**The *global TB portfolio model*: a tool for projecting the epidemiological impact of TB policy options**

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## Coding guidelines

Table 1. List of model parameters and their symbol as depicted in figure S1 and the model equations in the Supplementary document.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | | | Symbol (diagram and equation) | Symbol used in the code (see the GitHub link) |
| Natural history | | | | |
| Infection rate (number of annual infections per case) | | | ,  , |  |
| Per-capita annual rate of progression from ‘fast’ latent infection | | |  |  |
| Per-capita annual rate of stabilisation from ‘fast’ to ‘slow’ latent status | | |  |  |
| Per-capita annual rate of reactivation from ‘slow’ latent infection | | |  |  |
| Per-capita annual rate of self-clearance of latent TB | | |  |  |
| Per-capita annual rate of developing symptoms, amongst subclinical TB | | |  |  |
| Per-capita annual rate of TB mortality while untreated | | | (general population)  (among HIV) |  |
| Per-capita annual rate of TB self-cure | | |  |  |
| Protection from reinfection amongst those with prior infection | | |  |  |
| Per-capita annual rate of relapse in first two years after treatment completion | | |  |  |
| Per-capita annual rate of relapse in first two years after self-cure or incomplete treatment | | |  |  |
| Per-capita annual rate of relapse>two years after last TB episode | | |  |  |
| Per-capita annual rate of ‘stabilising’ from high to low relapse risk | | |  |  |
|  | | | | |
| Rate-of-presentation to care, first care-seeking visit | In 1997  In 2022 | |  |  |
| Rate-of-presentation to care, second and subsequent care-seeking visits | In 1997  In 2022 | |  |  |
| Probability that a TB patient visits public provider, per care-seeking attempt | In 2022 | |  |  |
| Per-capita rate of offering diagnosis | | |  |  |
| Probability of successful TB diagnosis and treatment initiation per care-seeking visit | | Public sector |  |  |
| Private sector |  |  |
| Per-capita annual rate of treatment completion | | |  |  |
| Per-capita annual rate of treatment interruption | | Public sector | Calculated using , for treatment completion rate , and assuming U[0.75, 0.95] for |  |
| Private sector |  |  |
| Demographics | | | | |
| Per-capita annual rate of background mortality | | | (general population)  (among HIV) |  |

### Model implementation

The model is implemented in both Matlab and Python and the code is hosted in a GitHub repository. The sections below define and describe the syntax and functions used:

* Table 2 defines states names and symbols used of compartments and variables in the model.
* Table 3 defines auxiliary measures (outputs) that are needed for fitting and display purposes.
* Table 4 defines the functions that structure the model setup, model calibration and projection steps.
* Table 5 states the natural history parameters and their data values and ranges, with references.
* Table 6 state parameters that are estimated within assigned ranges as part of the fitting process.
* Table 7 state time-dependent variables that are linked to interventions.
* Table 8 states the WHO data used for calibration purpose.

## Compartments and variables

Table 2: Defining compartments and variables.

|  |  |
| --- | --- |
| gps.vacc | Grouping by vaccination status |
| v0 | Unvaccinated |
| v1 | Vaccinated, immune |
| v2 | Vaccinated, waned immunity |
| gps.hiv | Grouping by HIV status |
| h0 | hiv-negative |
| h1 | hiv-positive |
| hart | hiv-positive, with ART |
| gps.strains | Grouping by drug resistance status |
| ds | Drug susceptible TB |
| mdr | Drug-resistant (rifampicin-resistant) TB |
| gps.provs | Grouping by provider type |
| pu | NTP provider (public, or notifying) |
| pr | non-NTP provider (private, or non-notifying) |
| U | Uninfected |
| Lf | Latent fast |
| Ls | Latent slow |
| Isc | Subclinical infection |
| I | Infection with clinical symptoms |
| E | Missed diagnosis and temporarily disengaged from care-seeking |
| Rlo | Recovered with low relapse risk, following treatment completion |
| Rhi | Recovered with high relapse risk, following treatment non-completion or self-cure |
| R | Long-term, ‘stabilized’ relapse risk |
| Dx | Presented for diagnosis |
| Tx | Initiated first line treatment |
| Tx2 | Initiated second line treatment |
| s.infectious | All the compartments contributing to spreading infection |
| s.infectious\_wosc | Compartments subject to TB mortality |
| s.prevalent | All compartments constituting prevalent TB |

## Outputs used in model calibration

Table 3: Auxiliary measures

|  |  |
| --- | --- |
| inc | Incidence rate (all TB, hiv +ve TB and RR-TB) |
| noti | Public sector notification (TB that is HIV-negative, HIV-positive, and on ART) |
| noti2 | RR-TB notification (initiating second line treatment) |
| mort | TB mortality (HIV negative and HIV coinfected mortality) |

## Model functions

Table 4: Model functions

|  |  |
| --- | --- |
| Model\_setup | To define all variables, parameters and assign their default values, as well as specifying posterior densities corresponding to input data |
| get\_address | To construct lookup tables for compartment numbers relating to each state variable |
| get\_distribution\_fns | Function to find log-density functions matching given data (e.g. incidence) and uncertainty intervals |
| make\_model2 | Specify the full model in matrix form, given all model parameters |
| goveqs\_basis2 | Calculate local gradient for given values of state variables (used in ODE solver) |
| goveqs\_scaleup | To capture linear scaleup of parameters between two time points (e.g. used for linear scale-up of interventions) |
| alloc\_parameters | Given a parameter vector x, to allocate parameter values (p: proportion, r: rate) |
| get\_objective | Given a parameter vector x, to simulate the model and calculate the log-posterior density |
| Get\_calibrations2 | To calibrate the model using MCMC |
| MCMC\_adaptive | Adaptive MCMC, using Haario et al |
| goveqs\_basis\_disruption | As for goveqs\_basis, but used during periods of disruption, allowing rates of diagnosis to vary |
| goveqs\_scaleup\_disruption | As for goveqs\_scaleup, but used during periods of disruption, allowing rates of diagnosis to vary |
| Show\_model\_fits1 | To show calibration results |
| Simulate\_forward | Forward projection with different intervention scenarios |
| Figure\_final | To plot incidence and mortality projection |
| jbfill | Function to show shaded areas for uncertainty intervals |
| linspecer | To specify color series for plotting |

## Natural history parameters

Table 5: Natural history parameters, assigned values and references.

|  |  |  |  |
| --- | --- | --- | --- |
| **Symbol** | **Definition** | **Assigned values** | **References/Note** |
| r.progression | Per-capita annual rate of progression from ‘fast’ latent infection (differentiated by HIV-status, h0, h1, hart) | [0.0826 0.8260 0.1652] | Calibration: Menzies (2018) [1] for hiv-ve and 10 times higher for hiv+ve and with ART its rate reduces by 80% |
| r.LTBI\_stabil | Per-capita annual rate of stabilization from ‘fast’ to ‘slow’ latent status (differentiated by HIV-status, h0, h1, hart) | [0.8720 0 0.8720] | Menzies (2018) [1] for HIV-ve and for HIV+ve with ART |
| r.reactivation | Per-capita annual rate of reactivation from ‘slow’ latent infection (differentiated by HIV-status, h0, h1, hart) | [0.0006 0.0600 0.0120] | Calibration: Menzies (2018) [1] for hiv-ve and 100 times higher for hiv+ve and with ART its rate reduces by 80% |
| r.relapse(1)  (ro\_lo) | Per-capita annual rate of relapse in first two years after treatment completion | 0.032 | Thomas A et al (2005) [2], Romanowski (2019)[3], Menzies (2009) [4] and Weis (1994) [5], with uniform prior using intervals of ± 5% |
| r.relapse(2)  (ro\_hi) | Per-capita annual rate of relapse in first two years after self-cure or incomplete treatment | 0.14 |
| r.relapse(3) | Per-capita annual rate of relapse >two years after last TB episode | 0.0015 | Most relapse occurs in first two years after recovery: Guerra-Assuncao (2015) [6] |
| r.mort | Per-capita annual rate of background mortality |  | Corresponds to average lifespan of 70 years (World Bank 2021) [7] |
| p.imm | Immune protection from reinfection | [0.8 0 0.8] | Assumption, with uniform prior using intervals of ± 25% |
| r.Dx | Per-capita rate of offering diagnosis | 52 | Assumption: corresponds to an average of 1 week to arrive at a diagnosis |
| p\_MDRrec2015 | Of diagnosed TB with rifampcin resistance, proportion that is recognized as such in 2015 (through DST) | [0.001 0] | It is assumed to be a very low value if data is not available for a country |
| p. Tx\_init2 | Proportion of second-line treatment initiation after diagnosis as RR | [0.88 0] | Assumption in absence of country specific data |
| p.SL\_trans | Amongst RR-TB incorrectly initiated on FL treatment, proportion that is subsequently transferred to second-line treatment | [0.88 0] | Assumption in absence of country specific data |
| p.Tx\_init | Of diagnosed patients, proportion initiating first-line treatment | [1 1] |  |
| r.Tx | Per-capita annual rate of first-line treatment completion | 2 | Corresponds to average duration of 6 months |
| r.Tx2 | Per-capita annual rate of second-line treatment completion | 0.5 | Corresponds to average duration of 2 years |
| p.cure | Proportion cure after successful completion of FL treatment | [1 1] |  |
| p.tsrsl | Proportion treatment completion of SL treatment | [0.48 1e-6] | Country specific |
| r.default2 | Per-capita annual rate of treatment interruption during SL treatment (r.default2) in public and private sector |  | Calculated using for values of given above |
| p.cure2 | Proportion cure after successful completion of SL treatment | [0.5 0] | Taken from country reports where available |
| prm.ART\_start | Year of ART initiation |  | Country specific |
| HIV\_incd | Data for annual HIV incidence: assume HIV burden scaled up linearly from 1980 to first data point in 1990 and then using HIV incidence data till 2019 |  | Country specific |
| prm.rHIV | Per-capita rate of HIV acquisition, adjusted in to give model agreement with HIV\_incd |  | Calibration: Estimated |
| r.self\_cure | Per-capita annual rate of TB self-cure | 0.17 (0.13 – 0.21) | Tiemersma et al., (2011) [8] for central value, with uniform prior using intervals of ± 15% |

## Parameters that are estimated during fitting

Table 6: Parameters that are estimated within assigned ranges as part of the fitting process

|  |  |  |
| --- | --- | --- |
| **Symbol** | **Definition** | **Assigned ranges** |
| r\_beta | Infection rate (number of annual infections per case) of DS TB | [0 - 40] |
| rfbeta\_mdr | Infection rate of RR-TB relative to DS TB | [0 - 1] |
| rfbeta\_hiv | Relative transmission rate for HIV +ve TB patients, relative to HIV -ve TB | [0 - 1] |
| r\_sym | Per-capita annual rate of developing symptoms, amongst subclinical TB | [0.1 - 100] |
| p\_pu | Proportion of care-seeking visits that are to the public sector | [0 - 1] |
| r\_cs (1997) | Rate-of-presentation to care, first care-seeking visit for symptomatic TB in 1997 | [0.1 - 100] |
| rf\_cs 2022 | Rate-of-presentation to care in 2022 relative to 1997 | [1 - 10] |
| r\_cs2 | Rate-of-presentation to care, second and subsequent care-seeking visits for symptomatic TB | [1 - 24] |
| r\_mort\_TB | Per-capita annual rate of TB mortality while untreated differentiated by HIV-status (hiv-ve and hiv+ve) | 1/6\*[0 - 2; 0 - 100] |
| p\_Dx | Probability of successful TB diagnosis and treatment initiation per care-seeking visit (in public and private sector) | [0.75- 0.9; 0.1- 0.3] |
| p\_TX\_complete | Proportion treatment completion (used to estimate per-capita annual rate of treatment interruption (r.default) in public and private sector) | [0.75 - 0.95; 0.4 - 0.8] |
| p\_MDRrec2022 | Of diagnosed TB with rifampcin resistance, proportion that is recognized as such in 2022 (through DST) | [0 - 1] |
| r\_MDR\_acqu | Per capita rate of acquired RR/MDR during treatment | [0 - 0.06] |
| r\_ART\_init | Per-capita rate of ART initiation | [0 - 10] |
| r\_HIV\_mort | Per-capita annual rate of HIV mortality while untreated | [0 - 10] |
| r\_self\_cure | Per capita annual rate of self-cure | 1/6\*[0.85 - 1.15] |
| p\_HIV\_relrate | Progression and activation rate among HIV positive, relative to HIV-negative people | [1 - 100] |

## Intervention parameters

Table 7: Interventions

|  |  |
| --- | --- |
| p.pu | This value increases with the private sector engagement intervention |
| r.cs/ r.cs2  (in the model ) | Parameter related to case-finding activity |
| p.DX(1), p.DX(2) | To improve diagnosis in public sector and private sector respectively |
| r.progression and r.reactivation | These parameters reduce with preventive measures |
| p.MDR\_rec | Increases to increase drug susceptibility testing |
| r.Tx2 | Intervention parameter to reduce the duration of second line treatment |
| p.cure2 | Intervention on second-line treatment success rate |
| r.default(1) | Increase of treatment completion and reduction of ILTFU can be modelled by reducing r.default(1). |
| p.PT\_PLHIV | Proportion reduction of progression rate resulting from TPT among PLHIV |
| r.cs3 | Per-capita rate of case-finding amongst sub-clinical TB |
| p.VE(1) | Vaccine efficacy on reduction of susceptibility (pre-exposure protection) |
| p.VE(2) | Vaccine efficacy on reduction of progression to active disease (post-exposure protection) |
| r.vacc | Per-capita annual rate of vaccination |
| r.waning | Per-capita annual rate of waning vaccine immunity |

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## Country-specific calibration targets

Table 8: WHO data used for calibration purposes

|  |  |
| --- | --- |
| popn | Population size in 2022 |
| data.inc\_all | Total TB incidence rate in 2000 and 2022 |
| data.inc\_h1 | HIV-positive TB incidence in 2022 |
| data.noti | TB notification rate in 2022 |
| data.mort\_H0 | HIV-negative TB mortality in 2000 and 2022 |
| data.mort\_H1 | HIV-positive TB mortality in 2022 |
| data.sym | Proportion of prevalent TB that has symptoms |
| data.mdr2015 | MDR/RR-TB incidence in 2015 |
| data.mdr2019 | MDR/RR-TB incidence in 2022 |
| data.mdriniTX | MDR/RR-TB cases started on second-line treatment in 2022 |
| data.ART\_covg | ART coverage in 2022 |
| data.HIV\_prev | Prevalence of HIV in 2022 |