Tuberculosis Module

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# Summary

The Tuberculosis module is responsible for assigning new tuberculosis (TB) infections to individuals through a transmission model and scheduling relevant health system interactions.

The bacteria *Mycobacterium tuberculosis* causes tuberculosis, which is prevalent throughout the world. TB is transmitted between people via infective airborne particles and most commonly causes pulmonary disease. The majority of people infected remain asymptomatic (latent TB) and the development of clinical disease is dependent on age and the competency of the immune system among other factors. The National TB Control Program in Malawi has implemented the WHO Stop TB Strategy, offering Directly Observed Treatment Short-course (DOTS) within a decentralised public] health system. Tuberculosis is one of the priority conditions for the Essential Health Package.

Infections due to drug-susceptible TB and multidrug-resistant TB are modelled separately and individuals can be infected with either, or both. If infected with two strains, any clinical disease is assumed to arise from the most recent infection. Multidrug-resistant (MDR) TB is defined as TB strains resistant to either rifampicin only or both isoniazid and rifampicin.

There are four points at which individuals have contact with the health system relating to TB: prevention, diagnostics (sputum smear test, Xpert test or chest x-ray), treatment and vaccination. BCG vaccination protects against progression to active TB and is managed by the childhood vaccinations module as part of the Expanded Programme on Immunization.

Once health care events such as testing or treatment initiation are scheduled, they enter the health system event queue and are executed chronologically subject to any resource constraints. After the event occurs, the individual’s health state may change as the disease progresses or treatment is started, or a sequence of linked health care system events can be triggered.

# Background

#### The Thanzi La Onse Model

As part of the Thanzi La Onse program a model is being developed which aims to capture the health experiences of the population of Malawi and the consequent interactions with the health care system.  The intent is that this model will help to inform future delivery of health care in Malawi.  The model is an individual based model – which means we explicitly simulate the individual life and health experiences of a representative proportion of population of Malawi.  The simulation initiates on 1 Jan 2010 and we attempt to simulate the attributes of the population at that point.  We can run the model forward to any specified future time point.   Each potential intervention and its associated diseases are being modelled.  This is being divided into separate disease/intervention modules.

#### General approach to decisions on modelling causal influences and effects of interventions

This module was designed in the context of an overall approach to modelling causal effects in general and causal effects of interventions in particular.  The overall intent is to adopt as simple a structure as can be conceived, whilst still capturing the essential elements of a disease and the interventions used to prevent or treatment.  We include a causal link between a “variable” (by which we mean a characteristic or property of an individual, whether that be demographic, social or biologic), and risk of disease or another variable if there is strong evidence from an overall body of studies that such a causal link exists and is at least moderately strong.  In informing such decisions we place particular value on RCTs or studies with a quasi-experimental design such as analyses based on an instrumental variable. There is no expectation that such studies will be from Malawi or even from Africa.  If there are such local studies and in the unlikely event that they provide strong evidence to suggest that the causal link is substantively different in Malawi then the intent is that this is taken into account and the Malawi-specific link included.

In the special case of a potential causal variable which relates to whether an individual has experienced or is experiencing an intervention the intent is to only include interventions if there is substantial RCT evidence of their beneficial effect, based on trials with objectively ascertained clinical endpoints with low risk of serious bias.  Whilst DCP-3 (and to some extent the Malawi EHP) provides an initial list of such interventions and the evidence to support them, where possible our intent has been to form our own opinion on intervention efficacy based on the source trials.

Unless there is evidence to the contrary, the intent is to summarize and incorporate intervention effects into the model as relative risks or rates rather than absolute differences due to the fact that such measures are less likely to differ substantively by context.   Interactions between characteristics (on the multiplicative scale) are only to be be incorporated if there is strong evidence.  Again, we have not intended to rely on data from Malawi or Africa for such evidence but if local evidence exists which strongly suggests a different effect than elsewhere then the intent is that this modified effect is incorporated in the model.

#### Demographic and social characteristics modelled

Based on data on the distribution of the population in Malawi according to geographic location we assign individuals a geographic location, which maps onto whether they are classified as living in a rural or urban area.  Informed largely by data from the Malawi DHS, variables are also created indicating the person’s wealth level (based on 5 quintiles), whether the person has access to improved sanitation, clean drinking water, hand washing facilities, and whether they experience indoor air pollution (wood burning stove).  We assign individuals a current education status (none, primary, secondary) which is updated 3 monthly from age 5 to 20.  From age 15 on there is a possibility of being assigned as being overweight, as using tobacco, drinking excess alcohol, and having low exercise.  Marital status (never, currently, widowed/divorced).  The status with regard to such variables for individuals can change over time.  The influences between these variables are described in detail in a separate document.

# Model structure

#### Individual properties managed by this module

This module updates properties for individuals relating to TB infection, testing and treatment status and preventive therapy. The full list of properties are detailed in Table 1. Updates to these properties occur through regular polling events, e.g. new TB infections or routine screening programmes, or through individual events, such as when a person seeks care for symptoms relating to TB or starts a new treatment regimen.

Table . Individual properties managed by the TB module.

|  |  |
| --- | --- |
| Property | Description |
| **Natural history** |  |
| tb\_inf | TB infection status:  uninfected  latent  active |
| tb\_strain | TB strain: drug-susceptible (ds) or multi-drug resistant (mdr) |
| tb\_date\_latent | Date of onset of latent TB |
| tb\_scheduled\_date\_active | Date active TB is scheduled to start |
| tb\_date\_active | Date of onset of most recent active TB episode |
| tb\_smear | Smear positivity status with current active infection:  False=negative  True=positive |
| **Testing status** |  |
| tb\_ever\_tested | Ever had a TB test |
| tb\_diagnosed | Current diagnosis of active TB |
| tb\_date\_diagnosed | Date most recent TB diagnosis |
| tb\_diagnosed\_mdr | Current diagnosis of MDR-TB |
| **Treatment status** |  |
| tb\_on\_treatment | Currently on TB treatment regimen (for DS- or MDR-TB |
| tb\_treatment\_regimen | Current treatment regimen:  Adult first-line  Child first-line  Adult re-treatment  Child re-treatment  MDR treatment |
| tb\_date\_treated | Date TB treatment started for most recent clinical episode (of DS- or MDR-TB) |
| tb\_ever\_treated | Whether person ever been treated for TB |
| tb\_treatment\_failure | Person has failed first line (non-MDR) TB treatment |
| tb\_treated\_mdr | Currently on treatment for MDR-TB |
| tb\_date\_treated\_mdr | Date started MDR-TB treatment for most recent episode |
| tb\_on\_ipt | Currently on IPT |
| tb\_date\_ipt | Date most recent course of IPT started |

#### Acquisition of new active TB infections

New active TB cases are assigned through two simulation events housed with the ActiveCasePoll which runs monthly. The first is a transmission model which determines the population-level risk of infection dependent on the current prevalence of untreated active infections. The second is an importation event, applying a fixed background rate of infection to all susceptible individuals, independent of current prevalence, representing new infections being seeded through population movement.

Two separate transmission and importation events occur every month and can give rise to either a drug-susceptible active TB infection or an active MDR-TB infection (Figure 1). The probability of an individual becoming infected through either of these routes is dependent on the population-level risk combined with a linear model which considers a number of risk factors to determine a person’s risk of disease, including age (divided into children under age 15 years and adults), BCG vaccination status, HIV infection (and ART use), lifestyle factors such as smoking or heavy alcohol use and whether the person is currently on IPT. We assume no differences in the age distribution of active infections at baseline beyond the two age categories and no differences in infection risk between sexes.

Equation 1 shows the risk of infection applied through the transmission model and is dependent on the prevalence of each strain in the population each month along with the prevalence of HIV-TB co-infection. We assume that the emergence of MDR-TB is primarily the result of transmission rather than incomplete treatment and that there is no fitness cost on transmissibility incurred by the MDR strain.(Shah, Auld et al. 2017)

The probability of an individual becoming infected with TB strain each month *s* (drug-susceptible or MDR) is calculated using the relative infectiousness (*wk*) of all individuals with active pulmonary TB infections (*Is,k*). The relative infectiousness (*k*) of active TB cases is lower for TB patients with concurrent HIV infections, due to faster disease progression, higher mortality rates and a lower probability of smear-positive TB – all of which are captured in the model. If co-infected HIV-TB patients are on ART, the relative infectiousness will be equal to that of HIV-negative patients. Approximately 40-50% of pulmonary TB cases will be smear-negative, with a lower relative infectiousness (0.22, 95% CI 0.16 – 0.32) due to the lower bacterial load. (Behr, Warren et al. 1999)

The transmission rate (*β*) is calibrated to data on the reported number of incident cases of active TB and is equal for both modelled strains. The probability of contact with an infectious case is described by *I / N*, where *N* is the population susceptible to TB infection. The susceptible population includes those already with latent infection leading to reinfection (if infected again with the same strain) or a new infection (if infected with a different strain). Individuals with a current active infection or on treatment are not susceptible to new infections. Additionally, those currently on treatment for TB or with latent infections do not contribute to transmission.

The population-level risk of infection is:

Once infected, onset of active disease is scheduled to occur at random dates distributed across the month. A separate event within the simulation controls the switch from uninfected to active disease, assigning symptoms to each affected individual and determining the smear status which will have implications for diagnosis. The proportion of new active cases assigned as smear-positive is 0.62 (95% CI 0.42 – 0.80) in HIV-negative individuals and 0.35 (95% CI 0.19 – 0.54) in PLHIV.(Vynnycky and Fine 1997, Corbett, Watt et al. 2003, Menzies, Cohen et al. 2012)

In a nationally representative survey, multidrug resistance was detected in 33 individuals from a sample of 1777 smear-positive cases and so we assign 0.0186 of active TB cases as MDR at baseline.(Abouyannis, Dacombe et al. 2014) We consider here only multidrug-resistant cases (resistant to either rifampicin only or both isoniazid and rifampicin) and don’t track extremely drug-resistant (XDR) cases. No XDR-cases had been reported in Malawi by 2017 although some resistance to second-line drugs has been documented.(Abouyannis, Dacombe et al. 2014, World Health Organization 2019) There are no significant fitness costs of resistant strains compared with drug-susceptible strains and the majority of cases occur through transmission (82%, 95% CI 56 – 97% of all incident MDR-TB cases in Malawi) rather than emerging through treatment pressure.(Luciani, Sisson et al. 2009, Kendall, Fofana et al. 2015, Shah, Auld et al. 2017)

We assume that there is no natural immunity protective against infection and the BCG vaccine offered in childhood will protect against both infection and active disease in children. The protective efficacy of BCG against active TB disease is 58% (risk ratio 0.42, 95% CI 0.23 – 0.77).(Roy, Eisenhut et al. 2014) BCG protection against TB will wane over time and we assume that 10 years post-vaccination, there is no further protection against disease.(Sterne, Rodrigues et al. 1998)

#### Relapse following treatment

Relapse, defined as a patient who has become culture negative through receiving treatment and becomes culture positive again, can occur after treatment completion or treatment default with annual rates of 0.032 and 0.14 per year respectively during the first two years. Two years following completion of treatment or treatment default, the risk of relapse falls to 0.0015 per year.(Thomas, Gopi et al. 2005, Menzies, Benedetti et al. 2009) The rate of relapse for HIV-infected individuals is significantly higher than for HIV-negative individuals (RR 4.7, 95% CI 2.5 – 8.9).(Driver, Munsiff et al. 2001) These relapse risks are applied to all treated individuals and will result in a new active infection with the same strain as before.

Relapse rates are assumed to be consistent between drug-susceptible and MDR-TB strains, although treatment success rates differ.

Table . Risk factors associated with active TB disease

|  |  |  |
| --- | --- | --- |
| Status | Relative risk of active TB | Source |
| Age in years |  |  |
| Adult > 15 | 1.0 |  |
| Child ≤ 15 | 0.1 | Assumed |
| BCG | 0.42 | (Roy, Eisenhut et al. 2014) |
| IPT |  |  |
| Child HIV- | 0.55 [0.40-0.75] | (Ayieko, Abuogi et al. 2014) |
| Adult HIV- | 0.4 | (Churchyard, Fielding et al. 2014)  (Smieja, Marchetti et al. 1999) |
| Child HIV+ | 0.31 [0.11-0.87] | (Zunza, Gray et al. 2017) |
| Adult HIV+ | 0.68 [0.54-0.85] | (Akolo, Adetifa et al. 2010) |
| Body mass index |  |  |
| BMI < 30 | 1.0 |  |
| BMI ≥ 30 | 0.4 | (Hanrahan, Golub et al. 2010) |
| Heavy alcohol use  (≥40g per day) | 2.9 | (Lönnroth, Williams et al. 2008) |
| Type 1 diabetes | 3.11 | (Jeon and Murray 2008) |
| Smoking status |  |  |
| Non-smoking | 1.0 |  |
| Current smoking | 1.3 | (Crampin, Glynn et al. 2004, Lin, Ezzati et al. 2007) |
| HIV status |  |  |
| HIV- | 1.0 |  |
| HIV+ (pre-AIDS) | 5 | Assumed to be the same as the risk of relapse |
| HIV+ with AIDS | 26.06 | (Williams, Granich et al. 2010) |
| On ART and virally suppressed |  |  |
| Child | 0.30 [0.21-0.39] | (Dodd, Prendergast et al. 2017) |
| Adult | 0.35 [0.28-0.44] | (Suthar, Lawn et al. 2012) |

These factors affect risk of active disease independent of treatment / infection history.

Graphical user interface

Description automatically generated with low confidence

Figure . Schematic showing the general structure of the TB module.

#### Symptoms associated with active TB

There are four common symptoms associated with active TB; fever, respiratory symptoms, fatigue and night sweats which are assigned to an individual on the same day as active disease onset. These symptoms are used to inform both the healthcare-seeking behaviour of each individual (as documented in the Healthcare seeking behaviour module) and clinical screening in health system interactions (HSI) detailed below. If a person is HIV+, the onset of active TB disease also schedules the onset of AIDS through the HIV module. The DALYs associated with active TB and TB-HIV co-infection are described in Table 3.

Table . TB specific symptoms and DALY weights

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| TB specific symptoms | HIV status | TB strain | DALY weight definition | DALY weight |
| Latent | Negative | Drug-susceptible | Latent tuberculosis infection, Asymptomatic | -- |
| Active | Negative | Drug-susceptible | Drug-susceptible tuberculosis, not HIV infected, has a persistent cough and fever, is short of breath, feels weak, and has lost a lot of weight | 0.333  (0.224 – 0.454) |
|  |  |  |  |  |
|  |  |  |  |  |
| Latent | Negative | MDR | Latent tuberculosis infection, MDR-TB, Asymptomatic | -- |
| Active | Negative | MDR | Multidrug-resistant tuberculosis, not HIV infected, has a persistent cough and fever, is short of breath, feels weak, and has lost a lot of weight | 0.333  (0.224 – 0.454) |
|  |  |  |  |  |
| Latent | Positive | Drug-susceptible | Latent tuberculosis infection, Asymptomatic | -- |
| Active - pulmonary | Positive | Drug-susceptible | Drug-susceptible HIV/AIDS - Tuberculosis without anaemia, HIV infected, has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss | 0.408  (0.274 – 0.549) |
|  |  |  |  |  |
|  |  |  |  |  |
| Latent | Positive | MDR | Latent tuberculosis infection, Asymptomatic | -- |
| Active - pulmonary | Positive | MDR | Multidrug-resistant HIV/AIDS - Tuberculosis without extensive drug resistance without anaemia, HIV infected, has a persistent cough and fever, shortness of breath, night sweats, weakness and fatigue and severe weight loss | 0.408  (0.274 – 0.549) |

#### Outcomes of active TB cases

If HIV-negative, the probability of death due to TB is calculated through a linear model incorporating age, smear status and TB treatment (Table 4). A random draw decides whether this person will die depending on this individual probability and the death will be scheduled to occur at a random point between one and six months after onset of active disease.(Asgedom, Tesfaye et al. 2018) If a death is not scheduled to occur, the individual will continue to be infected with active disease and will either be cured through treatment or will eventually self-cure after a mean duration of three years. This will reset their individual properties to a smear-negative latent infection.

If HIV-positive, the expected date of death is scheduled through the HIV module and is drawn from the distribution of times from AIDS onset to death (exponentially distributed with mean 18 months). If a person is on ART and virally suppressed, this scheduled death date will be cancelled. Additionally, virally-suppressed HIV-positive individuals can self-cure after three years.

Table . Probability of death due to active TB in HIV-negative cases

|  |  |  |  |
| --- | --- | --- | --- |
| Age, years | On treatment | Smear status | Probability of death |
| 0 – 4 | Yes | Positive | 0.05 |
|  |  | Negative | 0.05 |
|  | No | Positive | 0.7 |
|  |  | Negative | 0.2 |
| 5 – 14 | Yes | Positive | 0.06 |
|  |  | Negative | 0.06 |
|  | No | Positive | 0.7 |
|  |  | Negative | 0.2 |
| Adult | Yes | Positive | 0.107 |
|  |  | Negative | 0.107 |
|  | No | Positive | 0.7 |
|  |  | Negative | 0.2 |

Sources:

Untreated TB mortality rates (global): (Dye, Scheele et al. 1999)

Treated TB mortality rates averaged across 2011-2018 (Malawi): (Ministry of Health 2019)

# Health system interactions

#### Screening and testing

In the TB module, we include a health system interaction which details the process of screening and diagnosis of TB cases. Individuals are selected for screening based on the presence of TB-related symptoms where the annual rate of screening is derived from the numbers of active TB cases diagnosed reported by the National TB Programme. A further sample of the general population with no symptoms are selected randomly for screening, matching the overall reports of screening appointments recorded in Malawi. Persons newly diagnosed with HIV are also routinely referred for TB screening at each HIV follow-up appointment following the WHO guidelines.

Health surveillance assistants and doctors at every level of health facility routinely perform TB screening. The algorithm that defines a presumptive TB case comprises four criteria:

* Cough of two weeks or more
* Fever two weeks or more
* Weight loss
* Profuse night sweats two weeks or more

The presence of any of these criteria signifies a presumptive TB case and an immediate referral for TB testing will occur following the diagnostic algorithm detailed in Figure 2. The most widely available tool for TB diagnosis is a sputum smear test which is assumed to have 100% sensitivity in detecting smear-positive TB and 0% sensitivity in diagnosing smear-negative TB. Specificity of sputum smear is very high (>97%) and for simplicity we assume that it is 100% in all smear-positive cases. Positive results from a sputum smear test will trigger a referral for first-line TB treatment for drug-susceptible TB or a longer retreatment regimen if previously diagnosed and treated.

Gene-Xpert MTB/RIF is a molecular diagnostic test that can detect multidrug resistance and is offered as a secondary test for those cases who were smear-negative and are still suspected of having TB. Xpert is also offered to all relapse cases, treatment failure cases and is recommended as a first-line test for people with diagnosed HIV. If individuals are diagnosed with Xpert, they will then be referred for the appropriate treatment, first-line treatment if infected with a drug-susceptible strain and MDR treatment if infected with MDR-TB.

The availability of Xpert testing is constrained at the health facility level and is currently not available to all who are recommended to receive it. The National TB Control Programme has prioritised the following patients for Xpert testing:

* All smear-negative TB suspects
* All HIV-positive presumptive TB cases
* All hospitalised TB suspects
* All confirmed retreatment cases and suspected cases with MDR-TB

If the patient is unable to produce sputum (i.e. children under the age of 5 years), treatment will be offered on the basis of clinical diagnosis or chest x-rays if available. If a person is scheduled to have GeneXpert testing, but this is not available in their district at that time, they will be automatically referred for a sputum smear test. The sensitivity and specificity of each diagnostic test is detailed in Table 5.

Diagram

Description automatically generated

Figure . Diagnostic pathway for adults with suspected TB

#### Treatment

We follow the Malawi Treatment Guidelines for the management of drug-susceptible and MDR-TB cases, which includes the standard treatment regimens, regular clinical monitoring and follow-up sputum smear tests. The details of each treatment regimen and follow-up monitoring schedules are specified in ResourceFile\_TB.

The availability of consumables relating to TB treatment are detailed in the Consumables module, which lists every consumable availability by facility and by month. If a person requests a TB test (sputum smear or Gene Xpert) and the relevant consumables are not available, a repeat visit will be scheduled for a sputum smear. If a sputum test is not available, diagnosis will rely on clinical examinations. If treatment is not available, a repeat visit will be scheduled after one week up to a maximum of five repeat visits, after which the person will default from TB treatment.

The treatment success rates for drug-susceptible cases using first-line anti-tuberculosis treatment regimens reported through the National Tuberculosis Programme 2019 are 0.94 in children aged 0 – 4 years, 0.92 in children aged 5 – 14 years and 0.84 in adults. These success rates are equivalent in both HIV-negative and HIV-TB co-infected cases. Treatment success rates for multidrug-resistant cases fall to 0.60 for all age-groups. Treatment failure will trigger a follow-up referral for testing and retreatment, involving a longer treatment regimen (8 months for drug-susceptible TB, 24 months for MDR-TB) and we assume that all retreatment cases will clear active infection by the end of the treatment regimen.

#### Isoniazid preventive therapy

Isoniazid preventive therapy given over six months reduces the risk of active TB and is offered to people at high risk of active TB. It is recommended for PLHIV who are at high risk of TB and children aged ≤5 years who are close contacts of TB cases.(National AIDS Commission 2014) A six-month course of IPT reduces the risk of progression from latent to active disease although longer IPT regimens with additional rifampicin have shown high cure rates.(Johnson, Okwera et al. 2001, Samandari, Agizew et al. 2011, Houben, Sumner et al. 2014) A summary of the impact of IPT and ART (for PLHIV) on active TB is shown in Table 6.

The duration of protection conferred by a 6-month course of IPT against active TB is highly variable, from 200 days to up to two years.(Smieja, Marchetti et al. 1999, Samandari, Agizew et al. 2011) If combined with rifampicin, protection may last up to three years.(Johnson, Okwera et al. 2001) We assume here the duration of protection is one year, and IPT may be continued or re-initiated at any time if still meeting the eligibility criteria.

IPT is currently offered to three groups of people (Ministry of Health 2012):

* Household contacts aged ≤5 years of TB cases regardless of HIV status (six-month regimen)
* HIV-positive people living in ten high-risk districts (lifelong)
* Infants born to mothers with smear positive TB (six months)

IPT was available to HIV-positive pre-ART patients from July 2012 and expanded to provide continuous IPT for 36 months to all HIV-positive patients on ART in ten high burden districts (Lilongwe, Blantyre, Mangochi, Machinga, Chikhwawa, Mzimba North, Thyolo, Mulanje, Nsanje, Chiradzulu) at the end of 2016.(Ministry of Health 2016)

In the simulation, once an active TB case has been diagnosed, a health system request for IPT for paediatric contacts is initiated. Up to five children aged five years and under, without symptoms suggestive of TB, are randomly selected from the same district as the diagnosed case and allocated a six-month course of IPT. The probability of a child receiving IPT is derived by year using the performance review from the National TB Control Programme. After six months, another simulation event is scheduled which stops IPT although protection against clinical disease will last for a further 6 months.

In addition to this, during the “on\_birth” call in the simulation, infants born to mothers with diagnosed smear-positive TB are also randomly selected to start a six-month course of IPT. The probability of an infant receiving IPT is also derived from the coverage rates of household contacts aged under five years.People newly diagnosed with HIV are also scheduled to receive IPT at the same time as ART initiation. The probability of starting IPT is derived from the reported national coverage levels each year and we assume 90% retention every 6 months.

If IPT is not available at the time of the appointment, a repeat visit will be scheduled for a random date within the next two weeks, up to a maximum of five repeat visits.

Table . Characteristics of each diagnostic TB test

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Diagnostic test | Sensitivity |  | Specificity |  | Source |
|  | Smear positive | Smear negative | Smear positive | Smear negative |  |
| Sputum smear | 100 | 0 | 100 | 0 |  |
| Gene Xpert | 98  (97 - 99) | 68  (59 - 74) | 99  (98 - 99) | 99  (98 - 99) | (Steingart, Schiller et al. 2014) |
| Chest x-ray | 91  (88 - 93) | 80  (74 - 85) | 67  (62 - 71) | 67  (62 - 71) | (van Cleeff, Kivihya-Ndugga et al. 2005) |
| Clinical evaluation | 0.21  (0.12 – 0.33) | 0.21  (0.12 – 0.33) | 0.95  (0.92 – 0.97) | 0.95  (0.92 – 0.97) | (Vassall, van Kampen et al. 2011) |

Table . Protective efficacy of IPT/ART against active TB

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Subgroup** | **Intervention** | **Assumed value for model** | **Evidence to support assumption** | **Source** | **Notes** |
| **HIV-negative** | | | | | |
| Adult HIV- | IPT | 0.4 | 0-9 months adjusted rate ratio, 0.42; 95% CI, 0.20 to 0.88  9-18 months 0.93 (95% CI, 0.53 to 1.61  18- months  0.95 (95% CI, 0.62 to 1.46 | (Churchyard, Fielding et al. 2014) | Large Thibela TB study in gold miners South Africa |
|  |  |  | 6 / 12 months  RR 0.40 (0.31 – 0.52) | (Smieja, Marchetti et al. 1999) | systematic review of randomised controlled trials |
| Child HIV- | IPT | 0.55 | RR = 0.55, 95% CI 0.40, 0.75 | (Ayieko, Abuogi et al. 2014) |  |
| **HIV-positive** | | | | | |
| Child HIV+ | IPT | 0.31 | hazard ratio (HR) 0.31, 95% confidence interval (CI) 0.11 to 0.87 | (Zunza, Gray et al. 2017) | Low certainty evidence |
| Child HIV+ | ART | 0.3 | HR: 0.30; 95% CI 0.21 to 0.39 | (Dodd, Prendergast et al. 2017) | Meta-analysis |
| Child HIV+ | IPT + ART | 0.76 | risk ratio (RR) 0.76, 95% CI 0.50 to 1.14 | (Zunza, Gray et al. 2017) |  |
| Adult HIV+ | ART | 0.35 | HR 0.35, 95% CI 0.28 to 0.44 | (Suthar, Lawn et al. 2012) | Overall for any CD4 count  (1) less than 200 cells/µl (hazard ratio [HR] 0.16, 0.07 to 0.36)  (2) 200 to 350 cells/µl (HR 0.34, 0.19 to 0.60)  (3) greater than 350 cells/µl (HR 0.43, 0.30 to 0.63), and  (4) any CD4 count (HR 0.35, 0.28 to 0.44) |
| Adult HIV+ | IPT | 0.68 | RR 0.68, 95% CI 0.54 – 0.85 | (Akolo, Adetifa et al. 2010) | systematic review of randomised controlled trials. No mention of ART in trial participants |
| Adult HIV+ | IPT + ART | 0.63 | [HR] 0·63, 95% CI 0·41–0·94 | (Rangaka, Wilkinson et al. 2014) | Risk of active TB in PLHIV concurrently receiving ART. HR applies to those on ART and receiving IPT vs those on ART only |

# Further considerations

The model does not include distinctions between forms of extrapulmonary TB (tuberculous meningitis and miliary tuberculosis). Additionally, the mortality rates applied to those with TB are generalised across all forms of TB, both pulmonary and extrapulmonary. It is possible that mortality rates so differ between the different forms and this could be included at a later date.

We make the simplifying assumption that multidrug resistance is only transmitted from infectious cases or imported and does not emerge as a result of treatment failure following infection with a drug-susceptible strain. The transmission probability of MDR strains is equivalent to drug-susceptible strains under the assumption that drug resistance does not incur a fitness cost. The effect of these assumptions may be that we fail to capture clustering of MDR cases in people who have been previously treated and defaulted from treatment.

If people have active TB, we assume that they cannot be re-infected or infected with another strain. Likewise, once on treatment we consider people to be “immune” from re-infection until they return to a latent state.

The relationship between obesity, diabetes and TB is complex and non-linear. Obesity has been shown to be protective against active TB disease, however it is a major risk factor for diabetes, and diabetes is itself a risk factor for TB. One analysis showed a slightly increased risk of TB due to obesity which was mediated through diabetes (between 0.8% and 2.7% increased odds of TB) but a strong protective effect in the absence of diabetes (67% - 72% decrease in odds of TB). Individuals who were both obese and diabetic had a similar risk of TB compared with non-diabetic people with a health weight.(Lin, Wu et al. 2018) Here we assume a RR = 0.4 for people classed as obese and RR = 3.0 for those with diabetes. Individuals who are both obese and diabetic will therefore have a RR = 1.2, slightly higher than non-diabetic people with a healthy weight.

All-cause mortality among fully treated TB patients may remain significantly higher than a comparable population with latent TB although the mechanism for this remains unknown.(Miller, Wilson et al. 2015) There may be persistent health deficits resulting from TB such as pulmonary impairment which could predispose patients to other pulmonary diseases. There may also be common risk factors across diseases which contribute to higher overall mortality in this group. Here we assume that mortality rates return to pre-TB rates once treatment has started which may under-estimate the long-term mortality in people who have had active TB.

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