Modelling methods, Kiribati application

Epidemiological Modelling Unit,
School of Public Health and Preventive Medicine,
Monash University

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1 Model Structure

1.1 General features

We use a deterministic compartmental model including six types of compartments that represent different states of infection and disease. The model uses the same conceptual approach and similar assumptions to previously published models. Here we describe the model structure before applying any stratification.

1.2 Compartments

Model compartments represent sequential progressions through the processes of infection with, progression through and recovery from the phases of Tuberculosis. Reinfection is permitted in our model code structure, which is represented as transition from the recovered compartments back to the first infected compartment. The following compartments are implemented:

- Susceptible
  - A susceptible compartment (S) is used to represent individuals who have never been infected with Mycobacterium tuberculosis (M.tb)
- Latent
  - Latent TB infection (LTBI) is modelled using two successive compartments: early latent (E) and late latent (L) to capture the declining risk of disease progression over time from infection
- Infectious
  - The active disease compartment (I) represents individuals who have progressed to the active stage of TB disease
- Treatment
  - All diseased individuals who are detected are assumed to be started on treatment. Treatment may result in cure (progression to R), relapse (return to I) or death
- Recovered or Removed
  - Persons recovered or removed/died from Tuberculosis during the model simulation period.

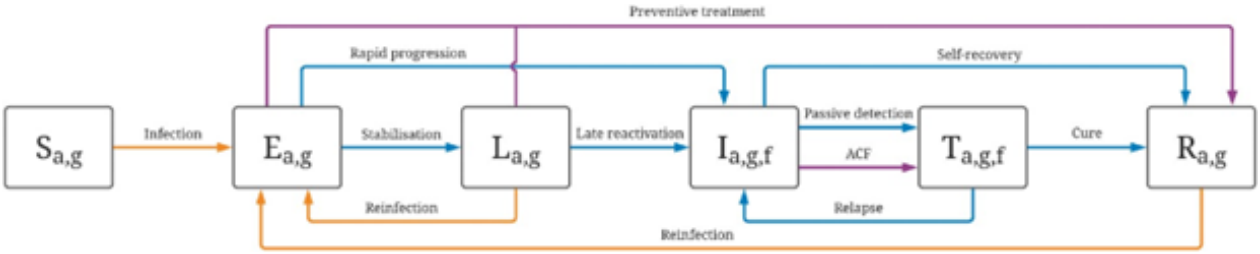

Figure 1: Unstratified compartmental model structure. S = susceptible, E: Early LTBI, L: Late LTBI, E = exposed, I = active, R = recovered/removed

2 Model stratification

2.1 Model stratification

All compartments of the base compartmental structure were stratified by age, location and organ status: Age

- Zero to 14 years
- 15 to 34 years
- 35 to 49 years
- 50 years and above

Location

- South Tarawa
- Other location

Organ status

- Pulmonary smear-posivtive
- Pulmonary smear-negative
- Extrapulmonary

2.2 Births and deaths

Births are modelled using time-variant crude birth rates that are multiplied by the modelled population size to determine the number of newborn individuals entering the model at each time. A time-variant and age-specific rate or non-TB-related mortality applies to all model compartments to simulate deaths from other causes than TB. We use estimates from the UN population division to inform the birth and mortality rates. We also apply additional death rates to the compartments I and T to reflect mortality induced by TB disease.

2.3 M.tb Tranmission

We use different levels of susceptibility to infection for individuals who are currently latently infected with M.tb or have recovered from active TB, as compared to infection-naive individuals. The effect of BCG vaccination is captured by reducing the susceptibility to infection of individuals under the age of 30 years old. We assume a 70% reduction in the susceptibility of BCG-vaccinated children under the age of 15 years old. A linear function is used to reflect the progressive loss of BCG immunity between the age of 15 and 30 years old.

3 Infectious seed

The infectious seed value is assigned at the start of simulation process. This value is subtracted from the total modelled population and assigned to the susceptible compartment, while all other compartments are assigned a starting value of zero. This process is undertaken before age stratification is applied, with the stratification process then splitting these values proportionately according to the starting age distribution of the population.

4 Progression Parameters

4.1 Progression from latent to active TB

We use the estimates reported in Ragonnet et al. to inform the modelled dynamics of activation from latent to active TB. These parameters vary by age, and a multiplier is used to incorporate uncertainty around the progression rates

4.2 Effect of diabetes

The model is not stratified by diabetes status. Instead, we model the effect of diabetes type 2 by increasing the rates of progression from latent to active TB using age-specific multipliers. For each age group, the value of the diabetes-effect multiplier depends on the age-specific proportion of diabetic individuals and the relative rate of TB reactivation for diabetic individuals compared to non-diabetic individuals.

4.3 Natural history flows

We use the estimates reported in Ragonnet et al. to model the rate of TB mortality in the absence of treatment and the rate of self-recovery. We use different rates of untreated TB mortality and self-recovery for smear-positive TB compared to smear-negative TB. The TB mortality and self-recovery rates associated with extrapulmonary TB are assumed to be the same as those of smear-negative TB.

4.4 Passive case detection of active TB

The detection rate is defined as the rate of progression from the active disease to the treatment compartment, as all detected individuals are assumed to be started on treatment at diagnosis in our model. This rate is calculated by multiplying the screening rate with the diagnostic test sensitivity. The screening rate can be interpreted as the reciprocal of the average time that diseased individuals take to seek care. The diagnostic sensitivity varies according to the organ status to reflect the relative differences in the difficulty to diagnose

smear-negative TB and extrapulmonary TB, as compared to smear-positive TB. We use a time-variant function to model the screening rate in order to capture detection improvements over time.

4.5 Treatment outcomes

Treated individuals can experience three different treatment outcomes: treatment success, relapse or death. The rate of treatment-induced recovery φ is set to the reciprocal of the duration of a completed treatment course. We then use the observed treatment success proportion (often referred to as "treatment success rate") as model input. In our model, it is calculated from $TSR = \frac{\phi}{\phi+\rho+\mu_\tau+\mu}$, where ϱ is the relapse rate, μ_τ is the excess mortality rate of individuals on TB treatment, and $\mu$is the non-TB-related mortality rate. Finally, we calculate the respective values of ϱ and μ_τ using the observed proportion of deaths among all negative treatment outcomes, denoted π. We have $\pi = \frac{\mu_\tau+\mu}{\rho+\mu_\tau+\mu}$ that we inject into the TSR equation.

5 Modelled Intervention

5.1 Population-based screening and treatment of LTBI

Mass LTBI screening and treatment is implemented as part of the intervention conducted in South Tarawa in 2022. This is modelled by making latently infected individuals (from E and L) transition to the recovered compartment (R). The rate associated with these flows is obtained by multiplying the LTBI screening rate with the sensitivity of the LTBI test employed and the individual-level efficacy of preventive treatment. The LTBI screening rate is implemented as a time-variant parameter that is stratified by location

5.2 Active case finding

Active case finding (ACF) is implemented to simulate the interventions linked to the detection of individuals with active TB implemented in South Tarawa. This is modelled by implementing an additional transition flow from compartment I to compartment T. The rate associated with this flow is obtained by multiplying the location-specific ACF screening rate with the sensitivity of the detection algorithm used for the ACF intervention. The ACF screening rate is implemented as a time-variant parameter.

5.3 Calculation of the screening rates

To simulate the interventions, we apply a positive rate of ACF and/or LTBI screening over the intervention periods. The screening rates are determined such that the modelled total proportion of the population screened corresponds to the true population proportion screened. The screening rate is set equal to $-log(1-coverage)$ for the year during which the intervention is implemented, where *coverage* is the total proportion of the population screened by the intervention.

6 Parameters

6.1 Target Parameters

Table 1: Parameters

Parameter	Range
Initial population size	200 - 800
Transmission scaling factor	0.002 - 0.01
Progression multiplier	0.5 - 2.0
Screening profile (inflection time), year	2000.0 - 2020.0
Screening profile (shape)	0.07 - 0.1
Screening profile (final rate), per year	0.4 - 0.55
Relative rate of passive TB screening in Ebeye (ref. Majuro)	1.3 - 2.0
Relative rate of passive TB screening in other islands (ref. Majuro)	0.5 - 1.5
Relative rate of TB progression for diabetic individuals	2.0 - 5.0
Relative risk of infection for individuals with latent infection (ref. Infection-naive)	0.2 - 0.5
Relative risk of infection for individuals with history of infection (ref. Infection-naive)	0.2 - 1.0
Efficacy of preventive treatment	0.75 - 0.85
Relative screening rate following ACF interventions (ref. Before intervention)	1.0 - 1.5
TB mortality (smear-positive), per year	0.335 - 0.449
TB mortality (smear-negative), per year	0.017 - 0.035
Self-cure rate (smear-positive), per year	0.177 - 0.288
Self-cure rate (smear-negative), per year	0.073 - 0.209

Table 2: Baseline inputs

Variable	Targeted value	Source
TB prevalence in Kiribati	.....	
TB notifications in Kiribati		Literature
· 2003	· 400	
· 2004	· 428	
· 2005	· 450	
· 2006	· 501	
· 2007	· 433	
· 2008	· 424	
· 2009	· 344	
· 2010	· 347	
· 2011	· 409	
· 2012	· 407	
· 2013	· 472	
· 2014	· 473	
· 2015	· 559	
· 2016	· 575	
· 2017	· 422	
· 2018	· 349	
· 2019	· 436	
· 2020	· 425	
Total population size in 2020	120000	2020 National Census