# Tuberculosis

# Flowchart



# Tuberculosis

# **Case Definition**

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. The case definition includes all forms of TB, including pulmonary TB and extrapulmonary TB, which are bacteriologically confirmed or clinically diagnosed. For TB, the ICD 10 codes are A10-A19.9, B90-B90.9, K67.3, K93.0, M49.0, P37.0, and ICD 9 codes are 010-019.9, 137-137.9, 138.0, 138.9, 139.9, 320.4, 730.4-730.6. For HIV-TB, the ICD 10 code is B20.0.

Latent TB infection is defined as an infection with *Mycobacterium tuberculosis*, without any symptoms or signs of active TB disease.

We separately estimated the incidence and prevalence of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis by HIV status. The case definitions are shown below.

(1) Multidrug-resistant TB without extensive drug resistance: a form of TB (among HIV-negative individuals) that is resistant to the two most effective first-line anti-tuberculosis drugs (isoniazid and rifampicin), but is not resistant to any fluoroquinolone and any second-line injectable drugs (amikacin, kanamycin, or capreomycin).

(2) Extensively drug-resistant TB: a form of TB (among HIV-negative individuals) that is resistant to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drugs.

(3) Drug-susceptible TB: TB (among HIV-negative individuals) that is susceptible to isoniazid and rifampicin.

(4) HIV/AIDS - Multidrug-resistant TB without extensive drug resistance: a form of TB (among HIVpositive individuals) that is resistant to the two most effective first-line anti-tuberculosis drugs (isoniazid and rifampicin), but is not resistant to any fluoroquinolone and any second-line injectable drugs (amikacin, kanamycin, or capreomycin).

(5) HIV/AIDS - Extensively drug-resistant TB: a form of TB (among HIV-positive individuals) that is resistant to isoniazid and rifampicin, plus any fluoroquinolone and any second-line injectable drugs.

(6) HIV/AIDS - Drug-susceptible TB: TB (among HIV-positive individuals) that is susceptible to isoniazid and rifampicin.

# Input data

# Model inputs

Input data for TB include annual case notifications, data from prevalence surveys, and estimated causespecific mortality rates (CSMR) of TB among HIV-positive and HIV-negative individuals. For latent TB infection (LTBI), input date include: (1) population-based tuberculin surveys, and (2) cohort studies examining the risk of developing active TB disease as a function of induration size. An updated systematic review was done for GBD 2020. The search terms, number of studies identified, and number of studies included are shown in the table below.

| Outcome          | Search Terms  | Total      | Number     |
|------------------|---|------------|------------|
|                  |   | number of  | of studies |
|                  |   | studies    | included   |
|                  |   | identified |            |
| Tuberculosis     | Pubmed: ("tuberculosis"[MeSH] OR                              | 479        | 3          |
|                  | tuberculosis[Title/Abstract]                                  |            |            |
|                  | OR TB[Title/Abstract] OR Mycobacterium                        |            |            |
|                  | tuberculosis[Title/Abstract] AND prevalence[Title/Abstract]   |            |            |
|                  | AND ("2017/09/01"[PDAT] : "2019/02/13"[PDAT]) NOT             |            |            |
|                  | (animals{SESH] NOT humans[MESH])                              |            |            |
|                  |   |            |            |
| LTBI (tuberculin | Pubmed: ("tuberculin survey"[tiab] OR (("risk"[MeSH Terms]    | 31         | 1          |
| surveys)         | OR "risk"[tiab] OR "risk of"[tiab]) AND ("tuberculosis"[MeSH  |            |            |
|                  | Terms JOR "tuberculosis" [tiab] OR "tuberculous" [tiab]) AND  |            |            |
|                  | (Injection [IVIESH Terms] OR Injection [tidb])) OR            |            |            |
|                  | (( TISK [IVIESH TETTIS) OK TISK [LIAD] OK TISK OJ [LIAD]) AND |            |            |
|                  | "IB[[IUD] AND ( III]ECLIOII [IVIESH TETTIS] OR                |            |            |
|                  | OP "latent TP infection"[figh] OP "latent                     |            |            |
|                  | tuberculosis"[MESH]) AND ("survey"[tigh] OR                   |            |            |
|                  | "surveys"[figh]) NOT (animals[MESH] NOT humans[MESH])         |            |            |
|                  | ("2017/09/01"[PDAT] · "2019/02/13"[PDAT])                     |            |            |
|                  |   |            |            |
|                  |   |            |            |
|                  | Google Scholar: ("tuberculin survey" OR "risk of              |            |            |
|                  | tuberculous infection" OR "risk of tuberculosis infection"    |            |            |
|                  | OR "risk of TB infection" OR "latent tuberculosis infection"  |            |            |
|                  | OR "latent TB infection") AND "survey". (09-08-2017 to        |            |            |
|                  | 2019/02/13).  |            |            |
| LTBI (cohort     | Pubmed: ("tuberculin"[tiab] OR ("tuberculin"[tiab] AND        | 118        | 2          |
| studies)         | "positive"[tiab]) OR "Mantoux"[tiab] OR ("Mantoux"[tiab]      |            |            |
|                  | AND "positive"[tiab]) OR "induration"[tiab]) AND              |            |            |
|                  | (active[tiab] AND ("tuberculosis"[MeSH] OR                    |            |            |
|                  | "tuberculosis"[tiab])) AND ("risk"[MeSH] OR "risk"[tiab])     |            |            |
|                  | AND ("prospective"[tiab] OR "follow up"[tiab] OR              |            |            |
|                  | "longitudinal"[tiab]) NOT (animals[MESH] NOT                  |            |            |
|                  | humans[MESH]) ( <i>"2018/06/01"[PDAT] :</i>                   |            |            |
|                  | "2019/02/13"[PDAT])   |            |            |

Input data for multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) include: (i) the number of MDR-TB cases, XDR-TB cases, new and retreated TB cases with a drug sensitivity testing (DST) result for isoniazid and rifampicin, and MDR-TB cases with DST for second-line drugs from routine surveillance and surveys reported to the World Health Organization, and (ii) the risk of MDR-TB associated with HIV infection from the literature.<sup>1</sup>



# PRISMA Diagram of TB All Forms Prevalence in GBD2020



# Prisma Diagram of Latent Tuberculosis Infectious in GBD2020

#### **Modelling Strategy**

#### Overview

Our TB modelling strategy has not changed substantially from GBD 2019, but we made refinements to our modeling approach: we used the Meta-Regression with Bayesian Priors, Regularization, and Trimming (MR-BRT) model as the primary analytical engine to predict MI ratios instead of a mixed-effects regression, and we used modeled excess mortality rate (EMR) as input in DisMod. First, we estimated risk-weighted prevalence of LTBI by location, year, age, and sex using data from population-based tuberculin surveys and cohort studies reporting the risk of developing active TB disease as a function of induration size. Next, we divided the inputs on prevalence (from surveys in low- and middle-income countries), incidence (notification data from countries with a four- or five-star rating, and estimated incidence for countries with a less than four-star rating), and cause-specific mortality rate (CSMR) by the risk-weighted LTBI prevalence in order to model TB among those at risk in each country. Next we run MR-BRT (with GBD super region fixed effects) using MI ratios (logit transformed) from locations with a 4- or 5star rating on causes of death with HAQ index as a covariate anchoring the lower end of the HAQ index scale with a data point from the Bangalore study<sup>2</sup> reporting that 49.2% of 126 untreated new pulmonary TB cases were dead at the end of the five-year follow up period, to predict age-sex specific MI ratios for all locations and years. We then estimated age-sex-specific incidence using the predicted MI ratios and CSMR estimates. Finally, we modeled remission as a function of the HAQ index and used estimated remission to convert MI ratios into excess mortality rates (EMR).

We used DisMod-MR 2.1, the GBD Bayesian meta-regression tool to generate consistent trends in all parameters. We then multiplied the DisMod-MR 2.1 outputs by the risk-weighted prevalence of LTBI to

get population-level estimates of incidence and prevalence. Because the outputs from DisMod-MR 2.1 are for all forms of TB, we split them into MDR-TB and XDR-TB by HIV status. To do so, we estimated the proportions of TB cases with MDR-TB for all locations and years, using data from notifications and survey data. We then estimated the proportions of MDR-TB among HIV-negative individuals and MDR-TB among HIV-positive individuals based on the risk of MDR-TB associated with HIV infection from a meta-analysis<sup>1</sup>. To split MDR-TB into MDR-TB with and without extensive drug resistance, we pooled the limited notification and survey data on the proportion of MDR-TB cases with extensive drug resistance by super-region, and applied these proportions to MDR-TB cases among HIV-negative and HIV-positive individuals, respectively.

# Modelling risk-weighted latent TB infection prevalence

Input data for modelling risk-weighted LTBI prevalence were from two sources: (i) population-based tuberculin skin test (TST) surveys, and (ii) cohort studies examining the risk of developing active TB disease as a function of induration size. First, we extracted the prevalence of tuberculin skin testing results by induration size using the most detailed induration categories reported by studies. Second, from cohort studies reporting on the relative risk of developing active TB disease as a function of induration size. In GBD 2020, we pooled the risk of developing active TB by induration size in millimeters using advanced MR-BRT to allow for integration over binned data. Third, we multiplied the LTBI prevalence by induration in millimeters ranging from 0-20+ with the relative risk of developing active TB at each induration size, and summed them up to derive risk-weighted LTBI prevalence for each age group.

Available evidence<sup>3</sup> suggests that people with very advanced HIV infection (CD4 counts <200 cells/mm<sup>3</sup>) may have a false-negative TST (0mm induration) due to profound immune suppression, but still have very high risk for TB. For those who are HIV-positive, but with higher CD4 counts, the risk for active TB increases with greater induration size as in HIV-negative individuals (ie, the shape of the tuberculin response curve is similar to that for the general population). To take into account the false-negative TST response in HIV cases with profound immune suppression, we first computed the proportion of HIV-positive individuals with CD4 counts <200 cells/mm for the 0 mm induration group using our HIV prevalence estimates for that particular category. We then multiplied that proportion by the relative risk of developing active TB disease in the 0 mm induration group compared with the 20+ mm induration group among HIV-positive individuals. The relative risk was computed using data from a prospective, multicenter cohort study of HIV-positive people in the United States.<sup>3</sup>

Additional evidence<sup>4</sup> indicates that lower doses of PPD (e.g. 1 TU RT23) in a tuberculin skin test yields smaller reactions compared to the standard dose (2 TU RT23; 5 TU PPD-S). In GBD 2020, we adjusted for this bias by collating data from studies that report the difference in reactivity between the standard dose and smaller doses in the same population. We used the reported mean difference from two studies<sup>4,5</sup> in the MR-BRT model to derive a pooled difference. We then added this pooled difference to every reported induration category from studies using lower doses of PPD to adjust the data to the level of the standard dose. In GBD 2020 we also utilized the MR-BRT model to derive adjustment factors for studies where the entire sample is BCG-positive and for studies where BCG status is mixed. The table below contains adjustment factors for BCG status in GBD 2020:

# Table 1: MR-BRT Crosswalk odds ratio for Latent Tuberculosis Infection

| Reference or alternative | Gamma | Beta Coefficient,    | Relative Odds ratio* |
|--------------------------|-------|----------------------|----------------------|
| case definition          |       | Logit (95% CI)       |                      |
| BCG Negative             | 0.36  |                      |                      |
| BCG Mixed                |       | 0.09 (-0.04 to 0.22) | 1.09 (0.97 to 1.25)  |
| BCG Positive             |       | 0.42 (0.39 to 0.45)  | 1.52 (1.48 to 1.57)  |

\*MR-BRT crosswalk adjustments can be interpreted as the factor the alternative case definition is adjusted by to reflect what it would have been had it been measured using the reference case definition. If the log/logit beta coefficient is negative, then the alternative is adjusted up to the reference. If the log/logit beta coefficient is positive, then the alternative down to the reference.

\*\*The adjustment factor column is the exponentiated beta coefficient. For log beta coefficients, this is the relative rate between the two case definitions. For logit beta coefficients, this is the relative odds between the two case definitions.

Using the risk-weighted LTBI prevalence (adjusted for a false-negative TST among people with advanced HIV infection, for non-standard PPD doses, and for BCG status) as input data, we ran a DisMod-MR 2.1 model with the HAQ index covariate to help inform variation over year and geography, with priors that at higher HAQ index values, LTBI prevalence decreases. To stabilize temporal trends we included a covariate for year with priors such that LTBI prevalence decreases over time.

#### Modelling TB incidence

Incidence inputs were from two different sources: (1) incidence from notification data for countries with a four- or five-star rating on their cause of death data<sup>6</sup> as a proxy for the quality of health-related administrative data systems, and (2) estimated incidence for countries with a less than four-star rating. We used the age- and sex-specific notifications (all new and relapse cases combined) in our analysis. Prior to 2013, notification data were available by case type (new pulmonary smear-positive, new pulmonary smear-negative, and new extra-pulmonary) and there were missing age data, especially for younger age groups in some countries. We imputed the missing age groups for the three forms of TB notifications. Smear-positive age-specific notifications were inflated with the proportion smear-unknown and relapsed cases only reported at the country-year level. Some countries reported only pulmonary smear-positive cases using a seemingly unrelated regression. All three types of notifications were added together to represent TB-all-form incidence for countries with a four- or five-star rating.

To generate incidence estimates for locations with a less than four-star rating, we implemented the MR-BRT model with age and sex dummies and super-region fixed effects, using MI ratios (logit transformed) from locations with a 4- or 5-star rating on causes of death as input data with HAQ index as a covariate anchoring the lower end of the HAQ index scale with a data point from a cohort study in the 1960s<sup>2</sup> reporting that 49.2% of 126 untreated new pulmonary TB cases were dead at the end of the five-year follow-up period, in order to predict age-sex-specific MI ratios for all locations and years. We then used the MI ratios and cause-specific mortality estimates to compute the incidence input for DisMod-MR 2.1 for locations with a less than four-star rating. In locations where MI ratio based incidence was lower than notification-based incidence, we dropped the MI ratio based incidence and allowed DisMod to estimate incidence by triangulating between mortality, prevalence, excess mortality, and remission. For comparisons between MI ratio based incidence and notification based incidence, we used the year 2010 and assumed a similar proportional difference across all other years. Finally, we computed the age-sexspecific incidence of TB among the latent TB-infected population, using TB incidence as the numerator and our estimated risk-weighted latent TB infection prevalence as the denominator.

# Modelling TB prevalence

Data from prevalence surveys reporting on pulmonary smear-positive TB and bacteriologically positive TB were included. Because incidence data are for all forms of TB, we adjusted prevalence surveys to account for extrapulmonary cases. We ran a spatiotemporal Gaussian process regression to predict location-year-age-sex-specific proportions of extrapulmonary TB among all TB cases using data on the three forms of TB from the incidence data above. We then computed the extrapulmonary inflation factor as 1+( proportion of extrapulmonary TB)), and applied it to data from prevalence surveys.

In GBD 2020, we used the MR-BRT model to derive adjustment factors for studies where the case definition was smear-positive TB rather than bacteriologically positive TB (reference). For the adjustment, we identified all prevalence surveys that provided comparisons of smear-positive TB and bacteriologically positive TB from the same sample. Overall, 16 prevalence surveys from Cambodia, China, Ethiopia, Gambia, India, Myanmar, South Korea, Philippines, Rwanda, and Vietnam were included as inputs in the MR-BRT model. The model also contained covariates for sex and age to reflect gradients across demographics. In GBD 2020 we also computed an adjustment factor to adjust studies that used symptoms only as a screening method compared to studies using both symptoms and chest X-ray during screening (reference). To derive the adjustment factor, we ran a MR-BRT model where data from six studies<sup>7,8,9,10,11,12</sup> comparing prevalence between using symptoms only as opposed to symptoms and chest X-ray in the same population as input. The adjustment factors are in the table below.

Finally, we computed the prevalence of TB among the TB-infected population, using TB prevalence as the numerator and our estimated risk-weighted LTBI prevalence as the denominator. We included two location-level covariates, namely, age-standardised adult underweight prevalence and log-transformed age-standardised Summary Exposure Variable (SEV) scalar for TB (a summary variable of the exposure levels of TB risk factors weighted by relative risk) to help inform variation of TB prevalence over year and geography.

| Reference or alternative case definition | Gamma | Beta Coefficient,<br>Log (95% CI) | Relative Odds<br>Ratio* |
|--|-------|-----------------------------------|-------------------------|
| Bacteriologically positive               | 0.23  |                                   |                         |
| Smear positive                           |       | -0.46 (-0.70 to -0.22)            | 0.63 (0.50 to 0.80)     |
| Symptoms and chest X-ray                 | 0     |                                   |                         |
| Symptoms only                            |       | -0.37 (-0.50 to -0.25)            | 0.69 (0.61 to 0.78)     |

# Table 2: MR-BRT Crosswalk Relative Odds Ratio for Tuberculosis Prevalence

\*MR-BRT crosswalk adjustments can be interpreted as the factor the alternative case definition is adjusted by to reflect what it would have been had it been measured using the reference case definition. If the log/logit beta coefficient is negative, then the alternative is adjusted up to the reference. If the log/logit beta coefficient is positive, then the alternative down to the reference.

\*\*The adjustment factor column is the exponentiated beta coefficient. For log beta coefficients, this is the relative rate between the two case definitions. For logit beta coefficients, this is the relative odds between the two case definitions.

# Modelling TB remission and excess mortality

In GBD 2020 we computed TB duration based on a systematic review of studies during the prechemotherapy era finding that duration from onset to cure or death is 3 years.<sup>13</sup> To anchor the lowest end of TB duration we assumed a duration of 6 months based on treatment regiments. We then linearly interpolated between 6 months and 3 years across the HAQ index to compute TB duration for every country-year. We converted duration into remission by taking the inverse (e.g. Remission = 1/duration). Using HAQ-based remission and estimated MI ratios, we computed excess mortality rate (EMR) with the following computation: EMR = MI\*Remission (formula derived from Prevalence=Incidence\*Duration)

# DisMod-MR 2.1

For each location, we included the following as input in the DisMod model: case notifications for locations with a four- or five-star rating, predicted MI-ratio-based incidence for locations with a less than four-star rating, prevalence survey data where available, predicted excess mortality estimates, HAQ-based remission, and CSMR (TB and HIV-TB combined) by age and sex.

The output from the DisMod model was for all forms of TB in TB-infected populations, including both HIVnegative and HIV-positive individuals. We computed the incidence and prevalence of TB among the entire population, by multiplying the prevalence of LTBI with the DisMod model estimates. Betas and exponentiated values from the DisMod model are shown in the table below.

| Covariate            | Parameter  | Beta (95% CI)       | Exponentiated beta (95% |
|----------------------|------------|---------------------|-------------------------|
|                      |            |                     | CI)                     |
| Sex (male)           | Prevalence | 0.34 ( 0.31 — 0.38) | 1.41 (1.36 — 1.46)      |
| Sex (male)           | Incidence  | 0.38 ( 0.38 — 0.39) | 1.47 (1.46 — 1.47)      |
| Age-standardised     | Prevalence | 2.39 ( 2.03 — 2.71) | 10.88 (7.61 — 15.10)    |
| proportion adult     |            |                     |                         |
| underweight          |            |                     |                         |
| Age-standardised SEV | Prevalence | 0.75 ( 0.75 — 0.76) | 2.12 (2.12 — 2.13)      |
| scalar (log-         |            |                     |                         |
| transformed)         |            |                     |                         |

\*MR-BRT crosswalk adjustments can be interpreted as the factor the alternative case definition is adjusted by to reflect what it would have been had it been measured using the reference case definition. If the log/logit beta coefficient is negative, then the alternative is adjusted up to the reference. If the log/logit beta coefficient is positive, then the alternative down to the reference.

\*\*The adjustment factor column is the exponentiated beta coefficient. For log beta coefficients, this is the relative rate between the two case definitions. For logit beta coefficients, this is the relative odds between the two case definitions.

#### HIV-TB incidence and prevalence

To distinguish HIV-TB from all forms of TB, we first estimated the proportions of HIV-TB cases among all TB cases using data on the number of TB cases recorded as HIV-positive and the number of TB cases with an HIV test result recorded in the WHO TB notifications register. We ran a mixed effects regression using the adult HIV death rate as a covariate to predict location-year-specific HIV-TB proportions, which were then applied to TB incident and prevalent cases from DisMod, to generate HIV-TB incident and prevalent cases by location and year. These cases were then age-sex split based on the age-sex pattern of estimated HIV prevalence by location-year to generate location-year-age-sex-specific HIV-TB incident and prevalent cases.

# Multidrug-resistant TB, extensively drug-resistant TB, and drug-susceptible TB

We ran spatiotemporal Gaussian process regressions to predict the proportions of new TB cases with MDR-TB, proportions of retreated TB cases with MDR-TB, and proportions of retreated cases among all TB cases for all locations and years. We calculated the proportions of new TB cases among all TB cases as *1- estimated proportions of retreated cases*. Next, we computed the weighted average of the proportions of new and retreated cases with MDR-TB at the 1000 draw level. We then used the weighted average proportions of MDR-TB, along with the HIV-TB and TB no-HIV incidence estimates, and the relative risk of MDR-TB associated with HIV infection from the literature<sup>1</sup> to compute the proportions of MDR-TB cases among HIV-negative TB cases (*PnoHIV<sub>c.v.a.s</sub>*) by location, year, age, and sex using the following formula:

$$PnoHIV_{c,y,a,s} = \frac{MDR_{c,y}}{\left(1 + \left(RR\frac{HIVTB_{c,y,a,s}}{TBnoHIV_{c,y,a,s}}\right)\right) TBnoHIV_{c,y,a,s}}$$

where  $MDR_{c,y}$  is the number of all MDR-TB cases among HIV-positive and HIV-negative individuals by location and year, *RR* is the relative risk of MDR-TB associated with HIV infection,  $HIVTB_{c,y,a,s}$  is the number of HIV-TB incident cases by location, year, age, and sex, and  $TBnoHIV_{c,y,a,s}$  is the number of TB no-HIV incident cases by location, year, age, and sex.

We then applied the predicted proportions of MDR-TB cases among HIV-negative TB cases to our predicted HIV-negative TB incident and prevalent cases to generate MDR-TB incident and prevalent cases by location, year, age, and sex. Next, we subtracted MDR-TB cases from all HIV-negative TB cases to generate drug-susceptible TB cases by location, year, age, and sex. To distinguish XDR-TB from MDR-TB, we aggregated the XDR-TB cases and MDR-TB cases (with drug sensitivity testing for second-line drugs) up to the super-region level and calculated the super-region-level proportions of XDR-TB among MDR-TB cases, which were then applied to MDR-TB cases in corresponding countries within the super-regions to produce XDR-TB cases by location, year, age, and sex. We linearly extrapolated XDR-TB prevalence and incidence back assuming the rates were zero in 1992, one year before 1993 when XDR-TB was first recorded in USA surveillance data.<sup>14</sup> Finally, we subtracted XDR-TB cases from MDR-TB cases to generate MDR-TB (without XDR) cases by location, year, age, and sex.

# HIV/AIDS - Multidrug-resistant TB, HIV/AIDS - extensively drug-resistant TB, and HIV/AIDS - drug-susceptible TB

To split HIV-TB into HIV-MDR-TB and HIV-drug-susceptible-TB, we first calculated the proportions of HIV-MDR-TB among all HIV-TB cases ( $PHIV_{c,y,a,s}$ ) for each location, year, age, and sex using the following formula:

# $PHIV_{c,y,a,s} = PnoHIV_{c,y,a,s}RR$

where *PnoHIV<sub>c,y,a,s</sub>* is the proportions of MDR-TB among all HIV-negative TB cases for each location, year, age, and sex and *RR* is the relative risk of MDR-TB associated with HIV infection. We then applied the predicted proportions of MDR-TB cases among HIV-TB cases to our estimated HIV-TB incident and prevalent cases to generate HIV-MDR-TB incident and prevalent cases by location, year, age, and sex. Next, we subtracted HIV-MDR-TB cases from all HIV-TB cases to generate HIV-drug-susceptible-TB cases by location, year, age, and sex. To separate out HIV-XDR-TB from HIV-MDR-TB, we applied the super-region level proportions of XDR-TB among MDR-TB cases, to HIV-MDR-TB cases in corresponding countries within the super-regions to produce HIV-XDR-TB cases by location, year, age, and sex. We linearly extrapolated HIV-XDR-TB prevalence and incidence back assuming the rates were zero in 1992, one year before 1993 when XDR-TB was first recorded in USA surveillance data.<sup>14</sup> Finally, we subtracted HIV-XDR-TB cases to generate HIV-MDR-TB (without extensive drug resistance) cases by location, year, age, and sex.

# New MDR-TB and XDR-TB cases among retreated cases by HIV status

Because we split TB incidence (new and relapse cases combined) by drug-resistance type, the above estimation did not capture new MDR-TB and XDR-TB cases arising from retreated TB cases other than relapse cases. We therefore separately estimated new MDR-TB and XDR-TB cases arising from retreated TB cases and added them to the incident cases estimated above. To do so, we first ran a spatiotemporal Gaussian process regression using notification data and HAQ index as a covariate to predict the proportion of retreated cases (excluding relapse cases) among all TB patients for all locations and years. Next, we computed retreated cases as (retreated proportion\*estimated incident cases)/(1-retreated proportion). We then computed the total number of TB cases by summing estimated incident cases and retreated cases. Similar to our estimation for MDR-TB and XDR-TB among TB incident cases by HIV status, we estimated MDR-TB and XDR-TB cases among all TB cases (incident cases and retreated cases combined) by HIV status. Finally, the number of retreated cases with MDR-TB was computed by subtracting MDR-TB among TB incident cases from MDR-TB among all TB cases (incident cases and retreated cases combined), separately for HIV-positive and HIV-negative individuals. Similarly, the number of retreated cases with XDR-TB was computed by subtracting XDR-TB among TB incident cases from XDR-TB among all TB cases, separately for HIV-positive and HIV-negative individuals. All computations were done at the 1000-draw level.

# **Disability weights**

The lay descriptions and disability weights for severity levels derived from the GBD disability weights study are shown below.

| Health state name | Lay description                                       | Disability Weights  |
|-------------------|---|---------------------|
|                   |   | (95% CI)            |
| Tuberculosis, not | has a persistent cough and fever, is short of breath, | 0.333 (0.224–0.454) |
| HIV infected      | feels weak, and has lost a lot of weight              |                     |
| Tuberculosis, HIV | has a persistent cough and fever, shortness of        | 0.408 (0.274–0.549) |
| infected          | breath, night sweats, weakness and fatigue and        |                     |
|                   | severe weight loss                                    |                     |

For drug-susceptible TB, MDR-TB without extensive drug resistance, and XDR-TB, we used the same disability weight [0.333 (0.224–0.454)] as in non-HIV-infected TB. For HIV-drug-susceptible-TB, HIV-MDR-TB without extensive drug resistance, and HIV-XDR-TB, we used the same disability weight [0.408 (0.274–0.549))] as in HIV-infected TB.

#### Source Counts

| Data                                    | Measure       | Total sources | Countries with data |
|---|---------------|---------------|---------------------|
| Tuberculosis                            | All measures  | 4048          | 194                 |
|   | Prevalence    | 147           | 167                 |
|   | Incidence     | 627           | 78                  |
|   | Relative risk | 36            | 26                  |
|   | Proportion    | 3579          | 193                 |
| Latent tuberculosis infection           | All measures  | 127           | 56                  |
|   | Prevalence    | 91            | 43                  |
|   | Relative risk | 36            | 26                  |
| Proportion of HIV-TB among all TB cases | All measures  |               |                     |
|   | Proportion    |               |                     |
| MDR-TB and MDR-HIV-TB proportions       | All measures  | 4413          | 192                 |
|   | Proportion    | 4413          | 192                 |
| XDR-TB and XDR-HIV-TB proportions       | All measures  | 85            | 84                  |
|   | Proportion    | 85            | 84                  |

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