

TB-MAC UGA Model to simulate TB interventions for South Africa – Model Description

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Overview of the mathematical model

We model infection dynamics of TB and HIV and several different interventions. The model is deterministic, compartmental and continuous-time, formulated as a set of ordinary differential equations. Hosts are compartmentalized according to 12 TB stages (Figure 1). There are 2 classes of susceptible hosts, those that are unprotected and those that are in (partially) protected, e.g. by receiving prior vaccination. Susceptibles can be infected through contact with infectious hosts. A fraction of newly infected hosts rapidly progress to disease (fast progression), others enter the latent stage. Latently infected hosts can again be in an unprotected or protected compartment. The protected compartment can be due to having received prior protection (e.g. vaccination) or because prophylaxis against disease was started during latency (e.g. IPT). Infected hosts are also stratified according to drug susceptibility as MDR or not MDR (nMDR) infected. Latent hosts can activate TB and progress to the diseased and infectious category. Initially, all hosts enter compartments in which they are not picked up by the health care system, the undiagnosed/hidden stage (again stratified by MDR status). Any protection received during the susceptible or latent state is assumed to have no effect during the disease stage. Once diseased and infectious hosts are diagnosed and enter the health system, they can enter either a low quality or high quality healthcare setting. Individuals that have been diagnosed can receive treatment. Successful treatment returns individuals to the susceptible category, unsuccessful treatment returns them to the diseased, hidden categories. Figure 1 shows a flow diagram for the 12 TB states of the model. In addition to these 12 TB compartments, hosts are also split into 3 HIV strata, namely HIV uninfected, HIV infected not on ART and HIV infected on ART. One additional stratification splits groups by age into 2 categories, children (<15 years) and adults. This leads to a total of $12 \times 3 \times 2 = 72$ compartments. Table 1 summarizes the model variables. Descriptions for each of the model components are provided in the following sections.

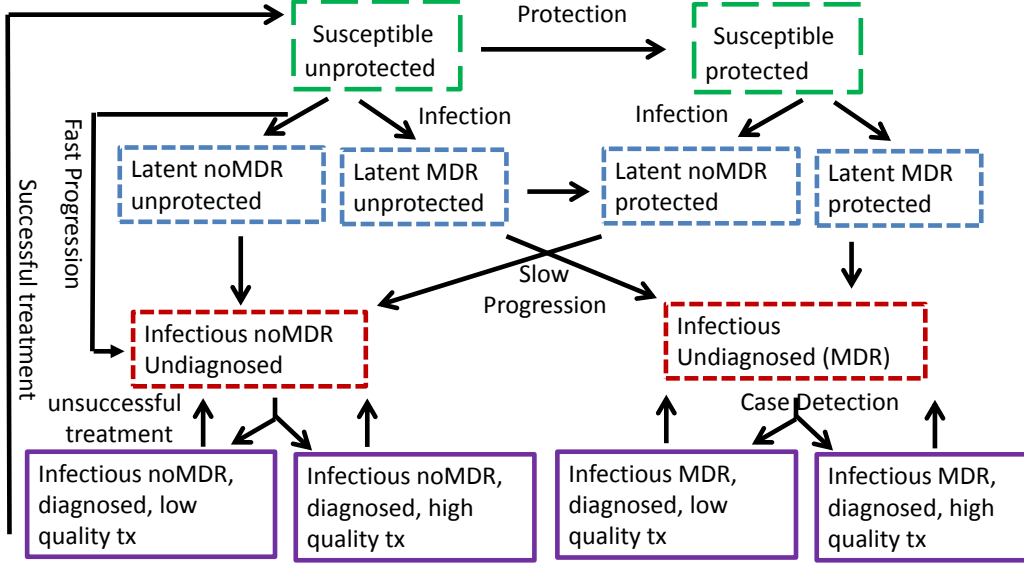


Figure 1: Flow diagram of the model. See the text for a description of the different compartments. Not all flows are shown, e.g. birth/death flows are not drawn. These TB-specific strata are replicated twice for children and adults, and 3 times for HIV negative, HIV positive not on ART and HIV positive on ART. This leads to a total of $12 \times 2 \times 3 = 72$ compartments. tx = healthcare/treatment setting.)

Symbol	Interpretation
$Su_{i,h}$	hosts susceptible to TB, unprotected
$Sp_{i,h}$	hosts susceptible to TB, protected
$Lus_{i,h}$	latently infected hosts, nMDR, unprotected
$Lur_{i,h}$	latently infected hosts, MDR, unprotected
$Lps_{i,h}$	latently infected hosts, nMDR, protected
$Lpr_{i,h}$	latently infected hosts, MDR, protected
$Ihs_{i,h}$	TB diseased hosts, undetected (hidden), nMDR
$Ihr_{i,h}$	TB diseased hosts, undetected (hidden), MDR
$Ibds_{i,h}$	TB diseased hosts, detected, bad healthcare setting, nMDR
$Igds_{i,h}$	TB diseased hosts, detected, good healthcare setting, nMDR
$Ibdr_{i,h}$	TB diseased hosts, detected, bad healthcare setting, MDR
$Igdr_{i,h}$	TB diseased hosts, detected, good healthcare setting, MDR

Table 1: Model variables. The indices indicate age categories ($i = C$ for children and $i = A$ for adults) and HIV classification ($h = n$ for no HIV infection, $h = u$ for infected untreated HIV, $h = t$ for infected treated HIV).

Population size, births and deaths

We model adults and children in South Africa (SA). The annual birth rate is set to a fixed 23.3/1000. Population size is estimated to be 52,386,000 in 2010. 29% of the population are below 15y of age.

Children are born without TB, most of them are HIV negative, 6% of children are assumed to be born with HIV, leading to an overall prevalence of HIV in children of around 3%. Children with HIV receive ART at the same level as adults. The HIV and ART status for children is set at birth and does not vary until they move into the adult compartments. Apart from being born with HIV, no further HIV infection is assumed to occur.

The rate of death in the absence of TB or HIV mortality is set to 1/100 years. This leads to a higher estimate of the lifespan than the actual estimated lifespan of 56. The difference comes from the fact that TB and HIV account for a fair amount of mortality.

Mortality is increased for hosts that either have TB disease or are HIV positive. Rates of excess mortality depends on age group, MDR and HIV status and ART treatment. Mortality due to HIV is modeled as follows: For adults that do not have active TB disease but are HIV positive and do not receive ART, life expectancy has been estimated to be around 5-10 years [6, 13], we set it to 10 years. Adults that have HIV and do receive ART have been estimated to live approximately twice as long as HIV infected hosts not on ART [5], we set it to 20 years. We assume the same lifespans for children.

Mortality due to TB is modeled as follows: Adults with active (untreated) non-MDR TB disease who are HIV negative live for approximately 8 years. This estimate is somewhat high, which can be understood as representing an average of those that die and those that might self-clear/recover [17]. For active TB and HIV positive adults not on ART, the life expectancy is shorter. We chose a value of 2 years. Good data is lacking on the survival for HIV infected hosts with active TB who receive ART; we make the assumption that they have a life expectancy that is halfway between HIV negative and HIV positive untreated TB cases. All death rates for hosts infected with MDR are assumed to be the same as non-MDR infections. We also assume the same values for children as for adults.

HIV infection and treatment

For this model, we assume that adults become infected with HIV at a constant annual rate. We do not explicitly model HIV transmission. The annual rate is set to achieve a 15% HIV prevalence in the adult population. A fraction of HIV positive hosts receive ART. The coverage of ART changes throughout the model simulation as specified in the TB-MAC specification documents. Rates at which adults become HIV positive and receive ART are independent of TB status. Children do not transition between HIV compartments, they are

categorized according to HIV status at birth, as described in the previous section. ART coverage in children follows the same scaling up as the one for adults.

TB infection

Individuals with TB disease are infectious and can infect uninfected hosts or re-infect hosts who harbor latent TB. The infection process is modeled with frequency dependent transmission, i.e. force is proportional to prevalence of diseased hosts [4]. The baseline for an infectious host with non-MDR TB and no HIV is 10 new infections per year (in a fully susceptible population). We assume that MDR has reduced transmissibility of 80% compared to non-MDR. Further, we assume that HIV co-infected individuals transmit at a rate that is 70% compared to baseline. Children are assumed to transmit at 40% compared to baseline. The reductions are multiplicative, i.e. an individual with HIV and MDR has a transmission of $0.8 \times 0.9 = 72\%$ compared to baseline.

Progression from TB latency to disease

Upon TB infection, newly infected individuals either rapidly develop disease (fast progression) or remain latent for an extended period and possibly develop disease later in life (slow progression). The fraction of fast progressors depends on HIV status. We assume 5% fast progressors for nMDR HIV negative individuals [21], and the same value for MDR TB. Among HIV positive individuals, the fraction of fast progressors is set to 20% [21]. ART treatment for HIV positive leads to fast progression fraction fraction that is the average of these 2 rates. Children are assumed to have the same fractions as adults.

Hosts that do not immediately progress to TB disease enter the latent stage. These hosts can eventually transition into the TB disease stage. This transition again depends on HIV status. The rate of transition from latent TB to TB disease for HIV negative adult hosts was estimated to be broadly in the range of 0.0003 – 0.0034 per year [12]. We set the rate to 0.0005 per year. For HIV positive hosts not on ART, transition from latent TB to TB disease occurs at faster rates [8]. Some estimates are 0.079 per year in [15], 0.054 per year in [2] and 0.034 in [20]. We use a value of 0.05 per year. While ART treatment of HIV positive hosts has been shown to reduce the incidence of TB [3], it is unclear if this is due to a reduced fraction of fast progressors or a reduced rate of slow progression. In the absence of more solid data, we assume that the presence of ART lowers the rate of slow progression somewhat, and set the rate of progression for this group to 0.0125 per year. We assume that MDR infections progress at the same rate as nMDR, and that there is also no difference in progression rates between adults and children. The latter assumption is made for simplicity in light of essentially no data that could provide reliable estimates of these rates for children.

Another transition from latent TB infection to TB disease can occur through re-infection. The risk of developing active TB following reinfection is smaller compared with TB disease following initial infection (i.e. fast progression). For HIV negative hosts, reported estimates of TB disease due to reinfection are in the range of 16% – 82% [16, 1, 18] compared to fast progression due to initial infection. We choose an intermediate value of 50% for our model. For HIV positive persons not on ART, we assumed the risk of activation due to re-infection was less reduced and assumed a 70% risk compared to fast progression following initial infection, similar to [7, 10]. For HIV positive hosts on ART, we assume the value to be the same as HIV negative hosts. Since drug resistance is still fairly low, we simplified our model and did not include re-infection with MDR strains. Children are assumed to have the same parameter values as adults.

Rates of progression and activation due to re-infection are modified by some of the intervention strategies, e.g. IPT for latently infected. This is specified in the main TB-MAC implementation documents.

TB treatment

Upon developing active TB disease, hosts initially enter a diseased, infectious, undetected/hidden stage. After some time, these hosts are diagnosed and thereby enter the healthcare system. One recent study in Uganda found that index cases had a median cough duration of 90 days, with a wide range between 1 - 730 days [11]. Another recent study in Uganda found that only 21% of patients with prolonged cough were referred for TB testing and 71% of those testing positive received treatment [9]. Combining the values for duration between infectiousness and detection/treatment with the fraction of those receiving diagnosis/treatment, we choose as an estimate a population level average time to diagnosis of 6 months, for all HIV and age groups. Hosts can enter either into a “low quality” or “high quality” healthcare setting. At baseline, 20% are assumed to enter the high-quality setting. This is scaled up during the simulation as specified in the TB-MAC documents. While in the healthcare system, a fraction of hosts can default, which we set to 17% for nMDR and 30% for MDR cases. Those non-defaulting will go onto treatment and, after an average of 1 month, leave the infectious stage. We assume that at baseline, 76% of treated nMDR individuals succeed in being cleared and return to the susceptible pool. The fraction is 50% for MDR cases. The remaining treatment failures return to the undetected/hidden TB disease compartment, from where they can get diagnosed again and go through the healthcare cascade again. Note that the model does not explicitly distinguish between first and consecutive treatment episodes.

Model Implementation

The model was implemented in R [14]. The code to reproduce all findings reported in the manuscript is available on the corresponding author’s webpage [19].

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