Estimating TB incidence and mortality in the context of the COVID-19 pandemic

Background document 1

WHO Global Task Force on TB Impact Measurement

Meeting of subgroup to review WHO methods for estimating TB disease burden

11–12 May 2022

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Questions for group work

1. What are your overall comments on the methods that have been developed to estimate TB incidence and mortality in 2020 and 2021 and to produce projections up to 2025?

2. Are there any revisions to these methods that are both necessary and feasible to implement in June-July 2022, in advance of using them to produce estimates for publication in the Global TB report 2022?

For example, related to:
- The selection of countries to be modelled
- Assumptions about notification trends beyond the latest available data points
- Assumptions about reductions in TB transmission during lockdowns and other COVID-related restrictions

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3. Do you have any suggestions for how methods being used to estimate TB incidence and mortality in the context of the COVID-19 pandemic could be improved in the coming year?

For example, related to:
- Assumptions about reductions in TB transmission during lockdowns and other COVID-related restrictions
- How to account for COVID-related impacts on broader TB determinants (e.g. income, poverty, undernutrition)
- The statistical approach for countries that are not directly modelled
- The appropriateness of dropping a drug-resistant TB structure from the models

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4. Do you have any other comments or suggestions related to the production or publication of TB incidence and mortality estimates?
Introduction

One of WHO’s core functions is monitoring the health situation and health trends. Each year, WHO publishes estimates of TB disease burden (incidence and mortality) at global, regional and country level, covering the period from 2000 until the latest complete calendar year, in the annual WHO Global TB Report. Using these estimates, an assessment of progress towards the WHO End TB Strategy milestones and targets (Table 1) is also included in the report.

Table 1. WHO End TB Strategy milestones and targets for reductions in TB incidence and mortality, 2020–2035

<table>
<thead>
<tr>
<th>INDICATORS</th>
<th>MILESTONES</th>
<th>TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>Percentage reduction in the TB incidence rate (compared with 2015 baseline)</td>
<td>20%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Since 2006, estimates of TB disease burden have been produced using standard methods that are periodically reviewed by the WHO Global Task Force on TB Impact Measurement (hereafter, the Task Force). Major reviews were undertaken in 2008-2009 and in 2015,1 with lighter reviews in 20162 and 2018.3

In the context of the COVID-19 pandemic, the production of estimates of TB incidence and mortality in 2020, for publication in the 2021 edition of the Global TB Report, required the use of new methods for many countries. These were developed in 2021 through a collaboration between WHO and Imperial College (London, UK). Dynamic models were used for 16 priority countries and a statistical model was developed to allow extrapolation of results from the dynamic models to other low and middle-income countries. The dynamic models were also used to publish projections of TB incidence and mortality for the period 2021–2025, for the 16 priority countries. This was the first time that the Global TB Report included such projections, rather than being restricted to historical time series of estimates that ended with the most recent complete calendar year.

The new methods used in 2021 were presented and discussed at the June 2021 meeting of WHO’s Strategic and Advisory Group for TB (STAG-TB); the work was described as “impressive”4 Separately from the STAG-TB meeting, there was also some peer-review by Task Force members with expertise in TB modelling.

In advance of the production of the 2022 edition of the WHO Global TB Report, a review of the new methods by a Task Force subgroup with expertise in methods used to produce TB disease burden estimates is required. This includes review of new work to extend and refine the methods developed in 2021, which was initiated in February 2022.

This background document provides the basis for the required review. It has 3 major sections:

1. **Methods used to estimate TB incidence and TB mortality in the period 2000–2019.** This provides a short description of the methods used for the period prior to the COVID-19 pandemic.

2. **Methods used to estimate TB incidence and TB mortality in 2020 and to produce projections for selected countries for 2021–2025.** An overview of the methods used to produce the estimates published in the 2021 edition of the WHO Global TB Report is provided.

3. **Further development of methods to produce estimates of TB incidence and TB mortality in 2020-2021 and projections for 2022-2025.** The new work initiated in 2022 to extend and refine the methods developed in 2021 is described and explained. The extended and updated methods are intended for production of estimates to be published in the 2022 edition of the WHO Global TB Report.

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1 https://www.who.int/groups/global-task-force-on-tb-impact-measurement/meetings/2015-03
2 https://www.who.int/groups/global-task-force-on-tb-impact-measurement/meetings/2016-04
3 https://www.who.int/groups/global-task-force-on-tb-impact-measurement/meetings/2018-05
4 https://www.who.int/publications/i/item/9789240040250
A detailed description of the methods used for the 2021 WHO Global TB Report is provided in an online technical appendix that was published in association with the report (see accompanying PDF).

Four questions that will be discussed during the Task Force meeting are listed on the inner cover page.

1 Methods used to estimate TB incidence and TB mortality in the period 2000-2019

1.1 TB incidence

The main methods used by WHO to estimate TB incidence at country level in the period 2000–2019 are shown in Fig. 1. They are described in more detail in a technical annex to the Global TB Report 2021. The methods adhere to global guidelines (GATHER) used by WHO for accurate and transparent reporting of health estimates.

Fig. 1. Main methods used to estimate TB incidence up to 2019

One of four methods was used:

1. Results from TB prevalence surveys combined with estimates of the duration of disease. This method was used for 29 countries that collectively accounted for about two-thirds of the global number of incident TB cases in 2019 (green);

2. Notifications adjusted by a standard factor to account for underreporting, overdiagnosis and underdiagnosis. This method was used for 139 countries (including most high-income countries and selected middle-income countries) that collectively accounted for about 6% of the global number of incident TB cases in 2019 (red);

3. Results from national inventory studies that measured the level of underreporting of detected TB cases. This method was used for eight countries that collectively accounted for about 17% of the global number of incident TB cases in 2019 (blue); and

4. Case notification data combined with expert opinion about case-detection gaps. This method was used for 39 countries that collectively accounted for 11% of the global number of incident TB cases in 2019 (pink).

6 http://gather-statement.org/
1.2 TB mortality

The best sources of data about deaths from TB (excluding TB deaths among HIV-positive people) are national vital registration (VR) systems in which causes of death are coded according to ICD-10 (although the older ICD-9 and ICD-8 classification are still in use in several countries), using ICD-10: A15-A19 and B90 codes, equivalent to ICD-9: 010-018, and 137. When people with AIDS die from TB, HIV is registered as the underlying cause of death and TB is recorded as a contributory cause. Since one third of countries with VR systems report to WHO only the underlying causes of death and not contributory causes, VR data usually cannot be used to estimate the number of TB deaths in HIV-positive people (a case fatality ratio (CFR) approach is used instead).

Up to 2019, two methods were used to estimate TB mortality among HIV-negative people (Fig. 2). These were:

- Direct measurements of mortality from VR systems or mortality surveys (derived from cause of death data reported to WHO or derived from estimates published by the Institute of Health Metrics and Evaluation, adjusted for differences in envelopes between WHO and IHME). These were used for 123 countries and territories that collectively accounted for 59% of TB deaths in 2019;
- Indirect estimates derived from multiplying estimates of TB incidence by estimates of the CFR obtained from literature reviews. This was used for the other 92 countries and territories.

Fig. 2. Main methods used to estimate TB mortality up to 2019

2 Methods used to estimate TB incidence and TB mortality in 2020 and to produce projections for selected countries for 2021-2025
(as published in the WHO Global TB Report 2021)

2.1 Background

In March 2020, the first warning signs of disruptions to TB services due to the COVID-19 pandemic became visible. These included a dramatic drop in weekly TB case notifications in India, where a real-time online TB case notification system is in place.

In May 2020, WHO published estimates of the impact of the COVID-19 pandemic on excess TB deaths globally in 2020; this was followed by other published modelling results, showing equally concerning global predictions about the impact of the pandemic on TB incidence and mortality. The key findings and messages from this modelling work were highlighted in the Global TB Report 2020; however, the main focus of the report, in terms of burden estimates, was the period 2000–2019. The report also featured provisional TB notification data for 14 high TB burden countries in the period January–June 2020, which illustrated the potentially major impact of disruptions associated with the COVID-19 pandemic on TB detection in some countries.

In February 2021, WHO initiated the regular reporting, visualization and publication of provisional national TB notification data on a monthly or quarterly basis (depending on the system in place at country level), using the existing online WHO global TB data collection system. This regular reporting is intended to provide timely information about disruptions to TB detection, to inform action. A further reason for collecting the data was to enable earlier-than-usual initiation of work required to produce estimates of TB incidence and TB mortality, accounting for COVID-related disruptions to detection and treatment. By mid-March 2021, 84 countries with >80% of estimated global TB incidence in 2019 and almost 90% of global TB notifications in 2019 had reported monthly or quarterly data for the whole of 2020.

In February and March 2021, WHO established a collaboration with Imperial College (London, UK), to start the work required to produce estimates of TB disease burden in 2020 and projections for 2021-2025. This collaboration built on modelling work already undertaken for countries in the South-East Asia Region, which has allowed national TB programme managers to explore the impact of different scenarios for COVID-related disruptions on TB disease burden.

2.2 Overview of methods

The main methods used to produce estimates of TB incidence and TB mortality in 2020 are shown in Fig. 3 and Fig. 4.

For TB incidence, country-specific models were used for 16 priority countries that accounted for most of the global drop in TB notifications in 2020 (compared with 2019); a statistical model based on extrapolation of model results was used for most other low and middle-income countries; extrapolation of the pre-2020 trend was used for a few low and middle-income countries in the African Region; and for high-income countries, notification data with a standard adjustment were used.

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10 http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf
11 https://www.who.int/teams/global-tuberculosis-programme/data
12 https://worldhealthorg.shinyapps.io/tb_pronto/
13 See also STAG-TB 2021, background document #1.
14 https://beta.avstaging.org/tbcovidapp/
For TB mortality, country-specific models were used for 14 of the 16 priority countries that accounted for most of the global drop in TB notifications in 2020 (compared with 2019); a statistical model based on extrapolation of model results was used for most other low and middle-income countries; extrapolation of the pre-2020 trend was used for a few low and middle-income countries; and VR data were used for all remaining countries, including 2 of the modelled countries (China and Russian Federation).

Fig. 3. Main methods used to estimate TB incidence in 2020

Fig. 4. Main methods used to estimate TB mortality in 2020
2.3 Country-specific modelling for 16 priority countries

Country-specific modelling focused on 16 priority countries (Fig. 5). These countries collectively accounted for 93% of the drop in global TB case notifications between 2019 and 2020 (from 7.1 million to 5.8 million).

**Fig. 5. The 16 countries with the largest contributions to the global drop in TB notifications in 2020, compared with 2019**

A set of dynamic TB models, fitted to country data and previously-published WHO estimates of TB burden, was developed to generate country-specific estimates of TB incidence and mortality in 2020 and projections for 2021–2025. The main data informing the models were monthly or quarterly notifications of TB cases between January 2020 and June 2021. The basic model framework is illustrated in Fig. 6. The model structure and source data were described in detail in the technical appendix to the Global TB Report 202115 and a summary was provided in the web pages of the report (see the sections on TB incidence and TB mortality).16

**Fig. 6. A Schematic illustration of the basic model structure**

Rates shown in the diagram are as follows: \( \lambda \), time-dependent force of infection; \( s \), per-capita transition rate from latent, fast to latent, slow; \( b \), per-capita hazard of breakdown to active disease in the first 2 years after infection; \( r \), per-capita hazard of reactivation thereafter; \( \gamma \), per-capita rate of self-cure; \( \mu_{TB} \), per-capita hazard of TB mortality; \( \rho \), per-capita rate of relapse; \( d \), per-capita rate of diagnosis and treatment initiation; \( k(t) \), time-dependent reduction in diagnosis and treatment initiation due to disruptions.

Countries were divided into three different categories, each with a dedicated model structure:

- countries where the private sector plays a strong role in the management of TB;
- countries with a high rate of HIV/TB coinfection; and

countries with a large burden of drug resistance.

A key part of the model is the per-capita rate of treatment initiation, $d$, which represents the rate at which people with untreated, prevalent TB are diagnosed and initiated on treatment.

Disruptions were modelled through a time-dependent factor $k(t)$, multiplying $d$. In the pre-pandemic period we fixed $k(t) = 1$, and calibrated the value of $d$, along with other model parameters, to match both a) WHO estimates for TB incidence and mortality and b) national notification data reported to WHO. This calibration was done using Bayesian methods, which allow uncertainty in WHO estimates to be propagated to uncertainty in model projections.

The modelling of disruptions associated with the COVID-19 pandemic focused on delays to diagnosis and treatment initiation. Disruptions to treatment continuity amongst those already on TB treatment were ignored, partly due to lack of systematic data, but also because a previous modelling analysis suggested that these types of disruptions are likely to have a weaker effect on incidence compared with disruptions to diagnosis and treatment initiation.

For data on the intensity and duration of disruptions, the monthly national notification data (or quarterly if monthly data were not available) reported to WHO were used. It was assumed that any reduction in notifications, compared with an extrapolation of pre-2020 trends, was due to delays to diagnosis and treatment initiation, rather than shortfalls in reporting. These delays may arise from patient-related factors (e.g. symptomatic patients being less willing or able to seek care during periods of anti-COVID restrictions) or from health system related factors (e.g. TB programmes having less diagnostic or staffing capacity than usual times). The model structure is agnostic to either of these factors, as the whole patient care-seeking journey is made implicit in the rate $r_{tx}$: this was a deliberate choice for this modelling work; usually, additional compartments to reflect patient delays separately from the diagnostic pathway would be included.

Assuming that treatment initiations are a reasonable proxy for notifications, the number of notifications in a given month $n$ is:

$$\text{Notifications in month } n = \int_{n}^{n+1} k(t) dI \, dt,$$

where $I$ is the number of individuals having active, infectious disease in Fig. 6. Using the full transmission model, the monthly value of $k(t)$ was adjusted in such a way as to yield treatment initiations consistent with the monthly notification data. The timeseries for $k$ determined in this way then formed the basis for model projections for incidence.

As much as lockdowns and social restrictions can control transmission of COVID-19, they may also have similar effects on TB transmission. It is unclear how strong these transmission reductions might be, in different settings. As a simple approach, it was assumed that in any setting experiencing a country-wide lockdown, there was a 50% reduction in TB transmission during that period of lockdown (with transmission returning to pre-lockdown levels as soon as restrictions are lifted). For any country implementing subnational lockdowns, this reduction was scaled downwards in proportion to the share of the country’s population undergoing those lockdowns.

Extensive sensitivity analyses were used to identify the most influential parameters and assumptions.

To produce projections for 2021–2025, the percentage increase in TB incidence and mortality were first estimated for 2020, for each country. A ‘best-case projection’ was then modelled, in which it was assumed that TB services return to normal in the month immediately after the last available data point; this is followed by estimation of the percentage increase in cumulative TB incidence and mortality between 2020 and 2025. Although artificial, this scenario serves as a lower bound for the excess cases that may occur over the next five years, in the absence of any remedial measures such as accelerated case-finding.

The projections for 2021–2025 that were published in the Global TB Report 2021 are shown in Fig. 7 and Fig. 8.

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Fig. 7. Projections of TB incidence 2021–2025 in 16 priority countries, as published in the WHO Global TB Report 2021. The black line shows a no-COVID counterfactual projection.

Fig. 8. Projections of TB mortality 2021–2025 in 16 priority countries, as published in the WHO Global TB Report 2021. The black line shows a no-COVID counterfactual projection.
The models have several limitations. These include:

- Uncertainty about key parameters. This includes the extent to which TB transmission intensity has been affected by lockdowns and other population-level restrictions put in place during the COVID-19 pandemic. There is little directly measured evidence about the different mechanisms that have been proposed (e.g. the potential for reductions in community TB transmission to be at least partially offset by increases in household transmission). The modelling uses an assumption of a 25–75% reduction in TB transmission during periods of lockdown. Country-specific data about the durations for lockdowns have been compiled, with transmission reductions assumed during these periods only. Where lockdowns occurred in some parts of the country and not others, the effect on TB transmission was scaled in proportion to the size of the population affected.

- COVID-related impacts on broader TB determinants are not yet accounted for. For example, falling income levels, worsening levels of undernutrition and increasing levels of absolute poverty due to the economic impact of the pandemic are all likely to increase the probability of developing TB disease among people already infected with *M. tuberculosis*. Declines in income may also affect health care seeking behaviour when people become unwell, causing delays in TB diagnosis and treatment. There is a strong association between the TB incidence rate and both average income and the prevalence of undernutrition.

- No age structure in the population.

- No separate classification of cases into pulmonary and extrapulmonary TB. Instead, an average infectiousness for both forms is assumed.

- Drug-resistant TB (DR-TB) is not explicitly considered. This is because, with the exception of the Russian Federation, the available notification data are for all cases, with no disaggregation. Estimates of the burden of DR-TB will be estimated based on previously published methods.\(^{18}\)

### 2.4 Non-modelled countries

For most low- and middle-income countries for which it was not possible to develop country-specific models within the available timeframe for inclusion in the Global TB Report 2021, TB incidence and mortality were estimated using a predictive statistical model based on the output from the modelled countries (e.g. predicting relative changes in incidence and mortality from changes in treatment coverage).

Incidence and mortality rate ratios for 2020 (estimated under COVID-19 disruptions over a counterfactual estimate based on pre-2020 trends) in the 16 modelled countries were predicted using linear regression models, with three predictor variables (the 2019 case detection ratio i.e. notifications / incidence; the relative drop in case detection between 2019 and 2020; and the 2019 mortality / incidence ratio) along with interaction terms. Models were selected based on the AIC criterion. The incidence rate ratio in 2020 was not found to be significantly associated with any of the tested predictor variables and a pooled ratio of 1.02 (SD 0.026) was used to predict incidence in the set of 111 countries with a 2020 shortfall in case detection compared with 2019. In contrast, the mortality model fit the data satisfactorily. Predicted ratios were constrained within the interval [1, 1.5].

For remaining countries, as explained in section 2.2 and shown in Fig. 3 and Fig. 4, incidence estimates were based on either notification data with a standard adjustment (all high-income countries) or on extrapolation of the pre-2020 trend (a few countries in the African Region); and mortality estimates were based on either VR data or extrapolation of the pre-2020 trend.

Further technical details are available in the technical appendix of Global TB Report 2021.\(^{19}\)

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\(^{19}\) https://www.who.int/publications/digital/global-tuberculosis-report-2021/technical-annexes

As of the end of April 2021, 98 countries had reported provisional monthly (n=68) or quarterly (n=30) case notification data for the whole of 2021, slightly more than the number that previously reported complete provisional data for 2020 by the same time point (n=88). Together, these 98 countries represent 90% of estimated incidence in 2019.

In total, provisional notifications for 2021 in the 98 countries amount to 5.8 million new and relapse cases (compared with 5.1 million for the same 98 countries in 2020). Assuming that countries that have not yet reported complete monthly or quarterly notifications for 2021 report numbers to WHO that are similar to those for 2020 (data are due to be reported to WHO by the end of May), the total global notifications for 2021 will be approximately 6.4 million (up from 5.8 million cases in 2020 but still 0.75 million or 11% lower than the 2019 baseline of 7.1 million).

These provisional data indicate insufficient progress in recovering levels of case detection in 2021 compared with 2020. The continued setbacks in case detection performance means that the number of untreated prevalent cases in the general population continues to grow for a second year, and the outlook for TB disease burden in the coming years is even worse than projections published in the Global TB Report 2021 (given, as explained in section 2.2, the modelling projections published in the report assumed a recovery of case detection from June 2021 onwards).

Provisional monthly TB notification data for 2020 and 2021 are shown for the 23 high TB burden countries that previously reported complete data for 2020 in Fig. 9 and Fig. 10.

Fig. 9 Trends in reported monthly TB notifications in 2020 and 2021, 16 high TB burden countries that reported monthly case notification data for the whole of 2020. The dashed black line indicates the average level of notifications in 2019.
Fig. 10. Trends in reported quarterly TB notifications in 2020 and 2021, 9 high TB burden countries that reported quarterly case notification data for the whole of 2020. The dashed blue line indicates the average level of notifications in 2019.

The Global TB Report 2022 will need to include estimates of TB disease burden at global, regional and country levels for the period 2000–2021 as well as updated projections up to 2025 for priority countries. For this purpose, a second phase of modelling work is ongoing. This is building and expanding on the methods described in section 2, as follows:

1. Model-based estimates of TB incidence and TB mortality in 2020 and 2021 and projections up to 2025 that account for the impact of disruptions caused by the COVID-19 pandemic will be produced for the 16 countries covered in the Global TB Report 2021 (see subsection 2.3). This will use the methods already developed in 2021.
2. Model-based estimates of TB incidence and TB mortality in 2020 and 2021 and projections up to 2025 that account for the impact of disruptions caused by the COVID-19 pandemic will be produced for 14 additional countries.
3. Refinement of statistical methods used to extrapolate results from modelled to non-modelled countries.

The 14 additional countries for which models will be used are those that ranked 17-30 in terms of their contribution to the overall drop in global TB notifications in 2020 compared with 2019. They are (in order of contribution): Ethiopia; Mexico; Papua New Guinea; Thailand; Nepal; Malaysia; Romania; Zimbabwe; Kazakhstan; Azerbaijan; Cambodia; Colombia; Lesotho; and Kyrgyzstan.

The statistical methods used to produce the 2020 estimates of TB incidence and mortality for most low and middle-income countries were relatively simple. With the set of modelled countries expanded to 30, there will be more data points to inform the statistical analysis. Global extrapolations using this broader country set will be used to refine the statistical analysis. Mechanistic, model-based approaches for extending country-specific modelled projections to global projections, for example by constructing models for geographic regions rather than for individual countries, are also being explored. More details will be provided during a presentation at the Task Force meeting.