HIV-negative populations is well-established in the literature.\(^{55-58}\) Whereas parameterisation of the HIV-positive parameter for TB reactivation \((v_H)\) in previous modelling studies has mostly employed data from somewhat limited literature from high-income settings.\(^{59}\) The major limitation of these data has been that the model parameters for HIV negative and HIV positive populations, although based upon available literature, do not come from the same study or setting, and the HIV-positive parameter is usually based upon data from high-income settings. A recent, unpublished systematic review and meta-analysis explored the relative risk of reactivation in HIV-positive versus -negative latently infected populations, only including studies in which both sub-populations were drawn from the same overall population.\(^{60}\) The subset of studies from the pre-ART era provided a meta-analysed relative risk \((v_{HRatio}; 7.54; 95\% \text{ CI } 3.94-14.45)\) from low-, middle- and high-income countries. This was employed in the model, to estimate the HIV-positive parameter \((v_H)\) based upon the ratio to the HIV-negative parameter \((v_H = v * v_{HRatio})\). Both \(v\) and \(v_{HRatio}\) were sampled in the calibration process.

Data availability to inform parameters for paediatric HIV-positive populations was very limited. No studies were identified to inform \(v_{HRatio}\) for paediatric populations,\(^{60}\) therefore in the model the adult ratio was applied to the paediatric HIV-negative parameter to estimate the paediatric HIV-positive parameter. Similar methods were applied to estimate paediatric values for \(p_H, f_H, u_iH/n_iH,\) and \(r_H\), by applying the ratio of the adult HIV positive:negative values for each parameter to the paediatric HIV-negative parameter.

Based upon available literature, antiretroviral therapy (ART) was assumed to decrease the HIV-positive parameter \((p_H, x_H, v_H, u_iH/n_iH,\) and \(r_H)\) by 70% of the difference between the HIV-negative and HIV-positive values in children and 65% in adults in HIV-positive populations in South Africa (see section 3.4.3 for details).\(^{61, 62}\)
Table 1: Natural history parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Description</th>
<th>Prior proposal range and constraints</th>
<th>References</th>
<th>Range of posterior values observed in 1000 calibrated model fits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Births</td>
<td>$B[k]$</td>
<td>Total number of births in year $k$</td>
<td>UN estimates of total crude birth rate per 1000 population applied to modelled population. 1950s birth rate pre-1950, and tracks annual UN data from 1990 onwards.</td>
<td>UN Population Division, revision 2012 (China) (63) and revision 2017 (South Africa and India)(32)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>$BH[k]$</td>
<td>Number of HIV Births in year $K$</td>
<td>HIV-positive birth rate calculated from Spectrum 0-4 years old HIV incidence rates. Assumed all HIV infections in 0-4 years category occurred in first 6 months of life. Assumed none pre-1990, and tracks annual estimates from 1990 onwards.</td>
<td>Stover et al 2010 and 2017 (36, 64)</td>
<td>n/a</td>
</tr>
<tr>
<td>Transmission</td>
<td>$\lambda[i,j]$</td>
<td>Mth transmission risk (force of infection) in time step $i$ for age $j$</td>
<td>Calculated in the model: $\lambda[i,j] = n_{cal}\sum_{y=1}^{y=ngrp} \eta[m,y]z\left(I[l,y] + I_p[l,y] + IH[l,y] + IH_p[l,y]\right)$</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>$n_{cal}xz$</td>
<td>Scaling and calibration factor for daily number of respiratory contacts</td>
<td>Scales respiratory contacts to annual number of contacts and calibrates to TB incidence</td>
<td>Calibration ranges (based upon preliminary analyses): China: 0-0.5 South Africa: 0.5-2 India: 0-1</td>
<td>0.19-0.28 0.63-1.99 0.38-1.0</td>
</tr>
<tr>
<td></td>
<td>$\eta[m,y]$</td>
<td>Daily number of respiratory contacts by age group $m$ and contacts in age group $y$</td>
<td>Based upon available data. Social contact data available for China and South Africa,(29, 30) and based upon POLYMOD data adapted to the 2015 population distribution for India.(31,32) Calibrated by $n_{cal}$ to match TB incidence.</td>
<td>Read et al 2014,(29) Johnstone-Robertson et al. (2011) data. (30) UNDESA 2017(62) Mossong et al 2008(31) Funk 2017(33)</td>
<td>n/a</td>
</tr>
<tr>
<td>Progression</td>
<td>$p[j]$</td>
<td>Proportion of (re-) infected Susceptible, Latents or Recovereds developing active (primary) TB, by year of age</td>
<td>$p[j &lt; 15] = 0.01-0.2$ $p[j \geq 15] = 0.08 - 0.2$ $p[j &lt; 15] = 0.5 - 0.8$ $p[j &lt; 15] = p[j &lt; 15] \times (p[j \geq 15]/p[j &lt; 15])$ ART decreases the proportion progressing by 70% of the difference between the HIV negative and HIV positive values in children and 65% in adults. Constraint: Parameter set only retained if elderly parameter selected was greater than or equal to adult parameter.</td>
<td>Dodd et al 2017 (61) Sutherland 1968(65) Ferebee 1970(66) Comstock 1982(67) Vynnycky 1996 (58) Di Perri et al. 1989(53, 54) Daley et al. 1992</td>
<td>$p[j &lt; 15] = 0.014-0.030$ $p[j \geq 15] = 0.08-0.17$ $p[j &gt; 15, &lt;65] = 0.14-0.2$ $p[j \geq 15] = 0.30-0.80$ $p[j \geq 65] = 0.21-0.36$ $p[j &lt; 15] = 0.022-0.077$ $p[j \geq 15] = 0.096-0.200$</td>
</tr>
<tr>
<td>$x$</td>
<td>Protection from re-infection or developing active TB due to being latently infected or recovered from infection</td>
<td>$(1-x)$ is the value for the level of protection afforded</td>
<td>$x = 0.25 - 0.41$</td>
<td>xH = 0.51-1.00</td>
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<tr>
<td>$v[j]$</td>
<td>Risk of reactivation in latently infected population</td>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j≥15] = 0.0001 - 0.0003$</td>
<td>$v_Hratio = 3.94 -14.45$</td>
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<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$v_Hratio = 3.94 -14.45$</td>
<td>ART decreases risk of reactivation by 70% of the difference between the HIV-positive and -negative rates in children and 65% in adults.</td>
<td>Constraints: Parameter set only retained if elderly parameter selected was greater than or equal to adult parameter.</td>
<td>$v[j &lt; 15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td>$v_Hratio = 3.94 -14.45$</td>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$v_Hratio = 3.94 -14.45$</td>
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<td>Constraints: Parameter set only retained if elderly parameter selected was greater than or equal to adult parameter.</td>
<td>$v[j &lt; 15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td>$v_Hratio = 3.94 -14.45$</td>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
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<td>Constraints: Parameter set only retained if elderly parameter selected was greater than or equal to adult parameter.</td>
<td>$v[j &lt; 15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td>$v_Hratio = 3.94 -14.45$</td>
<td>$v[j&lt;15] = 0.0001 - 0.0003$</td>
<td>$v[j ≥ 15] = 0.0001 - 0.0003$</td>
<td></td>
</tr>
<tr>
<td>$u_i$; $u_{int}$</td>
<td>Death risk for infectious untreated TB, varies by age</td>
<td>$u_i = 0.6$</td>
<td>$u_{int} = 0.9$</td>
<td>Tiemersma et al 2011(70)</td>
<td>Dodd et al 2017(61)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>$u_{int}$; $u_{int}$</td>
<td>Death risk for non-infectious untreated TB, varies by age</td>
<td>$u_{int} = 0.21$</td>
<td>$u_{int} = 0.3$</td>
<td>Tiemersma et al 2011(70)</td>
<td>Dodd et al 2017(61)</td>
</tr>
<tr>
<td>$rmortTB$</td>
<td>Calibration factor</td>
<td>Sampled to calibrate $u_i$ and $u_{int}$ to TB mortality. Range sampled: -1 to 1</td>
<td>$-0.96$ to $-0.75$</td>
<td>$-0.88$ to $0.98$</td>
<td>$-0.94$ to $0.96$</td>
</tr>
<tr>
<td>$uiscale$</td>
<td>Calibration factor, varies by age</td>
<td>$uiscale$ [j &lt; 15] = 0.2</td>
<td>$uiscale$ [j ≥ 15, &lt;65] = 0.2</td>
<td>$uiscale$ [j ≥ 65] = 0.2</td>
<td>$uiscale$ [j &lt; 15] = 0.98 to 2.00</td>
</tr>
<tr>
<td>$n$</td>
<td>Annual risk of natural cure for TB cases, varies by age for China</td>
<td>$n = 0.1$ to $0.25$</td>
<td>$n = 0.1$ to $0.25$</td>
<td>Ferebee 1970(66)</td>
<td>Springett 1971</td>
</tr>
<tr>
<td>$r$</td>
<td>Annual risk of relapse from recovered to active TB, varies by age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r[j &lt; 15] = 0.005 - 0.015$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r[j \geq 15] = 0.005 - 0.015$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r[d j \geq 15] = 0.2 - 0.65$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r[d j &lt; 15] = r[j &lt; 15] \times (r[d j \geq 15]/r[j \geq 15])$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ART decreases risk by 70% of the difference between the</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>HIV-positive and -negative rates in children and 65% in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adults.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>China: $r[j \geq 55, &lt;65] = (r[j &lt; 55] + r[j \geq 65])/2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r[j \geq 65] = 0.005 - 0.025$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>Scaling factor for TB-HIV parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.99 to 0.99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sampled to calibrate $\nu_{tb}, p_{tb}$ and $r_{tb}$ to TB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>epidemiology in HIV-positive populations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| | Scaling factor |
| | n/a            |
| | -0.38-0.20     |
| | n/a            |
3.2 Demographic and HIV incidence parameters

3.2.1 Births and deaths

The demographics in the China model were calibrated as described in an earlier publication of this model. The India and South Africa models were newly developed for this work, so are described below.

Demographic data, including age-stratified population size estimates for 2000 to 2050, were obtained from the UN population division 2017 revision. Reported population size estimates were available pre-2015, and for 2015-2050 UN medium fertility estimates were employed.

Model inputs to reproduce the age-stratified UN demographic estimates and predictions were the UN population division birth rates per 1000 population and probability of death for an individual of a given age group in a given time period for 1950-2050. A manually adjusted calibration factor for background mortality ($r_{mort}$) was employed to reflect migration.

The model was initiated in 1900; this burn in period ahead of the period of interest ensured the populations in the calibration and outcome periods had appropriate levels of historical exposure to produce relevant age-wise rates of infection and disease. The model was initiated with 1950 values in 1900, allowed to burn in during the 1900-1950 period, then in 1950 all compartments were rescaled by the same factor to match the overall UN population estimate for 1950. The model was calibrated for the 2000-2050 period to the overall population size and to three age stratifications: 0-14 years, 15-64 years and ≥65 years. The model alignment with the UN population data for South Africa and India are demonstrated in Figure 1 and Figure 2. The population size varied minimally between fits due to differences in TB mortality, therefore the ribbons representing this uncertainty were narrow. The uncertainty was slightly greater in South Africa due to the higher and wider range in mortality rates than in India.

![Figure 1: South Africa – modelled demographics. Comparison of median modelled population (solid line) and range (ribbon) to UN estimates of population size (circles) for 2000-2050 for all ages (top left, black), 0-14 year olds (top right, red), 15-64 year olds (bottom left, blue), and ≥65 year olds (bottom right, green).](image-url)
Figure 2: India – Modelled demographics. Comparison of median modelled population (solid line) and range (ribbon) to UN estimates of population size (circles) for 2000-2050 for all ages (top left, black), 0-14 year olds (top right, red), 15-64 year olds (bottom left, blue), and ≥65 year olds (bottom right, green).
3.2.2 HIV incidence

As discussed in section 1, HIV was only explicitly included in the South Africa model. HIV epidemiology was parameterized using age- and year-specific HIV incidence and AIDS-related mortality for South Africa from Spectrum data and projections. (36, 64)

HIV was introduced into the model in 1990. HIV infection in 5 year olds and above was parameterised by 5-year age group and year using Spectrum-reported parameters, and could occur in any timestep. (36, 64) Data suggest that HIV incidence in 0-4 year olds occurs mostly due to vertical transmission from mother-to-child in pregnancy, childbirth, or during breastfeeding; (64) therefore, HIV infections in the 0-4 age group were assumed to occur in the first 6 months of life in the model, by informing the birth rate of HIV positive children. This annual HIV positive birth rate was calculated based upon the Spectrum HIV incidence rates for 0-4 year olds over time. (36) HIV-negative birth rates were estimated by subtracting HIV positive births from the total newborn population. HIV incidence was therefore assumed to be zero in 1-4 year olds, as incidence in this age group was accounted for through the HIV-positive birth rate. The HIV structure was not stratified by CD4 count, as this level of HIV detail was not relevant to the research question.

Implementation of the appropriate HIV incidence and AIDS mortality parameters by age and over time ensured that age-wise and temporal trends of the HIV prevalence in the population were reflective of reported values. (17-19) The modelled HIV prevalence in South Africa 2000-2015 is compared to available data for HIV prevalence in children (<15 years) and adults (15 years and above) in Figure 3. (39)

![Figure 3: South Africa – Modelled HIV prevalence. Model median (lines) alignment with population-level HIV prevalence calculated using UNAIDS-reported HIV prevalent cases and UN population estimates (circles) in children 0-14 years (red, top) and adults 15 years and above (blue, bottom). (32, 39)](image-url)
3.3 Social mixing parameters

Heterogeneous age-specific social mixing patterns were incorporated into the modelled transmission parameter in the model. Previous TB vaccine models have mostly assumed random mixing patterns within modelled populations, but such homogenous mixing does not appropriately represent the reality of age-assortativity in contact patterns. Although the likelihood of transmission per contact event was assumed unaffected by age in the model, age-wise differences in social contact patterns were incorporated into estimation of the transmission parameter (λ). The social contact patterns were parameterised separately for each country based upon available data, described below.

The China model was parameterised using a recent social contact study conducted by Read et al. in Southern China. In the study enrolling 1,821 participants, the total and average daily number of contacts by age strata (0-5, 6-19, 20-64 and ≥ 65 years) were estimated from contact diaries. Contacts were defined as face-to-face conversation or skin-on-skin touch, so are broadly representative of the type of contact relevant to M.tb transmission.

The South Africa model was parameterised using data from the Johnstone-Robertson et al. contact diary study of 738 participants in a Cape Town township. Although not perfectly representative of the country-level population, data from this study were considered sufficiently generalisable to be used. Although a study of 8 sites in South Africa is available, the study does not report reciprocal contacts in children. The study data were also checked against estimates of mixing from the socialmixr R package in R that adapts the POLYMOD study to the population structure of the relevant country, and found relatively similar contact structures. In the Johnstone-Robertson study, contacts were defined as either skin-to-skin contact (a physical contact), or a two-way conversation with three or more words in the physical presence of another person but no skin-to-skin contact (a nonphysical contact), so are broadly representative of the type of contact relevant to M.tb transmission. The study estimated the median daily number of physical and non-physical contacts by age strata (0-4, 5-9, 10-14 and ≥ 15 years) from contact diaries.

Social contact data were not available in the published literature to parameterise the India model. Instead, the socialmixr R package was employed to adapt empirical data from the European POLYMOD study to the demographic structure of India in 2015. The POLYMOD study included nationally representative prospective diary-based social contact surveys across eight European countries. Contacts were defined in the study as either skin-to-skin contact (a physical contact), or a two-way conversation with three or more words in the physical presence of another person but no skin-to-skin contact (a nonphysical contact). Demographic data for India were derived from the UN Population Division 2017 World Population Prospects report. The POLYMOD contact matrices were collapsed in to four age groups (0-4, 5-9, 10-14 and ≥ 15 years), and assortativity matrices applied to India’s age structure to generate a contact matrix representative of India’s demographic structure.

In all of these empirical contact diary studies, reporting or participation biases produce asymmetry in the number of contacts between pairs of age groups in the reported contact matrix. Therefore, symmetry was achieved using the methods of Baguelin et al. by estimating the total number of contacts from all subjects in participant age group m with contact age group y, and for the age groups reversed, taking an average of the two, and converting back to a contact rate by dividing the number of contacts by the size of the participant age group (equation below):

\[ c_{ym} = \frac{1}{2} \left( d_{ym} * T_m + (d_{my} * T_y) \right) / T_m \]

where \(d_{ym}\) is average number of contacts of participants in group m with people in group y, \(d_{my}\) is average number of contacts of participants in group y with people in group m, and \(T_m\) and \(T_y\) are the number of participants in age group m and y, respectively.

In the model, these country-specific contact matrices were multiplied by the calibration and scaling factors (\(ncal\) and \(z\)), and by the proportion of the contact population that are infected \(T[l|yi] / T[l|ly]\). These were summed over the contact age groups to give M.tb transmission risk (force of infection) in time step i for age j \(T[i,j]\).
3.4   **TB and HIV control measures**

3.4.1   **BCG**

BCG coverage was assumed to remain at current levels in each country as existing coverage is high and not expected to be discontinued. Therefore, the impact of BCG is intrinsic to the calibration data, and thus was not explicitly modelled.

3.4.2   **Case detection rate and treatment success**

Case detection rates (CDR) were based upon WHO-reported estimates of case detection. To minimise short term reporting fluctuations in CDR data, a generalised logistic function was fitted to each country’s available CDR data for 1990 to 2012-2016 (depending on country data availability at time of model development), manually for the China model, and using the non-linear least squares function in R for the South Africa and India models. Therefore, case detection inputs were held at approximately the 1994 rate before this year. The equation for the GLF was as follows:

\[
\text{CDR}[k] = A + \left(\frac{K - A}{1 + ((Q*\exp(-\text{slope}*(k-\text{inflection}))))^{(1/Qv)}} \right)
\]

Where \(k\) is year, and \(A, K, \text{slope}, \text{inflection}\) and \(Qv\) were as fitted, summarised in Table 2 below. As part of model calibration to epidemiological data, a CDR scaling factor (\(\text{CDRscale}\), Table 3) was applied to the generalised logistic function (Table 2). Age-wise differences in case detection were reflected in the China model using age-specific calibration factors for older adults and the elderly. In India, the case detection was also adjusted to account for private sector treatment initiations and employed in the model as a treatment initiation rate, see section 3.4.4 for more detail.

**Table 2: Fitted parameters for case detection rate generalised logistic function**

<table>
<thead>
<tr>
<th>Country</th>
<th>A</th>
<th>K</th>
<th>slope</th>
<th>inflection</th>
<th>Q</th>
<th>Qv</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>21</td>
<td>89</td>
<td>0.065</td>
<td>1998</td>
<td>0.2</td>
<td>0.22</td>
</tr>
<tr>
<td>South Africa</td>
<td>54.49</td>
<td>69.76</td>
<td>0.74</td>
<td>2004.85</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>India</td>
<td>61</td>
<td>92</td>
<td>1.2</td>
<td>2015</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Figure 4: Calibrated case detection rate (%)**. For China (red), South Africa (yellow) and India (blue). Shaded area represents the range of calibrated values from 1000 model fits.
WHO-reported treatment success rates were inputted between 1994 and 2011-2015 (depending on country data availability). For the South Africa model, 3-point averaging was employed to smooth fluctuations in the treatment success data. The treatment success rate in 1994 was held constant before this period and for 2011-2015 held constant after this period.\(^{(48)}\) Although the lack of improvement could be considered somewhat pessimistic, given the high levels of case detection and treatment success reported in these countries in recent years, this was considered a feasible scenario.\(^{(84, 85)}\)

### 3.4.3 Antiretroviral therapy

Anti-retroviral therapy (ART) for management of viral load in HIV positive populations can also contribute towards TB prevention and control, as populations on ART with high CD4 counts tend to experience lower rates of TB than those with higher viral loads and low CD4 counts.\(^{(86)}\) In the HIV stratum in the South Africa country model, ART was accounted for by weighting of the TB disease parameters by ART coverage. Based upon available literature, ART was assumed to reduce the additional risk of TB progression due to HIV-positivity by 65% in adults and 70% in children.\(^{(61, 62)}\) Therefore the increase in risk of TB for HIV positive populations on ART was 30% and 35% (for children and adults, respectively) of the difference between the HIV negative and HIV positive (without ART) parameters. In the model, the impact of ART was incorporated by weighting of the relevant TB natural history parameters in the HIV stratum by the ART coverage. From 1990-2016, ART coverage in children and adults was parameterised separately based upon data available from Spectrum.\(^{(36, 38)}\) Between 2016 and 2022, ART coverage in both age groups was scaled up to meet the 90% coverage target of the 90:90:90 targets,\(^{(37)}\) and was held at 90% from 2022 onwards.

### 3.4.4 Private sector delivery of care

India and China both report a non-negligible contribution of private care to the overall provision of TB care services.\(^{(35, 87-89)}\) In China, although private providers exist, hospitals are often the first point of care for TB and are mostly state-owned.\(^{(87)}\) In addition, China’s centralised notification system helps to unify TB care under the national policy.\(^{(88)}\) Therefore, although in the China model the possibility of missed cases from the private sector was accounted for in the notifications calibration range (see 4.1.1), the proportion receiving private care was considered relatively small and treatment success was assumed similar to the publicly reported success rates.

In India, however, an estimated 60% of treatment occurs within the public National Tuberculosis Programme (NTP), with the remaining 40% of patients receiving treatment from private providers.\(^{(35, 89)}\) Treatment success in India differs between NTP and private sector care, with treatment success in the private sector estimated at 40%.\(^{(89)}\) and in the public sector WHO-reported treatment success ranged from 54-89% between 2001-2013.\(^{(34)}\) To account for this differential treatment success, a weighted average accounting for the proportion treated and the treatment success in these two sectors was calculated to give an overall treatment success. The weighted treatment success for India was estimated to improve from 48% to 69% success over 2001-2013. The 2001 weighted treatment success estimate was applied to years pre-dating available data, and treatment success was assumed to plateau after 2013.

Not only does treatment success differ in the private sector in India, but until very recently, the lack of a system for private cases to be notified meant that WHO-reported case detection in India did not account for cases detected and started on treatment in the private sector. Up to and including 2012, WHO-reported case detection in India only accounted for notification occurring in the public sector.\(^{(48)}\) Assuming all public sector treatments are notified, this accounts for only 60% of all treatment occurring in India,\(^{(35)}\) and does not account for the unnotified cases receiving treatment in the private sector. Between 2013-2015, the WHO case detection increasingly included private sector notifications, reaching 15% of total notifications in 2015 (contributing 40% of total treatment, so 26% of private treatments were notified), meaning in that year approximately 70% of all treatments were notified (60% public sector all notified + 0.26*40% private sector = 70%). In the other countries, it could be assumed that the case detection ratio was a good approximation of treatment initiation, whereas for India this was clearly not the case, and therefore the proportion detected and treated in India (treatment initiation ratio) needed to combine the public sector case detection ratio with those detected and treated in the private sector. Without this adjustment, the proportion of cases treated would be substantially underestimated. Until 2013, the WHO India case detection ratio only accounted for public sector treatment initiations (60% of total treatments), and from 2013-2016 included 5% increasing to 15% of private sector treatment initiations.\(^{(48)}\) Therefore, to estimate the treatment initiation ratio for parameterisation of the model, the WHO annual notifications were divided by the proportion of all treatment initiations notified in that year (0.6 up to 2012, increasing to 0.7 by 2015), and then the WHO incidence number divided by the estimate of all treatment initiations.\(^{(34)}\)
One study has estimated a range for the proportion of cases treated in the private sector, reporting a range of 34-57\% \( (35) \). Given a calibration factor (CDRscale) was already in place for the treatment initiation ratio, these ranges were not directly used to inform the treatment initiation ratio prior. Instead, they were used to estimate the range around the treatment initiation rate calibration target (see 4.1.3), therefore constraining the calibrated treatment initiation ratio.
Table 3: Control measure parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Description</th>
<th>Prior proposal range and constraints</th>
<th>References</th>
<th>Parameter range observed in 1000 model fits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CDR data for 1990 to 2012/2016 were used as the basis for developing a generalised logistic function to reflect increases in CDR over this period. CDR plateaued after this period.</td>
<td>WHO TB burden estimates (34)</td>
<td>China: n/a South Africa: n/a India: n/a</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td></td>
<td></td>
<td>CDR data for 1990 to 2012/2016 were used as the basis for developing a generalised logistic function to reflect increases in CDR over this period. CDR plateaued after this period.</td>
<td>WHO TB burden estimates (34)</td>
<td>China: n/a South Africa: n/a India: n/a</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td>CDR[k]</td>
<td>Case Detection Ratio (proportion of new active TB cases detected and started on treatment) in year k</td>
<td>CDR data for 1990 to 2012/2016 were used as the basis for developing a generalised logistic function to reflect increases in CDR over this period. CDR plateaued after this period.</td>
<td>WHO TB burden estimates (34)</td>
<td>China: n/a South Africa: n/a India: n/a</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td>CDRscale</td>
<td>Calibration factor for CDR</td>
<td>Calibrated to match TB prevalence, mortality and incidence. Range sampled: -0.5 to 2 CDR[k]=CDRscale*CDR[k]</td>
<td>WHO TB burden estimates (34)</td>
<td>CDRscale[j&lt;55] = 0.33-0.51 CDRscale [j ≥ 55, 65] = 0.09 – 0.28 CDRscale{ j ≥ 65} = -0.19 - 0.10</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td>CoT[k]</td>
<td>Treatment success proportion (cured or complete treatment) in year k</td>
<td>China/South Africa: WHO data for 1994 to 2011/2015 were used, then constant CoT at 2015 rate from 2011/2015 onwards. India: Estimated as weighted average of success in public and private sector. WHO data for public sector used 2001-2013, then constant CoT from 2013 onwards.</td>
<td>WHO treatment outcomes (34)</td>
<td>WHO treatment outcomes (34) WHO treatment outcomes (34)</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td>e</td>
<td>Relative case detection rate of non-infectious cases</td>
<td>0.4 – 0.8</td>
<td>Assumed</td>
<td>WHO treatment outcomes (34) WHO treatment outcomes (34)</td>
</tr>
<tr>
<td>Detection and Treatment</td>
<td>ART</td>
<td>Coverage of antiretroviral therapy in all HIV positive populations.</td>
<td>Spectrum data 1990-2016, followed by linear increase to reach 90% coverage by 2022 in adults. Maintained at 90% beyond 2022. Spectrum estimates from 1990-2050 used for children. Used 3-point averaging to smooth outliers.</td>
<td>Stover et al 2017 (36)</td>
<td>WHO treatment outcomes (34) WHO treatment outcomes (34)</td>
</tr>
</tbody>
</table>
4 Calibration methodology

4.1 Epidemiological calibration targets

Where available, the model was calibrated to age-stratified TB prevalence rate, TB incidence rate, TB notification rate and TB mortality rate data for each country. The calibration targets for each country are described below. Age stratifications for fitting were based upon the age groups in available data, so were not necessarily the same for each epidemiological outcome or each country.

4.1.1 China

For China, the model was calibrated to the bacteriologically-positive prevalence rate (≥15, 15-29, 30-59 and ≥60 years) in 2000 and 2010; notification rate (all-age, 0-14, 15-54, 55-64, and ≥65 years) in 2010; and mortality rate (all-age, 0-14, 15-59 and ≥60 years) in 2010 (Table 4). Country-specific age-stratified incidence rates are not reported by the WHO, therefore the model was fitted only to the WHO 2010 all-age incidence rate for China.(85)

Estimates and confidence intervals around age-stratified prevalence of bacteriologically-positive pulmonary TB disease were obtained from national prevalence surveys conducted in 2000 and 2010, reported in Wang et al. (2014).(90) Disease Surveillance Point data, considered nationally representative, were used to estimate mortality rates by age.(92) To align mortality estimates with the desired calibration age bands, age groups were combined using published crude data, and unadjusted rates estimated. Adjustments in the published analyses were not reproducible with the available data and methodological information, so uncertainty ranges around the point estimates were based upon estimated TB mortality mis-classification in China estimated in Wang et al. and Yang et al. at approximately 50%.(93, 94)

To ensure appropriate case detection rate in the fitting process, the model was calibrated to the all-age TB incidence rate in 2010 obtained from the WHO database.(85) Country-level TB incidence stratified by age is not currently reported by the WHO, therefore age-specific notification rates of all TB (including smear positive, smear negative, and extra-pulmonary TB) were employed for model fitting.(91) Up to 20% overreporting of notifications may occur due to the use of clinical algorithms as opposed to biological testing for diagnosis. Up to 20% underreporting was estimated as it was assumed that the reported data only captured public (CDC) notifications which constitute 80% of cases, and also some asymptomatic cases may be missed.(95, 96) Therefore, confidence intervals for calibration were +/-20% of the WHO-reported point estimates.
Table 4: Calibration targets for China

<table>
<thead>
<tr>
<th>Calibration Factor</th>
<th>Year</th>
<th>Age (years)</th>
<th>Estimate</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TB notification rate (/100,000/yr)(91)</td>
<td>2010</td>
<td>All</td>
<td>63.9</td>
<td>51.1</td>
<td>76.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-14</td>
<td>2.7</td>
<td>2.2</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-54</td>
<td>64.6</td>
<td>51.7</td>
<td>77.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55-64</td>
<td>104.4</td>
<td>83.5</td>
<td>125.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65+</td>
<td>143.1</td>
<td>114.5</td>
<td>171.7</td>
</tr>
<tr>
<td>TB Mortality Rate (/100,000/yr)(92)</td>
<td>2010</td>
<td>All</td>
<td>3.37</td>
<td>1.69</td>
<td>5.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-14</td>
<td>0.29</td>
<td>0.15</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-59</td>
<td>1.91</td>
<td>0.96</td>
<td>2.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60+</td>
<td>15.69</td>
<td>7.85</td>
<td>23.54</td>
</tr>
<tr>
<td>Microbiologically-positive pulmonary TB prevalence rate (/100,000/yr)(90)</td>
<td>2000</td>
<td>≥15</td>
<td>178</td>
<td>163</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-29</td>
<td>92</td>
<td>72</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30-59</td>
<td>155</td>
<td>126</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60+</td>
<td>596</td>
<td>510</td>
<td>698</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>≥15</td>
<td>116</td>
<td>101</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15-29</td>
<td>59</td>
<td>40</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30-59</td>
<td>99</td>
<td>77</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60+</td>
<td>346</td>
<td>294</td>
<td>407</td>
</tr>
<tr>
<td>All age TB incidence rate (/100,000/yr)(85)</td>
<td>2010</td>
<td>All age</td>
<td>78</td>
<td>72</td>
<td>83</td>
</tr>
</tbody>
</table>

4.1.2 South Africa

The model was calibrated to TB epidemiological data for South Africa (Table 5), stratified by both age and HIV status, where available. The epidemiological model calibration targets were bacteriologically-positive prevalence rate (all-age) in 2015;(97) TB incidence rates overall in 2000 and by age in 2016 (all-age, 0-14 years and ≥15 years),(32, 48, 98, 99) rate of all-age TB incidence in HIV-coinfected populations in the overall population in 2000 and 2016,(48) TB notification rate in all ages in 2000 and 2015.(48) age-stratified TB notification rate in 2015 (0-14 years and ≥15 years),(48) rate of TB notification in HIV-coinfected populations in the overall population in 2015 (all-age);(48) all-age TB mortality rate in 2000 and 2015;(48) and rate of TB mortality in HIV-coinfected populations in the overall population in 2000 and 2015 (all-age).(48) The majority of country-level data available for South Africa came from WHO sources, as described below.

The notification rate overall and HIV notifications with the total population as a denominator were available from WHO sources, for 2000 and 2015 to fit to temporal trends.(48) Historically, notification of paediatric TB was poor, therefore only the 2015 time point was calibrated to age-stratified notifications. The notification data do not have ranges given they are reported numbers, but since the modelled notifications are those notified and starting treatment, to account for possible underreporting of treatment initiation, or possible overreporting of clinically diagnosed false positives or those detected but not initiating treatment, a calibration range of +/-20% of the reported notifications was employed.

TB mortality rates in 2000 and 2015 overall and in HIV positive populations, both with the overall population as the denominator, were available from WHO sources.(48)
Incidence rates were available for the overall population and HIV-positive population in 2000 and 2016, both with overall population as the denominator.\(^{(48)}\) It was also possible to estimate the incidence rate for the overall population stratified by children and adult age groups in 2016, by applying the UN-reported population size to the WHO-reported incidence number in each age group.\(^{(32, 48, 99)}\)

Recent and high quality country-level estimates of prevalence do not exist for South Africa. However, calibration to prevalence was necessary to ensure appropriate case detection of the calibrated incidence rates and appropriate TB mortality in the model. Therefore the WHO-reported all-population prevalence for 2015 was employed for calibration.\(^{(97)}\)

### Table 5: Calibration targets for South Africa

<table>
<thead>
<tr>
<th>Calibration Target</th>
<th>Year</th>
<th>HIV status (numerator/denominator)</th>
<th>Age (years)</th>
<th>Estimate</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB notification rate ((/100,000\text{yr}))(^{(48)})</td>
<td>2000</td>
<td>All/All</td>
<td>All</td>
<td>331</td>
<td>265</td>
<td>397</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>All/All</td>
<td>All</td>
<td>519</td>
<td>416</td>
<td>623</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/All</td>
<td>0-14</td>
<td>180</td>
<td>144</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/All</td>
<td>(\geq 15)</td>
<td>661</td>
<td>529</td>
<td>793</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive/All</td>
<td>All</td>
<td>285</td>
<td>228</td>
<td>342</td>
</tr>
<tr>
<td>TB Mortality Rate ((/100,000\text{yr}))(^{(48)})</td>
<td>2000</td>
<td>All</td>
<td>All</td>
<td>185</td>
<td>132</td>
<td>247</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive/All</td>
<td>All</td>
<td>132</td>
<td>82</td>
<td>194</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>All</td>
<td>All</td>
<td>192</td>
<td>142</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive/All</td>
<td>All</td>
<td>150</td>
<td>103</td>
<td>207</td>
</tr>
<tr>
<td>TB incidence rate ((/100,000\text{yr}))(^{(32, 48, 99)})</td>
<td>2000</td>
<td>All/All</td>
<td>All</td>
<td>585</td>
<td>379</td>
<td>836</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive/All</td>
<td>All</td>
<td>355</td>
<td>224</td>
<td>515</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/All</td>
<td>All</td>
<td>781</td>
<td>543</td>
<td>1060</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/All</td>
<td>0-14</td>
<td>355</td>
<td>233</td>
<td>471</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All/All</td>
<td>(\geq 15)</td>
<td>958</td>
<td>638</td>
<td>1278</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive/All</td>
<td>All</td>
<td>461</td>
<td>315</td>
<td>635</td>
</tr>
<tr>
<td>Microbiologically-positive pulmonary TB prevalence rate ((/100,000\text{yr}))(^{(97)})</td>
<td>2015</td>
<td>All/All</td>
<td>All</td>
<td>696</td>
<td>390</td>
<td>1088</td>
</tr>
</tbody>
</table>

#### 4.1.3 India

The model was calibrated to TB epidemiological data for India (Table 6), stratified by age, where available. The epidemiological model calibration targets were age-stratified TB treatment initiation rate in 2007 (all-age, \(\geq 15\) years) and 2015 (all-age, 0-14 years, \(\geq 15\) years);\(^{(34, 48)}\) all-age TB mortality rate in 2015;\(^{(48)}\) age-stratified TB incidence rate in 2000 and 2015 (all-age, 0-14 years, \(\geq 15\) years);\(^{(32, 48, 99)}\) and all-age microbiologically-positive pulmonary TB prevalence rate in 2015.\(^{(98, 100)}\)

Due to issues discussed earlier (section 3.4.4) of WHO notification rates in India missing a substantial proportion of ‘notifiable’ cases from the private sector, and the adjustment of the case detection ratio in the model to become a treatment initiation ratio, the India model was calibrated to the treatment initiation rate instead of the case detection rate. Age-stratified TB treatment initiation rates for calibration were estimated based upon WHO-reported incidence and the estimated yearly treatment initiation ratio (see section 3.4.4).\(^{(34, 35, 48, 89)}\) The key source of uncertainty in the estimated treatment initiation rate was the proportion of cases treated in the private sector.
sector. The range on this proportion was assumed to be consistent with Satyanarayana et al. (34-57%).(35) therefore these data were used to estimate the range of treatment initiation rates for calibration. The 0-14 years estimates were not used as calibration targets for 2007, as detection and notification of paediatric TB data were of much lower quality at this earlier time point.

WHO data were used as the source of the mortality rate calibration targets.(48)

All-age TB disease incidence rates in 2000 and 2015 were based upon WHO-reported data.(48) WHO has not reported age-stratified incidence rates for India; however, a study by Dodd et al. estimated that 9% of incident cases occur in the paediatric population in India and the remainder in the adult population.(99) Given incidence has remained relatively stable in India over the 2000-2015 time frame, it was assumed that this proportion applied in both the 2000 and 2015. Therefore, the WHO-reported overall number of incident cases in each year were apportioned based upon the Dodd study,(99) and the UN population size estimates applied to calculate the estimate and range of the age-stratified incidence rate in 2000 and 2015.(32, 48, 99)

A nationally-representative prevalence survey has not yet been conducted in India, though many smaller regional prevalence surveys exist. A recent meta-analysis of nine of these subnational surveys estimated a smear positive prevalence of 159.38 (122.9–196.59) per 100,000 population,(98) and an updated analysis based upon the same surveys estimated the bacteriologically positive pulmonary TB prevalence at 253 (195-312) per 100,000 population.(100) This latter estimate aligns with the definition for the infectious compartment of the model, so was used for calibration.

**Table 6: Calibration targets for India**

<table>
<thead>
<tr>
<th>Calibration Factor</th>
<th>Year</th>
<th>Age (years)</th>
<th>Estimate</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB treatment initiation rate (/100,000/yr)(34, 48)</strong></td>
<td>2007</td>
<td>All</td>
<td>169</td>
<td>154</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15</td>
<td>247</td>
<td>224</td>
<td>344</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>All</td>
<td>182</td>
<td>163</td>
<td>255</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-14</td>
<td>38</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15</td>
<td>240</td>
<td>215</td>
<td>336</td>
</tr>
<tr>
<td><strong>TB Mortality Rate (/100,000/yr)(48)</strong></td>
<td>2015</td>
<td>All</td>
<td>35</td>
<td>27</td>
<td>43</td>
</tr>
<tr>
<td><strong>TB incidence rate (/100,000/yr)(32, 48, 99)</strong></td>
<td>2000</td>
<td>All</td>
<td>289</td>
<td>149</td>
<td>473</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-14</td>
<td>82</td>
<td>42</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15</td>
<td>372</td>
<td>192</td>
<td>609</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>All</td>
<td>217</td>
<td>112</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0-14</td>
<td>62</td>
<td>32</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥15</td>
<td>279</td>
<td>144</td>
<td>457</td>
</tr>
<tr>
<td><strong>All age microbiologically-positive pulmonary TB prevalence rate (/100,000/yr)(98, 100)</strong></td>
<td>2015</td>
<td>All</td>
<td>253</td>
<td>195</td>
<td>312</td>
</tr>
</tbody>
</table>
4.2 Epidemiological calibration

The model was calibrated separately for each country to data from each of the three countries. It was calibrated to available country-level age-stratified TB disease prevalence, incidence, mortality and notification rate data, and with HIV-coinfection stratification for South Africa, where available, as described in section 4.1. This comprised 18 epidemiological calibration targets for China, 16 for South Africa and 13 for India.

A multi-stage calibration method was used to fit the model to epidemiological data for each country.\(^{(40, 101)}\) Calibration was initialised for each country using a random sampling accept/reject method. Parameter combinations for input into the model were determined by random sampling from a uniform distribution across each parameter range (Table 1). ‘Acceptance’ was defined as modelled outputs within all calibration target ranges for that country (Table 4 to Table 6).

If at least one accepted parameter set was identified within the first million random samples for that country, the random sampling accept/reject method was continued. The acceptance rate was monitored again for efficiency at 5 million samples, and where efficiency was sufficient to achieve at least 1,000 fits within 15 million samples, this method was continued.

If no acceptances were identified within the first million samples, or efficiency was too low at 5 million random samples, an approximate Bayesian computation Markov chain Monte Carlo (ABC-MCMC)-based approach was used to improve sampling efficiency. ABC-MCMC was conducted in R using an easyABC package modified to accept seeded parameter values.\(^{(102)}\) Where accepted parameter sets had been identified through the random sampling method, these were employed as seeds for parallel 20,000-step ABC-MCMC chains. If fewer than 20 accepted sets had been identified, ‘near-acceptances’ were also employed as seeds for the ABC-MCMC chains. Where ‘near-acceptance’ was defined as parameter sets which reproduced all but one calibration target. Where no accepted parameter sets had been identified after 1 million runs, an adaptive ABC-MCMC method was employed, as described in previous publications.\(^{(8, 40)}\)

Results and uncertainty ranges were based upon 1,000 accepted parameter sets for each country. If more than 1,000 accepted parameter sets had been identified, 1,000 were randomly selected using the runif command in R.

Calibration of the China model required adaptive ABC-MCMC; results of the calibration are shown in Figure 5 to Figure 8.\(^{(8)}\) Calibration of the South Africa model required ABC-MCMC, seeded with acceptances and near-acceptances generated via the random sampling accept/reject method (4 acceptances and 43 near-acceptances in 5 million samples), as shown in Figure 9 to Figure 12. Calibration of the India model was achieved using random sampling (1,000 accepted parameter sets within 15 million random samples), as shown in Figure 14 to Figure 17.

4.3 Calibrated model

4.3.1 China

Calibration to the 18 country-specific epidemiological data ranges was achieved (Figure 5 to Figure 8). In the calibrated model, the incidence rate in China was estimated to continue to decline from 56.4 (51.6-59.5) per 100,000 in 2025 to 33.8 (27.8-37.9) per 100,000 population in 2050 (Figure 5). During the same period, mortality rates were predicted to decline from 2.0 (1.2-3.2) per 100,000 in 2025 to 1.1 (0.6-2.0) per 100,000 population (Figure 6, top left).
Figure 5: China - Modelled all-age incidence rate per 100,000 population 2000-2050. Black circle and vertical bar represents WHO estimates and ranges, solid horizontal line and shaded area represent modelled median and uncertainty range.

Figure 6: China - Modelled mortality rate per 100,000 population 2000-2050. For all-age population (top left, black), 0-14 year olds (top right, red), 15-59 year olds (bottom left, yellow), and ≥60 year olds (bottom right, green). Black circles and vertical bars represent empirical calibration data and estimated ranges, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges.
Figure 7: China - Modelled notification rate per 100,000 population 2000-2050. For all-age population (top left, black), 0-14 year olds (top centre, red), 15-34 year olds (top right, yellow), 35-64 year olds (bottom left, green), and ≥65 year olds (bottom centre, blue). Black circles represent WHO estimates and vertical bars the estimated ranges, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges.

Figure 8: China - Modelled bacteriologically-positive tuberculosis prevalence rate in 2000 and 2010. For ≥15 year olds (top left, black), 15-29 year olds (top right, red), 30-59 year olds (bottom left, yellow), and ≥60 year olds (bottom right, green). Black circles and bars represent empirical calibration data, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges.
4.3.2 South Africa

Calibration was achieved for the 16 calibration target for South Africa (Figure 9 to Figure 12).

In the South Africa model, the all-age incidence rate was estimated to continue to decline from 406 (276-612) per 100,000 in 2025 to 248 (129-419) per 100,000 population in 2050 (Figure 9, top figure, black line and shaded ribbon). Mortality rates were predicted to decline from 101 (68-152 per 100,000 in 2025 to 60 (33-105) per 100,000 population (Figure 11, black line and shaded ribbon).

Figure 9: South Africa - Modelled tuberculosis incidence rate per 100,000 population 2000-2050. For all-age population (top, black), all-age co-infected TB-HIV (top, orange), 0-14 year olds (centre, red), and ≥15 year olds (bottom, blue). Black circles and vertical bars represent calibration data estimates and ranges for 2000 and 2016, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note difference in y-axis scales.
Figure 10: South Africa - Modelled all-age bacteriologically positive TB prevalence rate per 100,000 population 2000-2050. Black circle and vertical bar represents estimates and ranges from empirical calibration data in 2015, solid horizontal line and shaded area represent modelled median and uncertainty range.

Figure 11: South Africa - Modelled all-age TB mortality rate (black) and TB-HIV mortality rate (orange) per 100,000 population 2000-2050. Black circle and vertical bar represents estimates and ranges from calibration data in 2015, solid horizontal line and shaded area represent modelled median and uncertainty range.
Figure 12: South Africa - Modelled notification rate per 100,000 population 2000-2050. For all-age population (top, black), all-age co-infected TB-HIV (top, orange), 0-14 year olds (centre, red), and ≥15 year olds (bottom, blue). Black circles and vertical bars represent point estimates and ranges for 2000 and 2016, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note difference in y-axis scales.
Although not calibrated to the proportion of incident TB cases occurring in HIV-positive populations, the modelled estimates aligned well with available data for 2000 and 2016 (Figure 13). (48)

Figure 13: South Africa - Proportion of incident TB cases occurring in HIV-positive populations 2000-2050. Solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges and black circles and vertical bars represent WHO data estimates and ranges for 2000 and 2016. (48)
4.3.3 India

Calibration was achieved for the 13 calibration targets for India (Figure 14 to Figure 17).

Modelled incidence rate projections for India were estimated to continue to decline from 165.6 (118.2-238.2) per 100,000 in 2025 to 147.0 (87.2-223.9) per 100,000 population in 2050 (Figure 14). Mortality rates were predicted to decline from 19.8 (12.9-29.7) per 100,000 in 2025 to 14.5 (7.4-24.4) per 100,000 population (Figure 15).

**Figure 14:** India - Modelled tuberculosis incidence rate per 100,000 population 2000-2050. *For all-age population (top, black), 0-14 year olds (centre, red), and ≥15 year olds (bottom, blue). Black circles and vertical bars represent calibration data estimates and ranges for 2000 and 2015, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note difference in y-axis scales.*
Figure 15: India - Modelled all-age mortality rate per 100,000 population 2000-2050. Black circle and vertical bar represents estimates and ranges from calibration data in 2015, solid horizontal line and shaded area represent modelled median and uncertainty range.

Figure 16: India - Modelled all-age bacteriologically positive prevalence rate per 100,000 population 2000-2050. Black circle and vertical bar represents estimates and ranges from empirical calibration data in 2015, solid horizontal line and shaded area represent modelled median and uncertainty range.
Figure 17: India - Modelled treatment initiation rate per 100,000 population 2000-2050. For all-age population (top, black), 0-14 year olds (centre, red), and ≥15 year olds (bottom, blue). Black circles and vertical bars represent point estimates and ranges for 2007 and 2015, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note difference in y-axis scales.
Although not calibrated to WHO notification data, alignment with these data has also been demonstrated (Figure 18 below).

**Figure 18:** India - Comparison of modelled notification rate to WHO-reported notification rates per 100,000 population 2000-2050. For all-age population (top, black), 0-14 year olds (centre, red), and ≥15 year olds (bottom, blue). Black circles represent WHO-reported notification rates and ranges for 2007 and 2015, solid horizontal lines and shaded areas represent modelled medians and uncertainty ranges. Note difference in y-axis scales.
5 Vaccination

Four main vaccine characteristics were varied in this research: vaccine efficacy for prevention of infection (VE-POI), vaccine efficacy for prevention of disease (VE-POD), efficacy by host infection status (P&PI, PRI and PSI), and duration of protection. In South Africa only, vaccine safety and efficacy in HIV positive populations was also explored. The key vaccine characteristics and implementation assumptions are summarised in Table 7 and Table 9, and described in full in this section.

Table 7: Vaccine characteristics and implementation assumptions

<table>
<thead>
<tr>
<th>Characteristic/Assumption</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Efficacy for prevention of infection (VE-POI)</td>
<td>Range: 0-100% Interval: 10%</td>
</tr>
<tr>
<td>Efficacy for prevention of disease (VE-POD)</td>
<td>Range: 0-100% Interval: 10%</td>
</tr>
<tr>
<td>Vaccine safety in HIV positive populations (South Africa only)</td>
<td>Safe or unsafe for delivery to HIV-positive populations</td>
</tr>
<tr>
<td>Vaccine efficacy in HIV positive populations (South Africa only)</td>
<td>Equivalent to HIV-negative (VE-POI/D above), or 20% reduction compared to HIV-negative populations</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>Values: 2yrs, 3, 5, 7, 10, 15, 20, 25, lifelong Waning: Exact</td>
</tr>
<tr>
<td>Population protected by vaccine</td>
<td>Pre- and post-infection (P&amp;PI), pre-infection (PRI) or post-infection (PSI)</td>
</tr>
<tr>
<td>Type of protection</td>
<td>Leaky</td>
</tr>
<tr>
<td><strong>Implementation assumptions</strong></td>
<td></td>
</tr>
<tr>
<td>Epidemiological setting</td>
<td>China, South Africa and India</td>
</tr>
<tr>
<td>Year of vaccine introduction</td>
<td>2025</td>
</tr>
<tr>
<td>Time horizon of vaccination</td>
<td>2025-2050</td>
</tr>
<tr>
<td>Vaccination schedule</td>
<td>Annual routine vaccination of 9 year olds; Mass vaccination of all aged ≥10 years in 2025 &amp; mass campaigns at 10-yearly interval or duration of protection, whichever longer (scenario analysis with 5-yearly mass campaigns)</td>
</tr>
<tr>
<td>Coverage</td>
<td>Routine: 80%; Mass: 70% In South Africa: For scenarios in which the vaccine is safe for HIV-positive populations, coverage assumed the same regardless of HIV status.</td>
</tr>
</tbody>
</table>

All combinations of the four main vaccine characteristics were explored, leading to 3,267 combinations of characteristics in both India and China (11 VE-POI x 11 VE-POD x 9 durations of protection x 3 populations protected by vaccine), and 13,068 combinations in South Africa due to the additional variation in safety and efficacy in HIV-positive populations.

5.1 Vaccine efficacy

5.1.1 Vaccine efficacies for prevention of infection versus disease

Both vaccine efficacy for prevention of infection and for prevention of disease were varied from 0-100% in 10% intervals, independently and in combination with each other (i.e. 121 vaccine efficacy combinations).
Vaccine efficacy can be modelled as ‘all-or-nothing’ or ‘leaky’. All-or-nothing vaccination could not be used to model a vaccine with simultaneous efficacy against infection and disease, as was the research question here. Therefore, leaky protection was assumed. With leaky protection, the proportion of a population moved to the vaccine stratum is equal only to the coverage, and the vaccine efficacy is modelled as the percentage reduction in the relevant natural history parameters. Prevention of infection vaccine efficacy ($\text{eff}I$) was applied to the infection parameter ($\lambda$) by multiplying it by ($1 - \text{eff}I$). Prevention of disease efficacy ($\text{eff}D$) was applied in the same manner to development of disease parameters, which are the proportion developing primary active disease ($\theta$), and risk of reactivation from the latent ($\psi$) and recovered classes ($\rho$). In this leaky protection model, the vaccinated population could develop infection and disease, just with a lower risk than the unvaccinated population.

The modelled vaccines were not assumed to affect infectiousness of disease, severity of disease, case fatality ratio, likelihood of natural cure, or case detection.

Inclusion of HIV in the South Africa model required consideration of the possible impact of HIV infection on vaccine efficacy. Clinical efficacy of other vaccines has been demonstrated in HIV positive populations, such as influenza and PCV7 vaccines, even at CD4 counts <200.\(^{24, 25}\) Immune markers of immunogenicity have indicated a range of from 20% reduction up to equivalent vaccine immunogenicity in HIV positive populations compared to HIV-negative populations (e.g. HPV, Hepatitis A, and Hepatitis B).\(^{24, 25}\) Therefore, two scenarios of efficacy were explored in this model – one of equivalent efficacy and one of 20% reduction in efficacy in HIV-positive populations. Safety in this population is discussed in section 5.2 below, as was an implementation consideration based upon vaccine safety.

5.1.2 Host infection status for efficacy (pre- versus post-infection)

Previous exposure of the immune system to $M.\text{tb}$ may impact the immune response to the vaccine antigen. Therefore, the efficacy of a given candidate may be reliant upon whether the vaccinated individual is $M.\text{tb}$-naïve, currently latently infected or ever-infected. Therefore, four infection status combinations were modelled (Table 8). Pre-infection vaccines were assumed to prevent development of active disease only in never-infected individuals ($\theta_S > 0, \theta_L = 0, \theta_R = 0$). Post-infection (PSI) vaccines were assumed efficacious when delivered to either latently infected populations or those who had recovered from active disease ($\theta_S = 0, \theta_L > 0, \theta_R > 0$). A vaccine effective pre- and post infection (P&P), producing immunity in all except those with active disease ($\theta_S > 0, \theta_L > 0, \theta_R > 0$), was modelled to estimate the greatest preventative vaccine impact given the efficacy and other vaccine parameters. Therapeutic vaccines were not explored in this study, so none were considered effective in the populations with active disease.

Table 8: Host infection statuses in which each vaccine type is effective

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Never infected (S)</th>
<th>Latently infected (L)</th>
<th>Active Disease (I or NI)</th>
<th>Recovered from disease (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRI</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PSI</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>P&amp;P</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

5.1.3 Duration of protection and waning

Modelled durations were 2, 3, 5, 7, 10, 15, 20, 25 years and lifelong. The minimum expected duration of protection anticipated from clinical trials is two years. Although it is unlikely that data on immune responses of any longer than five years would be known at registration, given BCG is known to protect for at least 10 years, potentially longer,\(^{46}\) it is possible that these longer durations of protection would be possible with new vaccines. Vaccine waning was assumed to be exact. No immunosenescent waning was assumed.

5.2 Vaccine implementation and coverage

Vaccine implementation was assumed to start in 2025 in all three countries, with immediate scale-up. Vaccination was assumed to be implemented as routine plus mass vaccination. The assumption of immediate scale up may have slightly over-estimated the level of impact, as such campaigns are usually rolled out over several years.

TB vaccination was modelled as delivered routinely to nine-year olds, assumed to co-deliver with the Human Papilloma Virus vaccine (HPV) as part of the school-based vaccination platform. HPV has already been
implemented as part of the routine vaccine schedule for nine-year olds in South Africa. In India, HPV vaccine is currently a “recommended”, but not a “mandatory” vaccine, meaning that it is not routinely provided. However, the recommendation by the Indian Advisory Committee on Vaccines and Immunisation Practices is for delivery of the HPV vaccine to 9-14 year olds and WHO recommends delivery to ages 9-13 years.\(^{44, 103}\) Vaccination at the lower end of this range is anticipated long-term,\(^{104}\) and it is anticipated that this may become a routinely delivered vaccine in the future. Although HPV vaccination is not currently implemented in China,\(^{105}\) WHO recommends delivery to ages 9-13 years,\(^{44}\) and vaccination at the lower end of this range is anticipated long-term.\(^{104}\) To aid comparison of results across the three settings, routine coverage of the new TB vaccine was modelled in all three settings at 80%. This was based upon a combination of HPV coverage of nine-year olds in South Africa (87%),\(^{41, 44, 103}\) and gross secondary school enrolment ratio in China (94.3%) and in India (74%) in 2015.\(^{67}\)

Mass campaigns vaccinating adolescents and adults (>9 years old) were implemented starting in 2025, and were modelled with a frequency of the duration of protection or 10 years (whichever was longer). Although this covers a wider age group than might be anticipated once the vaccine is available, this ensures the peak ages of infection and disease will be covered by this vaccination campaign in all three epidemiological settings. A 10-year interval between mass campaigns was considered the most feasible, informed by stakeholder experience of other campaigns.\(^{106}\) Coverage of mass campaigns was assumed at 70% in all three settings. Experience from serial vaccination suggests approximately a 10% drop in coverage between doses, and Menafrivac campaigns in sub Saharan Africa achieved coverages of 70-98% of 1-29 year olds.\(^{43}\) Routine elderly influenza vaccination coverage in China has been relatively low (36-49%).\(^{43, 107-109}\) as was a mass adult (15-70 years) Japanese encephalitis vaccination campaign in India (58%).\(^{110}\) Therefore, given these data, and the broader age range for vaccination in this model than in the Menafrivac campaigns, the lower end of the Menafrivac coverage was considered an appropriate assumption (70%). The coverage assumptions were not varied, as implementation was not the focus of this research.

In HIV-positive populations in South Africa, safety was modelled as the binary options of safe or unsafe. Most subunit vaccines would be hoped to be safe for HIV-positive populations. However, some live attenuated vaccines (e.g rBCG vaccines) may be unsafe in HIV-positive populations. Therefore, both the scenarios of being safe and unsafe for delivery to HIV-positive populations were explored in the model. Coverage in HIV-positive populations was assumed the same as HIV-negative populations in scenarios where the vaccine was safe for HIV-positive populations. In scenarios where the vaccine was contraindicated in HIV-positive populations, vaccine was not delivered to HIV-positive populations; however, vaccinated HIV-negative populations becoming infected with HIV maintained vaccine protection.
### Table 9: Vaccine parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Description</th>
<th>Prior proposal range and constraints</th>
<th>References</th>
<th>Parameter range observed in model fits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>$θ_{[k,j]}$</td>
<td>Proportion of Susceptibles, Latents or Recovereds aged $j$ that move to the vaccine strata in year $k$ (equal to coverage)</td>
<td>Routine (9 year olds) = 80% from 2025 onwards Mass campaigns ($\geq$10 years) = 70% in 2025 and every 10 years (though 5 years explored in scenario analyses)</td>
<td>Assumed. Based upon secondary school attendance, HPV coverage, and coverage in MenafriVac campaigns (41-43, 103)</td>
<td>80% (routine) and 70% (mass)</td>
</tr>
<tr>
<td></td>
<td>$effI$</td>
<td>Efficacy in preventing $M.\text{tb}$ infection</td>
<td>0-100% in 10% intervals</td>
<td>Assumed</td>
<td>0-100% in 10% intervals</td>
</tr>
<tr>
<td></td>
<td>$effD$</td>
<td>Efficacy in preventing TB disease</td>
<td>0-100% in 10% intervals</td>
<td>Assumed</td>
<td>0-100% in 10% intervals</td>
</tr>
<tr>
<td></td>
<td>$D$</td>
<td>Duration of vaccine efficacy</td>
<td>2, 3, 5, 7, 10, 15, 20, 25 years and lifelong. Duration is exact, and no immunosenescent waning was assumed.</td>
<td>Assumed</td>
<td>2 years to lifelong</td>
</tr>
<tr>
<td></td>
<td>$VEH$</td>
<td>Reduction in vaccine efficacy and vaccine safety due to HIV infection (South Africa only)</td>
<td>Equal VE to HIV negative populations (1), 20% reduction in VE (0.8), and a vaccine not delivered to HIV negative populations due to safety/efficacy issues were explored (0).</td>
<td>Assumed Crum_Cianflone et al 2014 and Nicolini et al 2015 (24, 25)</td>
<td>0, 0.8, 1</td>
</tr>
</tbody>
</table>
6 Outcome estimation

The primary outcome of interest, the percentage incidence rate reduction compared to the no new vaccine baseline in 2050, was estimated for all evaluated vaccine scenarios. The values reported are the median and uncertainty range based upon the values from the 1,000 calibrated parameter sets, estimated by calculating the percentage reduction for each scenario in each of the 1,000 calibrated parameter sets, and estimating the median of those thousand incidence rate reductions. Similarly, the number of cases averted over the 2025-2050 period was calculated as the difference between the cumulative cases 2025-2050 in the baseline versus vaccine scenario for each of the 1,000 calibrated parameter sets, then the median estimated.

The proportion new transmission versus reactivation/relapse was estimated annually for the 1,000 calibrated baseline scenarios. New transmission was estimated from the model based upon the number of incident cases in a given year arising from fast progression to disease following recent infection. Reactivation/relapse was estimated as the number of incident cases arising from reactivation from the latent compartment or relapse from the recovered compartment in the model. The relative contribution of these two types of incidence was estimated annually in each of the 1,000 calibrated scenarios, and median and range reported.

7 Supporting epidemiological data and information

7.1 New transmission versus reactivation/relapse

As observed in figure 2B of the main paper, a key epidemiological outcome was the proportional contribution of newly transmitted infections compared to reactivation or relapse disease from existing infection.

As reported in earlier work, China was estimated to be undergoing a transition from a transmission-driven to a reactivation-driven epidemic. At vaccine introduction in 2025, 60% (UR: 53-64%) of all cases were estimated to be a result of reactivation, increasing to 75% (UR: 68-80%) by 2050. In the year of vaccine introduction, less than 1% of all new cases were estimated to occur in the vaccine-ineligible age group (<9 years, not shown).

The model calibrated to the South African epidemic and parameterised with South African control measures was estimated to become a slightly more reactivation/relapse-driven epidemic, but with substantial overlap of the uncertainty ranges, over the modelled period. In 2000, 29% (UR: 16-57%) of all new active cases were estimated to result from reactivation. At vaccine introduction in 2025, the estimated proportion arising from reactivation had increased to 58% (UR: 44-70%), and this remained largely stable until 2050. Therefore, the proportion of new active cases arising as a result of reactivation was anticipated to increase over the 2000-2050 time horizon. In the HIV positive population most cases were due to reactivation, whereas in the HIV-negative population the majority of cases were due to recent transmission (Figure 19). The proportion due to recent transmission declined in the early 2000s in both populations due to improvements in TB care and prevention.

India was estimated to remain a new infection/transmission-driven epidemic over the modelled time period. In 2000, only 15% (UR: 8-21%) of all new active cases were estimated to result from reactivation. At vaccine introduction in 2025, the estimated proportion arising from reactivation had increased to 36% (UR: 21-46%), and this remained largely stable until 2050. Therefore, although the proportion of new active cases arising as a result of reactivation was anticipated to increase over the 2000-2050 time horizon, the epidemic remained new infection(transmission)-dominated throughout this period.
Prevalence of latent TB infection (LTBI) was estimated by age in each of the three country models, for comparison to available data and modelled estimates (Table 10). The models were not calibrated to prevalence of LTBI data due to uncertainties in the sensitivity and specificity of LTBI tests and lack of country representative of the available LTBI data.

Highly age-stratified LTBI estimates measured in 2013 by TST and Quantiferon were available for four rural sites in China. As discussed in an existing publication of this model, the age-stratified modelled LTBI prevalence estimates were found to align closely with the published age-stratified Quantiferon data (Figure 20, grey bars and red diamonds). The overall modelled prevalence of infection in the China population in 2013 was 16% (UR: 13-19%), ranging from 1% (1-2%) in children aged 5-9 years up to 37% (31-42%) in the elderly. TST estimates from the Gao LTBI prevalence study were higher than modelled LTBI estimates, but this is likely attributable to the impact of non-tuberculosis mycobacteria and BCG vaccination on the specificity of TST, whereas the modelled latently infected populations are true positives. The modelled outputs were compared to two other recently published models. Our modelled estimates were generally lower than the other two modelled estimates (Table 10), however one of the comparator models was calibrated before the public availability of the Gao study, and the other model was calibrated to TST data, so it is unsurprising that the previously modelled estimates were higher.

Several studies of LTBI prevalence were available from townships in South Africa. The modelled LTBI prevalence in children in this study was on the lower end of the available estimates from epidemiological studies, but given the empirical studies were conducted in high TB burden townships, the lower estimates are thought to be more nationally-representative. Our results showed good alignment with available epidemiological estimates of adult LTBI prevalence. Our results showed good alignment with previously modelled estimates.

Data availability for LTBI prevalence in India was limited mostly to paediatric TST studies, and available studies were not nationally representative. Modelled estimates were slightly higher but consistent with available paediatric data. No adult LTBI empirical study was available, but an unverified source suggested an LTBI prevalence in India of 40%, with which the modelled estimates also aligned. The modelled adult LTBI estimates showed good agreement with IHME modelled estimates. These estimates were higher than
predicted in one of the comparator models, (112) but this model was calibrated prior to updated estimates of TB burden in India, which increased estimates of active disease, and consequently impacts modelled estimates of latent infection.

Table 10: Comparison of modelled latent *Mycobacterium tuberculosis* prevalence to published empirical data and two recent multi-country models

<table>
<thead>
<tr>
<th>Source (Year of data) Model/Data</th>
<th>China</th>
<th>South Africa</th>
<th>India</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15yrs</td>
<td>All</td>
<td>&lt;15yrs</td>
<td>All</td>
</tr>
<tr>
<td>This study Model</td>
<td>1% (5-9yrs) (2013)</td>
<td>16% (13-19%) (2013)</td>
<td>13% (7-23%) (2015)</td>
</tr>
<tr>
<td>IHME input Data</td>
<td>4% (0.5-14yrs (2000)[113, 123]</td>
<td>-4% to ~34% by age stratum of QFN (2000) [113, 123]</td>
<td>29% (2005) [113]</td>
</tr>
<tr>
<td>Other sources Data</td>
<td>3% (5-19 yrs QFN) [111]</td>
<td>28% (TST &gt;10 mm) [111]</td>
<td>-15-32% (TST) [114, 115]</td>
</tr>
<tr>
<td>Houben et al. (2014) [112] Model</td>
<td>2% (2-2%)</td>
<td>26% (21-31%)</td>
<td>14% (13-15%)</td>
</tr>
<tr>
<td>IHME (2015) [113] Model</td>
<td>-14%</td>
<td>-28%</td>
<td>-22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 20: China - Age-stratified latent TB infection prevalence in 2013, modelled and empirical data. Grey bars and error bars denote modelled median estimates and uncertainty ranges. Empirical data from Gao et al. (2013) are infection prevalence as measured by TST (blue circles) and QuantiFERON (red diamonds). [111]
8 Supporting vaccine data and information

8.1 Uncertainty ranges

Total ranges around the median estimates, based upon the complete range of the 1,000 calibrated parameter sets for each country, represent uncertainty in TB natural history parameters. These uncertainty ranges are presented throughout the main article, and plots of uncertainty around the primary outcome for a subset of vaccines explored are presented below.

8.1.1 China

Figure 21: China - Medians and uncertainty ranges for estimates of incidence rate reduction in 2050. For combinations of durations of efficacy of 5 years and 10 years, vaccine efficacies for prevention of infection and prevention of disease of 20% and 100%, for P&PI (red), PRI (green) and PSI (blue) vaccines.
**8.1.2 South Africa**

![Graph showing TB incidence rate reduction in 2050 compared to no new vaccine (%).](image)

**Figure 22:** South Africa - Medians and uncertainty ranges for estimates of incidence rate reduction in 2050. For combinations of durations of efficacy of 5 years and 10 years, vaccine efficacies for prevention of infection and prevention of disease of 20% and 100%, for P&PI (red), PRI (green) and PSI (blue) vaccines.
8.1.3 India

Figure 23: India - Medians and uncertainty ranges for estimates of incidence rate reduction in 2050 compared to no new vaccine. For combinations of durations of efficacy of 5 years and 10 years, vaccine efficacies for prevention of infection and prevention of disease of 20% and 100%, for P&PI (red), PRI (green) and PSI (blue) vaccines.

8.2 Cases Averted

Although South Africa experienced much higher rates of disease (406 (UR: 276-612) per 100,000 in 2025 in South Africa; 165.6 (UR: 118.2-238.2) per 100,000 in 2025 in India; 56.4 (51.6-59.5) per 100,000 in China), given it is a much smaller population than India or China, the number of cases averted was lower, with a P&PI vaccine with 100% vaccine efficacy against both infection and disease averting 4.3 million (UR: 2.5-7.0m) cases and 0.9 million (UR: 0.5-1.6m) deaths over 2025-2050, compared to 51.0 million (UR: 32.9-74.8m) cases and 4.3 million (UR: 2.5-7.0m) deaths 2025-2050 in India and 11.6 million (UR: 10.2-12.6m) cases and 270,000 (UR: 145,000-483,000) deaths in China

8.2.1 China

A P&PI vaccine with 100% vaccine efficacy against both infection and disease could avert 3.6 million (UR: 3.1-3.9m) cases with two years duration of protection (Figure 24, left panel), 7.7 million (UR: 6.7-8.4m) with five years protection (Figure 24, centre panel), and 11.6 million (UR: 10.2-12.6m) cases by 2050 with 10 years protection (Figure 24, right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy...
against both infection and disease could avert 1.0 million (UR: 0.8-1.1m) cases with two years duration of protection, up to 3.4 million (UR: 3.0-3.9m) cases with 10 years duration of protection.

A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against both infection and disease were both 60%, two to ten years’ protection would prevent 2.5 million (UR: 2.2-2.7m) to 8.2 million (UR: 7.2-9.1m) cases during 2025-2050 (Figure 24). For a 10 year protection vaccine, if VE-POI were then increased to 80%, an additional 0.2 million cases would be averted; whereas if instead VE-POD were increased to 80%, an additional 1.7 million cases would be averted.

Additional years of protection would also avoid additional cases and deaths. For example, for a 100% VE-POD vaccine the average annual additional number of cases averted when increasing duration from two to three years was 1.5 million. With increasing duration, the absolute number averted continued to increase, but the additional gains per year added were smaller, for example, increasing from seven to 10 years protection gains on average 0.7 million additional averted cases per year.

Figure 24: China - Median cumulative number of cases averted in China for the period 2025-2050. For pre- and post-infection vaccine compared to no new vaccine baseline, by percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here. To note, in this figure the colour scale differs from the other country figures, with purple representing 55 million in the India results, 12 million in the China results and 5 million for South Africa.

8.2.2 South Africa

A P&I vaccine with 100% vaccine efficacy against both infection and disease and safe and efficacious in HIV-positive populations could avert 1.4 million (UR: 0.8-2.1m) cases with two years duration of protection (Figure 25, left panel, uncertainty ranges not shown), 2.8 million (UR: 1.7-4.5m) with five years protection (Figure 25, centre panel), and 4.3 million (UR: 2.5-7.0m) cases 2025-2050 with 10 years protection (Figure 25, right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy against both infection and disease could avert 0.5 million (UR: 0.3-0.6m) cases with two years duration of protection, up to 1.5 million (UR: 0.9-2.3m) cases with 10 years duration of protection.

A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against infection and disease were both 60%, two to ten years’ protection would avoid 1.1 million (UR: 0.6-1.5m) to 3.2 million (UR: 1.6-5.0m) cases during 2025-2050, respectively. For a 10 year protection vaccine, if VE-POI were then increased to 80%, an additional 0.1 million cases would be averted; whereas if instead VE-POD were increased to 80%, an additional 0.3 million cases would be averted.

Additional years of protection would also avoid additional cases and deaths. For example, for the vaccine 60% efficacious against infection and disease, the average annual additional number of cases averted when increasing duration from two to three years was 0.4 million. With increasing duration, the absolute number averted continued to increase, but the additional gains per year added were smaller, for example, increasing from seven to 10 years protection gained on average 0.2 million additional averted cases per year.
Figure 25: South Africa - Median cumulative number of cases averted in South Africa for the period 2025-2050. For pre- and post-infection vaccines safe and efficacious in HIV-positive populations compared to no new vaccine baseline, by percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here. To note, in this figure the colour scale differs from the other country figures, with purple representing 55 million in the India results, 12 million in the China results and 5 million for South Africa.

8.2.3 India

Figure 26: India - Median cumulative number of cases averted in India for the period 2025-2050. For pre- and post-infection vaccines safe and efficacious in HIV-positive populations compared to no new vaccine baseline, by percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here. To note, in this figure the colour scale differs from the other country figures, with purple representing up to 55 million in the India results, 12 million in the China results and 5 million for South Africa.

A P&PI vaccine with 100% vaccine efficacy against both infection and disease could avert 18.7 million (UR: 11.9-28.7m) cases with two years duration of protection (Figure 26, left panel, uncertainty ranges not shown), 37.1 million (UR: 24.8-55.3m) cases with five years protection (Figure 26, centre panel), and 51.4 million (UR: 32.6-76.6m) cases 2025-2050 with 10 years protection (Figure 26, right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy against both infection and disease could avert 6.2 million (UR: 4.0-10.2m) cases with two years duration of protection, up to 21.8 million (UR: 13.7-34.6m) cases with 10 years duration of protection.
A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against both infection and disease were both 60%, two to ten years’ protection would avoid 14.5 million (UR: 9.4-23.0m) to 42.2 million (UR: 286.9-63.8m) cases during 2025-2050. For a 10 year protection vaccine, if VE-POI were then increased to 80%, an additional 1.3 million cases would be averted; whereas if instead VE-POD were increased to 80%, an additional 4.8 million cases would be averted.

8.3 Mortality impact

Mortality rate reduction (MRR, %) in 2050 compared to the no new vaccine baseline was also estimated in the vaccine scenarios. The mortality rate reductions were similar to the incidence rate reduction estimates in terms of trends. The MRRs for 2-5 years duration of protection were greater than the equivalent IRRs, whereas for seven years and above the mortality rate reduction was marginally lower than the incidence rate reduction.

8.3.1 China

With two years duration of protection and very high vaccine efficacy against disease it is possible to achieve a MRR of 22% (UR: 20-23%), and with 5 years protection up to 55% (UR: 53-58%).

A P&PI vaccine with 100% vaccine efficacy against both infection and disease could avert 82,000 (UR: 45,000-147,000) deaths with two years duration of protection (Figure 28, left panel), 173,000 (UR: 94,000-308,000) deaths with five years protection (Figure 28, centre panel), and and 270,000 (UR: 145,000-483,000) deaths by 2050 with 10 years protection (Figure 28, right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy against both infection and disease could avert 21,000 (UR: 11,000-38,000) deaths with two years duration of protection, up to 74,000 (UR: 40,000-135,000) deaths with 10 years duration of protection.

A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against both infection and disease were both 60%, two to ten years’ protection would prevent 56,000 (UR: 30,000-100,000) to 185,000 (UR: 101,000-333,000) deaths during 2025-2050 (Figure 28).

Figure 27: China - Median mortality rate reduction (MRR, %) for pre- and post-infection vaccine compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here.
8.3.2 South Africa

With two years duration of protection and 100% vaccine efficacy against infection and disease it was possible to achieve a mortality rate reduction of 25% (UR: 17-33%), with 5 years protection 73% (UR: 66-79%), and with 10 years protection 83% (UR: 78-87%).

A P&PI vaccine with 100% vaccine efficacy against both infection and disease and safe and efficacious in HIV-positive populations could avert 0.3 million (UR: 0.2-0.5m) deaths with two years duration of protection (Figure 29, left panel, uncertainty ranges not shown), 0.6 million (UR: 0.4-1.0m) deaths with five years protection (Figure 29, centre panel), and 0.9 million (UR: 0.5-1.6m) deaths 2025-2050 with 10 years protection (Figure 29, right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy against both infection and disease could avert 0.1 million (UR: 0.1-0.2m) deaths with two years duration of protection, up to 0.3 million (UR: 0.2-0.5m) deaths with 10 years duration of protection.

A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against infection and disease were both 60%, two to ten years’ protection would avoid 0.2 million (UR: 0.1-0.4m) to 0.7 million (UR: 0.4-1.2m) deaths during 2025-2050.

Figure 29: South Africa - Median mortality rate reduction (%) for pre- and post-infection vaccines (P&PI) safe and equally effective in HIV-positive populations compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here.
8.3.3 India

With two years duration of protection and 100% vaccine efficacy against infection and disease it was possible to achieve a mortality rate reduction of 34% (UR: 28-43%), with 5 years protection 72% (UR: 62-81%), and with 10 years protection 89% (UR:83-93%).

A P&PI vaccine with 100% vaccine efficacy against both infection and disease could avert 1.6 million (UR: 0.9-3.2m) deaths with two years duration of protection (left panel, uncertainty ranges not shown), 3.1 million (UR: 1.7-6.1m) deaths with five years protection (centre panel), and 4.3million (UR: 2.5-8.4m) deaths 2025-2050 with 10 years protection (right panel). At the lower end of the efficacy spectrum, a vaccine with 20% vaccine efficacy against both infection and disease could avert 0.5 million (UR: 0.3-1.1m) deaths with two years duration of protection, up to 1.8 million (UR: 1.0-3.6m) deaths with 10 years duration of protection.

A vaccine efficacy of 60% was considered an achievable target with new vaccines, therefore if vaccine efficacy against both infection and disease were both 60%, two to ten years’ protection would avoid 1.2 million (UR: 0.7-2.5m) to 3.5m (UR: 2.0-7.0m) deaths during 2025-2050. Additional years of protection would also avoid additional cases and deaths.

Figure 31: India - Median mortality rate reduction (%) for pre- and post-infection vaccines (P&PI) compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here.
8.4 Incidence rate reduction in 2035 and cases averted 2025-2035

Incidence rate reductions were estimated in 2035 to align with the WHO End TB strategy, in addition to the estimated cases averted for 2025-2035. Overall, similar trends were observed by prevention of infection and disease efficacy characteristics in both 2035 and 2050 in all three settings. A lower percentage incidence rate reduction compared to baseline was estimated in 2035 than in 2050 for durations of five years and above, whereas a higher percentage reduction in incidence rate was estimated in 2035 than 2050 for the two and three year durations of protection. This is due to the timing of vaccine waning relative to the time point at which impact is measured. In 2035, all vaccines had recently been boosted and therefore populations were protected in all duration scenarios; whereas in 2050, the shorter vaccine durations had already waned following the most recent (2045) mass campaign.

Given the importance of timing of measurement with respect to mass vaccination campaigns for the incidence rate reduction outcome, calculation of the cumulative number of cases averted was a valuable additional measure as it was less sensitive to the timing of vaccination versus measurement.

8.4.1 China

In 2035, a 100% vaccine efficacy two-year duration vaccine could avert up to 1.7 million (UR: 1.5-1.8m) cases (Figure 34, left panel), a 5-year duration vaccine up to 3.5 million (UR: 3.1-3.7m) cases (centre panel), and a 10-year duration vaccine up to 5.6 million (UR: 5.0-6.0m) cases (right panel). Whereas the same vaccines were estimated to avert 3.6 million (UR: 3.1-3.9m), 7.7 million (UR: 6.7-8.4m) and 11.6 million (UR: 10.2-12.6m) cases by 2050 (Figure 24).
8.4.2 South Africa

A description of the trends in incidence rate reduction was given at the beginning of this section, so are not discussed again here.

As expected, the numbers of cases averted were substantially lower in 2035 than in 2050 (Figure 36). In 2035, a 100% vaccine efficacy against infection and disease vaccine with two-year duration of protection averted up to 0.6 million (UR: 0.4-0.9m) cases (left panel), a 5-year duration vaccine up to 1.2 million (UR: 0.7-1.8m) cases (centre panel), and a 10-year duration vaccine up to 1.8 million (UR: 1.2-2.9m) cases (right panel). Whereas by 2050 the same vaccines were estimated to avert 1.4 million (UR: 0.8-2.1m), 2.8 million (UR: 1.7-4.5m) and 4.3 million (UR: 2.5-7.0m) cases (Figure 24). However, the impact achieved by 2035 was a significant impact over a relatively short period of time.
Figure 35: South Africa - Median incidence rate reduction (%) for pre- and post-infection vaccines (P&PI) safe and equally effective in HIV-positive populations compared to no new vaccine baseline in 2035. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here.

Figure 36: South Africa - Median cumulative number of cases averted for the period 2025-2035 for pre- and post-infection vaccines safe and effective in HIV-positive populations compared to no new vaccine baseline. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel). Although a variety of durations were explored, 2 years (left panel), 5 years (centre panel) and 10 years (right panel) duration of protection, all with 10-yearly mass vaccination campaigns, are presented here. To note, in this figure the colour scale differs from the China and India figures, with purple representing 55 million in the India results, 12 million in the China results and 5 million in the South Africa results.

8.4.3 India
In 2035, a 100% vaccine efficacy against infection and disease vaccine with two-year duration of protection averted up to 6.6 million (UR: 4.8-9.7m) cases (left panel), a 5-year duration vaccine up to 13.0 million (UR: 9.2-18.9m) cases (centre panel), and a 10-year duration vaccine up to 19.3 million (UR: 13.0-28.0m) cases (right panel). Whereas by 2050 the same vaccines were estimated to avert 18.7 million (UR: 11.9-28.7m), 37.1 million (UR: 23.6-55.3m) and 51.4 million (UR: 32.6-76.6m) cases (Figure 24).
8.5 Vaccine impact with reduced efficacy or contraindication in HIV-positive populations in South Africa

In the results presented in earlier outcomes, vaccines were assumed safe and efficacious in HIV-positive populations. However, some candidates, such as live attenuated vaccines, may not be safe in HIV-positive populations. Even for those vaccines that were safe in this population, the vaccine efficacy may be reduced by the immune compromise caused by HIV co-infection.

In the scenario where HIV-co-infection was assumed to cause a relative 20% reduction in vaccine efficacy compared to HIV-negative populations, incidence rate reductions were still substantial, but reduced when compared to the equal efficacy scenario (Figure 4 main article, left versus central panel). An example of 100% efficacy is discussed in the main text, but to give a more feasible example, a P&PI vaccine with 10 years protection and 60% efficacy against infection and disease in HIV-negative populations reduced the 2050 incidence rate by 64% (UR: 55-72%) with a 20% efficacy reduction in HIV-positive populations compared to HIV-negative populations, compared to 67% (UR: 60-74%) when equally efficacious. When contraindicated in HIV-positive
populations (though if vaccinated before HIV infection, was assumed to be efficacious, but with a 20% efficacy reduction compared to when HIV-negative) this vaccine led to a 2050 incidence rate reduction of 52% (UR: 36-63%) (Figure 4 main article, right panel).

Given the model predicted that the epidemic in HIV-positive populations was more reactivation-driven during the vaccination period, and in HIV-negative populations was more transmission-driven, when the vaccine was contraindicated in HIV-positive populations, the relative impact of prevention of infection versus disease vaccines changed. In the case of contraindication in HIV-positive populations, prevention of infection and prevention of disease vaccines deliver a more similar level of impact, though with higher incidence rate reductions achieved by prevention of disease efficacy. Whereas when safe and efficacious in both populations, important levels of impact were delivered by both vaccine efficacies, but vaccine efficacy for prevention of disease had a noticeably greater impact than vaccine efficacy for prevention of infection (as evidenced by the more horizontal bars in Figure 4 main article, left versus right panel).

Given the HIV-negative TB epidemic in South Africa was transmission-driven, if a candidate were contraindicated in HIV-positive populations, the vaccine would be tackling a transmission-driven epidemic. In this case, prevention of infection efficacy in pre-infection populations could become more important as a target for vaccine development. If multiple candidates were to come to market with differing efficacies pre/post infection or efficacy against infection versus disease, in a setting like South Africa there may be merit in considering differentiation of the candidates delivered to HIV-positive versus negative populations.

8.6 Five-yearly mass campaigns

A scenario analysis was conducted to explore the primary outcomes with frequency of mass campaigns shortened to every five years. Main analyses implemented mass campaigns every 10 years. However, in some settings, or if the vaccine were shown to be highly effective but with short duration of protection, there may be sufficient political will to deliver mass campaigns more frequently. Five years was considered the shortest likely frequency, so a scenario analysis of 5-yearly campaigns was conducted. Results are presented in the following sections.

Conducting mass campaigns this frequently over the long term could potentially prove incredibly costly, and a challenge to sustain momentum in the campaigns, especially as burden of disease declines. However, annual mass campaigns of 1-29 year olds with the Menafrivac vaccine achieved very high coverages year on year. Therefore, if a short duration vaccine were developed and cost-effectiveness analyses were to suggest that 5-yearly mass campaigns were cost effective, there may be value in considering the feasibility of more frequent mass campaigns.

8.6.1 China

Increasing the frequency of mass campaigns to every 5 years improved the achievable impact in all duration scenarios below 10 years duration of protection (Figure 39). For the two-year duration of protection vaccines, the incidence rate reduction more than doubled (104-120% increase) when mass vaccination was conducted 5-yearly as opposed to 10-yearly. For 3 to 7 year duration of protection vaccines, the incidence rate reduction achieved increased by approximately a quarter to nearly two thirds.
Figure 39: China - Median incidence rate reduction (IRR, %) for pre- and post-infection vaccine with 5-yearly mass vaccination campaigns compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panel).
8.6.2 South Africa

Increasing the frequency of mass campaigns to every 5 years improved the achievable impact in all duration scenarios below 10 years duration of protection. With 5-yearly boosting, even the shortest duration of protection explored (2 years) reduced incidence rates by 47% (UR: 42-53%) with a 100% efficacious vaccine against infection and disease.

Figure 40: South Africa - Median incidence rate reduction for pre- and post-infection vaccine safe and effective in HIV-positive populations with 5-yearly mass vaccination campaigns compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panels).
8.6.3 **India**

As for the other countries, increasing the frequency of mass campaigns to every 5 years improved the achievable impact in all duration scenarios below 10 years duration of protection. With 5-yearly boosting, even the shortest duration of protection explored (2 years) reduced incidence rates by 57% (UR: 53-65%) with a 100% efficacious vaccine against infection and disease.

![Figure 41: India- Median incidence rate reduction for pre- and post-infection vaccine with 5-yearly mass vaccination campaigns compared to no new vaccine baseline in 2050. By percentage efficacy against infection (x-axis), percentage efficacy against disease (y-axis), and duration of protection (as indicated in top left corner of panels).](image-url)