WHO Global Task Force on TB Impact Measurement

Report of a subgroup meeting on methods used by WHO to estimate TB disease burden
11–12 May 2022
Geneva, Switzerland
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1. MEETING PURPOSE, OBJECTIVES, EXPECTED OUTCOMES AND OVERALL APPROACH</td>
<td>2</td>
</tr>
<tr>
<td>2. METHODS FOR ESTIMATING TB INCIDENCE AND MORTALITY IN THE CONTEXT OF THE COVID-19 PANDEMIC</td>
<td>4</td>
</tr>
<tr>
<td>3. METHODS FOR ESTIMATING THE INCIDENCE OF RIFAMPICIN-RESISTANT TB</td>
<td>8</td>
</tr>
<tr>
<td>4. NEXT STEPS</td>
<td>10</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>11</td>
</tr>
<tr>
<td>ANNEX 1: Meeting agenda</td>
<td>13</td>
</tr>
<tr>
<td>ANNEX 2: List of participants, and those who were invited but could not attend</td>
<td>15</td>
</tr>
<tr>
<td>ANNEX 3: Methods for estimating TB incidence and mortality – template for group work</td>
<td>18</td>
</tr>
<tr>
<td>ANNEX 4: Methods for estimating the incidence of RR-TB – template for group work</td>
<td>20</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The report was written by Anna Dean and Katherine Floyd. It was finalized following review by all meeting participants. The funding required by WHO to hold the meeting was provided by the United States Agency for International Development (USAID) and the government of Japan.
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. Estimates of the incidence of drug-resistant TB specifically were added to the report in 2016, with a focus on rifampicin-resistant TB (RR-TB).

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).

The Task Force was established in 2006, convened by the TB monitoring, evaluation and strategic information (TME) unit of WHO’s Global TB Programme (GTB). Its initial aim was to ensure a robust, rigorous and consensus-based assessment of whether 2015 TB targets for reductions in TB disease burden (in terms of incidence, prevalence and mortality), set in the context of the United Nations (UN) Millennium Development Goals (MDGs, 2000–2015) and WHO Stop TB Strategy (2006–2015), were achieved at global, regional and country levels. Its current mission is to ensure robust, rigorous and consensus-based assessment of progress towards milestones and targets for reductions in TB disease burden set in the Sustainable Development Goals (SDGs, 2016–2030) and WHO End TB Strategy (2016–2035), at global, regional and country levels; and to guide, promote and support analysis and use of TB surveillance and survey data for policy, planning and programmatic action. SDG 3 includes a target to “End the TB epidemic” by 2030, with TB incidence (per 100 000 population) defined as the indicator for assessment of progress. The End TB Strategy milestones and targets are shown in Table 1.

Table 1. The WHO End TB Strategy milestones and targets

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Milestones</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2020</td>
<td>2025</td>
</tr>
<tr>
<td>Reduction in annual number of TB deaths (compared with baseline of 2015)</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>Reduction in TB incidence rate (compared with baseline of 2015)</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>Percentage of TB patients and their households facing catastrophic costs due to TB disease</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

To fulfil this mission, the Task Force has defined major strategic areas of work (1). These are:

- Strengthening surveillance. This includes strengthening of national disease notification systems, for direct measurement of TB incidence; and strengthening of national vital registration (VR) systems, for direct measurement of the number of deaths caused by TB.
- Priority studies to periodically measure TB disease burden. These include national TB prevalence surveys, national surveys of drug resistance among TB patients, national surveys of costs faced by TB patients and their households, and mortality surveys.
- Periodic review of methods used by WHO to estimate the burden of TB disease.
- Analysis and use of TB surveillance and survey data.

The first two strategic areas of work focus on direct measurement of TB disease burden (epidemiological and, in the case of cost surveys, economic). The underlying principle for the Task Force’s work since 2006 has been that estimates of the level of and trends in disease burden should be based on direct measurements from routine national surveillance systems and surveys as much as possible. The ultimate goal is that in all countries, TB incidence and mortality can be reliably tracked using surveillance data from national disease notification and VR systems.

The first comprehensive reviews of methods used by WHO to produce estimates of TB disease burden under the umbrella of the Task Force were completed in 2006 (at the first Task Force meeting) and in
2008–2009. The methods used to produce WHO’s assessment of whether the 2015 targets were achieved (published in the 2015 WHO Global TB Report) followed a thorough review at a Task Force meeting held in March 2015. Subsequent reviews of methods were part of Task Force meetings held in 2016 and 2018.

In the context of new methods for estimation of TB incidence and mortality required in the context of the COVID-19 pandemic as well as recent challenges and developments related to estimates of the incidence of RR-TB, it was necessary to convene a meeting of a Task Force subgroup to conduct an up-to-date review of methods used by WHO to produce estimates of TB disease burden.

This report of the meeting has four major sections:
1. Meeting purpose, objectives, expected outcomes and overall approach;
3. Methods for estimating the incidence of RR-TB;
4. Next steps.

There are four annexes which provide the meeting agenda, the list of participants and the two templates used for group work.

1. MEETING PURPOSE, OBJECTIVES, EXPECTED OUTCOMES AND OVERALL APPROACH

1.1 Purpose

The purpose of the meeting was an up-to-date review of methods being used by WHO to produce estimates of TB disease burden, with a focus on two major topics.


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, United Kingdom of Great Britain and Northern Ireland). In February 2022, work to expand and refine these methods was initiated.

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), at which the work was commended as “impressive”. There was also some peer-review of methods by experts in TB modelling in July 2021. However, the methods required a fuller review and discussion at a Task Force meeting focused on methods used by WHO to produce estimates of TB disease burden.

2. Methods for producing estimates of the incidence of drug-resistant TB, with a focus on estimates of the incidence of rifampicin resistance

From 2016 to 2020, estimates of the incidence of RR-TB at global, regional and country levels were published in the annual WHO Global TB Report, according to the methods reviewed and agreed upon at the Task Force meetings held in 2016 and 2018 (2016 (2) – p.38; 2017 (3) – p.45; 2018 (4) – p.50; 2019 (5) – p.58; 2020 (6) – p.56). Estimates were always for the most recent complete calendar year only (e.g. 2015 in the case of the 2016 report; 2019 in the case of the 2020 report), with no attempt to produce and publish time-series at global, regional or country levels.

In general, published estimates of the incidence of RR-TB have always been well-accepted by WHO Member States and partner agencies. However, there were also challenges, among which a leading one was difficulties in explaining changes to the annual number of estimated incident cases of RR-TB in consecutive global TB reports (especially the global aggregate).

Following discussions in GTB/TME in late 2021, a potential solution to this problem was identified:
the development and use of new methods to enable publication of time-series of RR-TB incidence estimates, for the period 2015–2021. In February 2022, WHO initiated work on the development of such methods through a collaboration with the University of Sheffield (United Kingdom). Prior to their potential use for production of estimates to be published in the WHO Global TB Report 2022, Task Force review was required. Since the new methods for producing time series still require use of the existing method to produce estimates for a single calendar year, review of the new methods also had the benefit of including an up-to-date review of the existing method.

1.2 Objectives

There were two meeting objectives:


1.3 Expected outcomes

There were three expected outcomes from the meeting:

2. Suggestions for improvements to proposed methods for producing estimates of TB incidence and mortality in 2020–2021 and projections for 2022–2025, categorized into a) those which could be implemented in the near-term (by end July 2022) and b) those to be explored in the coming year.
3. Suggestions for how to improve proposed methods for producing estimates of the incidence of RR-TB, categorized into a) those which could be implemented in the near-term (by end July 2022) and b) those which could be explored in the coming year.

1.4 Overall approach

Two background documents were prepared for the meeting: one for each of the two major topics being covered.

Background document 1, on methods to estimate TB incidence and mortality in the context of the COVID-19 pandemic, was circulated one week in advance of the meeting to all participants as well as those who were invited but unable to attend. There was no request to send in comments in advance of the meeting, but following feedback from a few people, minor updates were made to the document and a second version was shared the day before the meeting (see Background document 1) (7).

Background document 2, on new methods for producing RR-TB incidence estimates for the period 2015–2021, was circulated three weeks in advance of the meeting to all participants as well as those who were invited but unable to attend. An initial round of feedback was requested, based on three questions that were posed in the document. The WHO secretariat in collaboration with Pete Dodd (University of Sheffield) produced a revised version that addressed all feedback received (almost all meeting participants, as well as three people invited but unable to attend in person, provided feedback); the list of questions for discussion during the meeting was also revised. This updated draft (see Background document 2) (8) was shared in advance of the meeting.

In the opening session of the meeting (see the Agenda in Annex 1), Katherine Floyd provided an overview of the work of the Task Force as a whole as well as an explanation of the meeting objectives and expected outcomes (see presentation) (9). The rest of the first day was used to present and discuss methods for producing estimates of TB incidence and mortality in the context of the COVID-19 pandemic. The second day of the meeting was used to present and discuss methods for production of estimates of RR-TB incidence to be published in the WHO Global TB Report 2022. For both topics,
there was an interactive presentation, followed by group work on the questions posed in the respective background document, followed by feedback in plenary. The secretariat then prepared a draft synthesis of feedback (in the form of a short set of PPT slides) for review by all, which was then finalized.

The list of participants is provided in Annex 2. This includes those who were unable to attend but who nonetheless provided comments on the background documents. Overall, 23 people reviewed the background documents in advance of the meeting, of whom 19 attended in person. Participants included experts in statistics, modelling and epidemiology from academia; representatives from government institutions in high TB burden countries; representatives from major technical and funding partner agencies; and WHO staff from GTB, the Regional Office for Europe and the department at headquarters responsible for surveillance of antimicrobial resistance.

2. METHODS FOR ESTIMATING TB INCIDENCE AND MORTALITY IN THE CONTEXT OF THE COVID-19 PANDEMIC

Following introductory remarks by the WHO secretariat (Philippe Glaziou), an interactive presentation (i.e. allowing for questions and answers during the presentation) covering the material included in Background document 1 was given by Nim Arinaminpathy (Imperial College London) (see presentation) (10).

Background document 1 explained the methods that were used to produce estimates of TB incidence and mortality in all countries in 2020 as well as projections for 2021–2025 for the subset of countries (n=16) for which country-specific models were used; and how these methods were being expanded and refined to produce estimates for 2021 and projections for 2022–2025.

The background document was accompanied by a technical appendix. A detailed explanation of the methods used to produce estimates published in the Global TB Report 2021 had previously been published as an online appendix to the report, at the time of report release in October 2021. A summary was also provided on the web pages that accompanied the main report PDF (11, 12).

In essence, the methods used to produce estimates of TB incidence and mortality in 2020 were as follows:

- Dynamic models were used for 16 priority countries. These were the countries that accounted for the largest share – 93% collectively – of the global drop in TB notifications between 2019 and 2020. In the time available for this work in 2021, 16 was the maximum number of countries for which it was feasible to develop a country-specific model.
- A statistical model was used to extrapolate results from the dynamic models to other low and middle-income countries.
- The methods used for high-income countries up to 2019 (i.e. a standard adjustment to notification data for estimation of TB incidence and cause-of-death data from national vital registration (VR) systems for estimation of TB mortality) were retained for use in 2020.

The dynamic models were also used to publish projections of TB incidence and mortality for the period 2021–2025, for the 16 priority countries.

In 2022, the expansion of the methods developed in 2021 consisted of two elements:

- Increasing the number of country-specific models from 16 to 30. The 14 additional countries were selected according to the same criteria as the original 16 i.e. they were the next 14 countries that made the largest contribution to the global reduction in TB case notifications between 2019 and 2020.
- Refinement of the statistical model used to extrapolate results from modelled to non-modelled low and middle-income countries.

The presentation was followed by group work to discuss the four questions posed in the background document.

1 Participants were divided into four groups, each of which also had a facilitator and rapporteur (assigned in advance).
These were:
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?
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?
4. Do you have any other comments or suggestions related to the production or publication of TB incidence and mortality estimates?

For questions 2 and 3, a standard template was provided for documentation of responses (Annex 3).

There was support for the overall approach used by WHO in 2021 to produce estimates of TB incidence and mortality in 2020, in terms of the combination of country-specific dynamic models for countries with the biggest shortfalls in TB notifications in 2020 vs 2019, a statistical model for other low and middle-income countries, and continued use of notification data from national disease surveillance systems and cause-of-death data from national VR systems for high-income countries. There was also support for continued use of this overall approach in 2022 (to produce estimates for 2020 and 2021), in the absence of any better alternatives, as well as expansion of the number of countries covered by country-specific dynamic models and refinements to the statistical model.

Table 2. Methods for producing estimates of TB incidence and mortality in 2020 and 2021: main suggestions* for a) June-July 2022 and b) the next year

<table>
<thead>
<tr>
<th>Next 2 months</th>
<th>Coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suggestion</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>External review of all documentation for country-specific models developed in 2021 (Model parameter values, priors, fits, posteriors, code, UI bounds)</td>
<td>6 people volunteered; review scheduled to start week of 6 June.</td>
</tr>
<tr>
<td>Refine the statistical approach used to extrapolate results from modelled to non-modelled low and middle-income countries, based on the increased number of country-specific models (30 in 2022 vs. 16 in 2021)</td>
<td>This was already planned; it was useful that this was reinforced and supported at the meeting.</td>
</tr>
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* i.e. the suggestion was made all or most groups and there was no disagreement among participants.

At the same time, all groups (and modelling experts in particular) expressed a need for more detailed documentation related to the country-specific dynamic models and an external review of this documentation (Table 2), without which they were not able to thoroughly assess the models and provide fully-informed feedback (for example, about corrections or refinements that might be needed, or limitations that might need further consideration or explanation) and/or endorsement. Such an external review was the main, and top priority suggestion, for the period June–July 2022,2 made by all groups and about which there was full consensus. The model documentation required to enable a

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2 The period in which revisions needed to be made to inform estimates to be published in the Global TB Report 2022.
thorough review was also clearly specified: parameter values, priors, fits, posteriors, code, and bounds for uncertainty intervals (Table 2).

Following a request from the WHO secretariat during the meeting for volunteers to contribute to this review, six reviewers were identified. Detailed model documentation covering all listed elements was prepared in a format suitable for review in the three weeks that followed the meeting; this was then sent to each reviewer by the WHO secretariat on 7 June, with a request for feedback by 21 June. Five reviews were received. Three from Group 1, one from Group 4. See the group work synthesis for the composition of groups and the details related to the suggestions.

The other major suggestion for the period June–July 2022 was to refine the statistical model used to extrapolate results from modelled to non-modelled low and middle-income countries. This had already been planned, and it was helpful that this was supported during the meeting. Specific suggestions included:

- To consider modelling for countries that might help to improve the statistical model – for example, that would improve the regional representativeness of modelled countries (e.g. it was noted that no countries in West Africa had been modelled);
- To consider using a regional approach to the extrapolation of results.

In terms of suggestions for improvements to methods that could be explored over the coming year, the top priority (commented on by all groups) was to try to find ways to better reflect the impact of COVID-related restrictions and associated behaviour changes on TB transmission, in the country-specific models. The models developed in 2021 assume drops in transmission during periods of lockdowns but there are no assumptions about reductions in transmission during other periods, when restrictions and modified behaviour may also have affected transmission.

Specific suggestions included:

- Exploring the use of economic and/or mobility data as a proxy for the extent to which restrictions were in place, both during and outside periods of “lockdown”;
- Exploring new evidence that might help to understand the impact of COVID-related restrictions on TB incidence. Two examples that were mentioned were the India prevalence survey implemented 2019–2021 (with some clusters sampled before COVID, and some afterwards); and a recent (currently unpublished) subnational research study that measured TB prevalence before and during the COVID-19 pandemic in Uganda.

The second major topic that was highlighted and commented on by all groups was how to account for COVID-related impacts on broader TB determinants, such as income, poverty and nutrition, in the country-specific models. It was acknowledged that this is hard to do.

Specific points included:

- The appropriate data may not be available for the relevant time period (e.g. due to reporting lags for some SDG indicators that are associated with TB incidence);
- The value of investing time in improving the models to include these aspects depends on for how much longer WHO uses models to produce estimates of TB incidence and mortality;
- One option to consider is use of a multiplication factor to reflect how the case fatality ratio might have changed due to negative impacts on broader TB determinants;
- Errors in model results that arise from not incorporating impacts on broader TB determinants will increase over time.

Other miscellaneous suggestions (in each case, from one of the four groups only) were:

- In-depth analyses (“deep dives”) for specific countries. The example of India was highlighted, where TB notification as well as TB prevalence survey data during the COVID-19 pandemic are available.

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3 Feedback was used to refine the methods used to produce estimates for the Global TB Report 2022 and associated model documentation. A short document to summarize the key points made by reviewers, and how these were addressed, was prepared. This was then shared with all reviewers.

4 Three from Group 1, one from Group 4.
• More disaggregated analyses of who experienced disruptions (e.g. by age, sex, disease severity). This has implications for the link between incidence and mortality and warrants further investigation.
• Review of assumptions about the relationship between notifications and incidence for Ukraine and neighbouring countries.
• Adding more compartments related to the national history of TB in country-specific models (e.g. for subclinical disease).

Although not related to methods per se, there was a major topic about which comments were made by all groups, as well as by those who were invited but not able to attend the meeting: projections of TB incidence and mortality. These had been included in the Global TB Report for the first time in 2021, given that this was a topic about which questions were frequently being asked and it was considered necessary to indicate the possible trajectory of TB incidence and mortality and when impacts might peak. The rationale for the inclusion of projections in the 2021 edition of the report was understood, but at the same time considerable reservations were expressed about including projections as a “regular” or standard component of the report.

Comments were expressed in a variety of ways.

If projections are retained in the next Global TB Report, the following suggestions were made:
• Continue to assume recovery after the last data point, including to allow direct comparison with previously-published projections;
• Include uncertainty intervals;
• Add scenarios (e.g. different scenarios for recovery of TB detection and treatment, such as the most likely as well as best and worst-case scenarios);
• Projections could be a “featured topic” rather than included as part of the main report findings and messages;
• Review/assess the accuracy of the projections already published;
• Be very cautious/careful about how the results are communicated, including:
  o Make it very clear that projections are based on the assumption of recovery after the last data point;
  o Make it very obvious where the cut-off point is in terms of the availability of data (e.g. in plots, using a change in line colour or a vertical cut-off line);
  o Be very clear that the projections are “scenarios” and not “predictions”.

The overall balance of comments was against the inclusion of projections in the Global TB Report 2022. Major points that were made included:
• There is substantial uncertainty about future trajectories;
• There is potential for reputational damage if the projections are not correct (although this might be addressed by showing scenarios);
• The report should focus on results up to the latest calendar year (the latest status of progress) as opposed to projections.

Finally, there were three bigger-picture and inter-related questions or comments, which relate to both methods for producing estimates of TB disease burden and the work of the Task Force more broadly:
1. Is the use of country-specific modelling in production of TB disease burden estimates by WHO for the short-term only (during periods of COVID-related disruptions) or also for the longer-term?
2. There is a need to start from the data as much as possible (in line with Task Force strategic areas of work 1 and 2).
3. It is crucial to continue investments in strengthening TB surveillance and periodic surveys (e.g. prevalence surveys).

The question will need to be discussed in the next meeting of the Task Force.

The final version of the PPT synthesis of feedback from group work, following its presentation to all meeting participants during Day 2 and its circulation for review, is available here (see presentation) (13).
3. METHODS FOR ESTIMATING THE INCIDENCE OF RIFAMPICIN-RESISTANT TB (RR-TB)

An interactive presentation (i.e. allowing for questions and answers during the presentation) covering the material included in Background document 2 was given by Anna Dean, Philippe Glaziou and Pete Dodd (see presentation) (14). In addition, Pete Dodd presented provisional results for a) estimates of the global and regional proportions of TB cases with RR-TB between 2015 and 2020 and b) estimates of the global absolute number of TB cases with RR-TB between 2015 and 2020.

Background document 2 provided a detailed explanation of the existing methods used to produce estimates of RR-TB incidence for a single calendar year (including data sources, data inclusion criteria, data coverage, formula, process for country review), the main limitations of and concerns about the current methods, and the new methods proposed for production of time-series for 2015–2021. The background document was accompanied by a technical appendix.

In essence, the new methods proposed for production of time series of estimates for 2015–2021 consisted of two elements:

- Estimation of the proportions of new and previously treated TB cases that have RR-TB (as well as other combinations of resistance) at global, regional and country level, for the period 2015–2021. This estimation uses surveillance and survey data from 2000 onwards, since earlier data inform trend analysis.
- Use of the time series of estimates of proportions of new and previously treated TB cases with RR-TB, in combination with the existing method (formula) used to produce estimates of a single calendar year. The formula combines use of the proportions estimated for 2015–2021 alongside other parameters (these include TB incidence overall, the proportion of TB cases that are relapses, the risk that an incident case of TB will fail treatment or be lost to follow-up, and the relative risk of RR-TB in relapse compared with new cases).  

The presentation was followed by group work to discuss the five questions posed in the background document. These were:

   - Yes, as they are
   - Yes, with some improvements
   - No
   
   Please give reasons for your answer

2. If the methods are considered suitable with some improvements, what improvements can be suggested that are:
   - Necessary and feasible to implement in the near term (June-July 2022), in time for their use in producing estimates of RR-TB incidence to be published in the WHO Global TB Report 2022;
   - Worth exploring in the next year.

3. If the necessary and feasible improvements are made, for which of the following levels do you think estimates of trends in RR-TB incidence should be published in the WHO Global TB Report 2022?
   - Global (yes, no)
   - Regional (yes, no)
   - Country (yes, no)
   
   Please give reasons for your answer

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5 The formula is provided in Annex 4 (see pp22–23). The formula is explained in detail in Background document 2.
4. Do you agree with the table that provides a proposed summary of how indicators related to RR-TB can be used (Table 6)?

*Please give priority attention to the row for estimates of RR-TB incidence (text in red). Other comments would be welcome if time permits.*

5. Do you have any other comments or suggestions related to the production or publication of estimates related to drug-resistant TB?

For the most substantive of the five questions (Question 2), a template was provided (Annex 4).

The key outcomes of the discussions were:

- **All groups were strongly in favour of the proposed new methods.**
  - It was unanimously agreed that these overcame a major limitation of the previous approach (production and publication of estimates for a single calendar year only). The new work by Pete Dodd on the development of new methods to enable production of time series of estimates was highly appreciated by all.

- **There was agreement that estimates of RR-TB incidence 2015–2021 can be produced using the new methods to estimate trends in the proportion of new and previously treated TB cases with RR-TB 2015–2021, in combination with the existing formula for estimating RR-TB incidence for a single calendar year.**
  - No changes to the formula were proposed, following a thorough review of each element (as part of question 2; see Annex 4).

- **There were some suggestions for updates that may (or may not) be improvements to how values for the parameters used in the existing formula (i.e. the formula for estimating RR-TB incidence in a given calendar year) are estimated.** However, there were no strong and consistent suggestions across all groups; each specific suggestion was mentioned by a single group only (these related to data inclusion criteria; and the estimation of values for \( f \), \( p \), and \( \rho \)).

  - Consider using the percentage of TB cases that are bacteriologically confirmed as a filter for inclusion/use of surveillance data related to the proportions of new and previously treated cases with RR-TB for a given year. The reason was that if the overall percentage of TB cases with bacteriological confirmation is too low, there could be instability in estimated values of the proportions of new and previously treated cases with RR-TB.
  - Consider estimating the values of \( f \) (the risk that incident cases of TB return for retreatment following failure or loss to follow-up) and \( r \) (the proportion of people with a new episode of TB who were relapse cases) using data for a 3-year period (as opposed to the current 5-year period), and assess the values of \( f \) and \( r \) during the COVID-19 pandemic compared with the previous 4 years. The reason was that the values of these parameters could be affected by the COVID-19 pandemic, but this might not be adequately captured when using 5 years of data.
  - Explore extreme values to assess the influence of using data for both relapse and other retreatment cases to estimate \( p_r \) (the proportion of previously treated cases with RR-TB). The reason was that combined data for these two groups are what is usually available, while ideally data for treatment failures or loss-to-follow-up cases only would be used.
  - Review the current assumption that \( \rho \) (the relative risk of RR-TB in relapse compared with new cases) does not vary with \( p_n \) (the proportion of new cases with RR-TB). It may be appropriate to refine this assumption: for example, such that as \( p_n \) decreases, \( \rho \) gets close to a minimum.

- **RR-TB incidence estimates should be produced using the proposed methods and published in the Global TB Report 2022, for global, regional and country levels.**

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6 For example, for the period June–July 2022, there were two specific suggestions from Group 1, three from Group 3 and two from Group 4. See the group work synthesis for the composition of groups and the details related to the suggestions.

7 The proportion of incident cases that fail treatment or are lost to follow-up, the proportion of previously treated cases that have RR-TB, and the relative risk of RR-TB in relapse compared with new TB cases, respectively.
• There was agreement with the proposed approach to future use of RR-TB incidence estimates.
  o Appropriate uses include providing an indication of the total disease burden associated with RR-TB, supporting advocacy efforts for TB, providing one of the inputs required for the disease burden formula used by the Global Fund to inform resource allocation for TB among countries eligible to apply for grants, and assessment of trends in the disease burden associated with RR-TB.
  o It was acknowledged that estimates of the incidence of RR-TB are relatively imprecise, that limitations in currently available TB diagnostics mean that it is not possible to detect a large proportion of these incident cases of RR-TB, and that many of the incident cases of RR-TB are among people not diagnosed with TB at all, or who are diagnosed but not notified. Country-level planning and associated setting of treatment targets needs to account for these realities.

The final version of the PPT synthesis of feedback from group work, following its circulation to all meeting participants for review, is available here (see presentation) (/5).

4. NEXT STEPS

The main next steps were:

• Preparation of documentation related to the country-specific models used to produce estimates of TB incidence and mortality in a format suitable for external peer-review, followed by its review by external reviewers (i.e. those who volunteered during the meeting plus one additional reviewer who was suggested by a meeting participant) by the end of June 2022. This process was completed according to the agreed schedule.

• Drafting of a meeting report followed by its posting on the Task Force website alongside all other relevant meeting materials (background documents, presentations, syntheses of group work). This process was completed in July 2022.

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8 Detection of RR-TB is only possible among people with bacteriologically confirmed TB; 59% of notified cases of pulmonary were bacteriologically confirmed in 2020.

9 This topic is discussed in further detail in Background document 2 (section 4).
REFERENCES


ANNEX 1: Meeting agenda

DAY 1: Wednesday, 11 May 2022

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<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>09:15 – 10:00</td>
<td>Arrival, registration, coffee</td>
<td></td>
</tr>
<tr>
<td>10:00 – 10:30</td>
<td>Welcome and introduction of participants Declaration of conflict of interest</td>
<td>Jaap Broekmans (Chair) All</td>
</tr>
<tr>
<td>10:30 – 11:00</td>
<td>The WHO Global Task Force on TB Impact Measurement</td>
<td>Katherine Floyd</td>
</tr>
<tr>
<td></td>
<td>• Overview</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Objectives and expected outcomes of this meeting</td>
<td></td>
</tr>
<tr>
<td>11:00 – 11:20</td>
<td>Coffee break</td>
<td></td>
</tr>
<tr>
<td>11:20 – 12:30</td>
<td>Introductory remarks</td>
<td>Philippe Glaziou</td>
</tr>
<tr>
<td></td>
<td>Presentation with interactive Q&amp;A (focused on questions for clarification)</td>
<td>Nim Arinaminpathy</td>
</tr>
<tr>
<td></td>
<td>Methods for estimating TB incidence and mortality that account for the impact of the COVID-19 pandemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Background document 1)</td>
<td></td>
</tr>
<tr>
<td>12:10 – 12:30</td>
<td>Explanation of group work</td>
<td>Katherine Floyd</td>
</tr>
<tr>
<td>12:30 – 14:00</td>
<td>Lunch</td>
<td>Anna Dean</td>
</tr>
<tr>
<td>14:00 – 15:30</td>
<td>Group work: Questions on inner cover page of Background document 1</td>
<td>All in groups</td>
</tr>
<tr>
<td>15:30 – 15:50</td>
<td>Coffee/tea break</td>
<td>All in groups</td>
</tr>
<tr>
<td>15:50 – 17:15</td>
<td>Continuation of group work (if necessary), followed by feedback in plenary, followed by plenary discussion</td>
<td>All in groups</td>
</tr>
<tr>
<td>17:15 – 17:30</td>
<td>Wrap up of Day 1</td>
<td>Jaap Broekmans</td>
</tr>
</tbody>
</table>
### DAY 2: Thursday, 12 May 2022

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:30 – 09:45</td>
<td>Introduction to Day 2</td>
<td>Jaap Broekmans</td>
</tr>
<tr>
<td>9:45 – 11:00</td>
<td><strong>Objective 2: Methods for producing estimates of the incidence of drug-resistant TB, with particular attention to new methods for time-series of RR-TB estimates for 2015–2021</strong></td>
<td>Anna Dean, Philippe Glaziou, Pete Dodd</td>
</tr>
<tr>
<td></td>
<td>Presentation with interactive Q&amp;A (focused on questions for clarification)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methods for estimating the incidence of drug-resistant TB, including new methods for estimating RR-TB trends for 2015-2021</td>
<td></td>
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<tr>
<td></td>
<td>(Background document 2)</td>
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<tr>
<td>11:00 – 11:20</td>
<td><strong>Coffee break</strong></td>
<td></td>
</tr>
<tr>
<td>11:20 – 12:45</td>
<td><strong>Group work</strong>: Questions on inner cover page of Background document 2</td>
<td>All in groups</td>
</tr>
<tr>
<td>12:45 – 14:00</td>
<td><strong>Lunch</strong></td>
<td>All in groups</td>
</tr>
<tr>
<td>14:00 – 15:30</td>
<td>Continuation of group work (if necessary), followed by feedback in plenary, followed by plenary discussion</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td><strong>Coffee/tea break</strong></td>
<td></td>
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<tr>
<td>15:30 – 15:50</td>
<td><strong>Objectives 1 and 2; quick updates on related topics; next steps</strong></td>
<td></td>
</tr>
<tr>
<td>15:50 – 16:30</td>
<td>Main outcomes and next steps</td>
<td>Chair, WHO secretariat</td>
</tr>
<tr>
<td></td>
<td>Brief updates on related topics*</td>
<td>Meeting participants</td>
</tr>
<tr>
<td></td>
<td>*This is only if time permits...</td>
<td></td>
</tr>
<tr>
<td>16:30 – 17:00</td>
<td>Wrap up and closing</td>
<td>Jaap Broekmans, Tereza Kasaeva</td>
</tr>
</tbody>
</table>
ANNEX 2: List of participants, and those who were invited but could not attend

1. Jaap Broekmans
Independent consultant
The Hague
NETHERLANDS

2. Ibrahim Abubakar
University College London
London
UNITED KINGDOM

3. Sevim Ahmedov
USAID
Washington, DC
UNITED STATES OF AMERICA

4. Sandra Alba
Royal Tropical Institute (KIT)
Amsterdam
NETHERLANDS

5. Nim Arinaminpathy
Imperial College London
London
UNITED KINGDOM

6. Juan Carlos Bossio
National Institute of Respiratory Diseases (INER)
Santa Fe
ARGENTINA

7. Macarthur Charles
Program Support and Evaluation (PROSE), Global Tuberculosis Branch, Division of Global HIV and Tuberculosis, Center for Global Health, U.S. Centers for Disease Control and Prevention
Atlanta, GA
UNITED STATES OF AMERICA

8. Melanie Chitwood
Yale School of Public Health
New Haven, CT
UNITED STATES OF AMERICA

9. Ted Cohen
Yale School of Public Health
New Haven, CT
UNITED STATES OF AMERICA

10. Pete Dodd
University of Sheffield
Sheffield
UNITED KINGDOM

11. David Dowdy
Bloomberg School of Public Health
Baltimore, MD
UNITED STATES OF AMERICA

12. Mohammad Noor Farid
National Institute of Health Research and Development
Jakarta
INDONESIA

13. Rein Houben
London School of Hygiene & Tropical Medicine (LSHTM)
London
UNITED KINGDOM

14. Sandip Mandal
Indian Council of Medical Research
New Delhi
INDIA

15. Raghuram Rao
National Tuberculosis Elimination Programme
New Delhi
INDIA

---

10 Not able to participate in person but provided comments on background documents remotely.
16. Finn McQuaid
London School of Hygiene & Tropical Medicine (LSHTM)
London
UNITED KINGDOM

17. Nick Menzies
Harvard T.H. Chan School of Public Health
Boston, MA
UNITED STATES OF AMERICA

18. Harry Moultrie
National Institute For Communicable Diseases (NICD)
Johannesburg
SOUTH AFRICA

19. Nnamdi Nwaneri
The Global Fund
Geneva
SWITZERLAND

20. Sulistyo
Directorate for Disease Control and Prevention
Ministry of Health
Jakarta
INDONESIA

21. Edine Tiemersma
KNCV Tuberculosis Foundation
Amsterdam
NETHERLANDS

22. Richard White
London School of Hygiene & Tropical Medicine (LSHTM)
London
UNITED KINGDOM

23. Norio Yamada
Research Institute of Tuberculosis
Tokyo
JAPAN

11 Not able to participate in person but provided comments on background documents remotely

Representative from China
WHO Regional Office for Europe

24. Giorgi Kuchukhidze
Division of Country Health Programmes
WHO EURO
Copenhagen
DENMARK

WHO Headquarters

Global Tuberculosis Programme (GTB)
TB Monitoring, Evaluation & Strategic Information unit (TME)

25. Katherine Floyd
Unit Head

26. Anna Dean
Technical Officer

27. Philippe Glaziou
Team Lead, Global Monitoring, Estimates & Projections
TB Prevention, Diagnosis, Treatment, Care & Innovation unit (PCI)

28. Matteo Zignol
Unit Head

29. Dennis Falzon
Team Lead
TB Vulnerable Populations, Communities & Comorbidities unit (VCC)

30. Kerri Viney
Team Lead, GTB

AMR Surveillance, Prevention and Control (SPC)
Evidence and Emerging AMR unit

31. Olga Tosas Auguet
Technical Officer

32. Barbara Tornimbene
Technical Officer
**ANNEX 3: Methods for estimating TB incidence and mortality – template for group work (questions 2 and 3)**

**Question 2:** Are there any revisions to the proposed 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?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Is any revision necessary and feasible to implement in the next 2 months? (Yes, No)</th>
<th>If Yes: Revision suggested</th>
<th>If Yes: Reason(s) why the revision proposed would be an improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection of countries to be modelled</td>
<td></td>
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<tr>
<td>Assumptions about notification trends beyond the latest available data points</td>
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<tr>
<td>Assumptions about reductions in TB transmission during lockdowns and other COVID-related restrictions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistical approach for countries not directly modelled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other – please add topic as appropriate</td>
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<tr>
<td>Other – please add topic as appropriate</td>
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</tbody>
</table>
**Question 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?

<table>
<thead>
<tr>
<th>Topic</th>
<th>Should a better approach be explored in the coming year? (Yes, No)</th>
<th>If Yes: Suggestions (if any, at this point) for how a better approach could be developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assumptions about reductions in TB transmission during lockdowns and other COVID-related restrictions</td>
<td></td>
<td></td>
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<tr>
<td>Accounting for COVID-related impacts on broader TB determinants (e.g. income, poverty, undernutrition)</td>
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<tr>
<td>Statistical approach for countries not directly modelled</td>
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<tr>
<td>No structure for drug resistance in the current models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other – please add topic as appropriate</td>
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<td></td>
</tr>
<tr>
<td>Other – please add topic as appropriate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX 4: Methods for estimating the incidence of RR-TB – template for group work (question 2)

### 1. Data inclusion criteria

<table>
<thead>
<tr>
<th>Current method</th>
<th>Is there a better approach that is both necessary and feasible to implement in the next 2 months? (Yes, No)</th>
<th>If Yes: Alternative approach suggested</th>
<th>If Yes: Reasons why the alternative approach would be an improvement</th>
<th>If No: Suggestions (if any) for improvements that could be explored in the coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance data on the proportions of new and previously treated cases with RR-TB used if:</td>
<td>For example, are there alternative or additional criteria that should be used? (e.g. related to the concerns that have been expressed about year-to-year fluctuation in the proportions observed in reported surveillance data, or the reliability of data in countries where there have been large drops in total TB notifications during the COVID-19 pandemic)?</td>
<td>For example, should a different cut-off be used?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>test results for RR-TB available for ≥80% of bacteriologically confirmed new and/or previously treated patients with pulmonary TB;</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>the ratio of new patients to patients with unknown treatment history is at least 4:1;</td>
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</tr>
<tr>
<td>data are not older than 15 years;</td>
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<tr>
<td>there are no obvious data irregularities, following clarifications with NTPs.</td>
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</tr>
</tbody>
</table>

For example, are there alternative or additional criteria that should be used? (e.g. related to the concerns that have been expressed about year-to-year fluctuation in the proportions observed in reported surveillance data, or the reliability of data in countries where there have been large drops in total TB notifications during the COVID-19 pandemic)?

If surveillance data not available, survey data used provided they are ≤15 years old. For example, should a different cut-off be used?

---

12 For a few countries each year, data are excluded, usually due to reported values being implausible (e.g. this can happen as a result of data reporting errors). See section 1.2 and Table 3.

13 Of note, the proportion of non-notified cases (out of all estimated incident TB cases) has varied considerably among countries for many years.
### 2. Formula to estimate RR-TB incidence in a single year, at country and global levels

\[
I_{rr} = I\left[(1 - f)p_n((1 - r) + rp) + fp_r\right]
\]

<table>
<thead>
<tr>
<th>Current method</th>
<th>Is there a better approach that is both necessary and feasible to implement the next 2 months? (Yes, No)</th>
<th>If Yes: Alternative approach suggested</th>
<th>If Yes: Reasons why the alternative approach would be an improvement</th>
<th>If No: Suggestions (if any) for improvements that could be explored in the coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportions of new ((p_n)) and previously treated ((p_r)) cases with RR-TB are approximated using national survey and surveillance data for notified TB cases. It is assumed that these proportions are the same among non-notified cases (i.e. cases that were either not diagnosed, or that were diagnosed but not reported).(^1)(^4)</td>
<td>For example, is there a better assumption that could be used?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>For countries without survey and surveillance data, the values of (p_n) and (p_r) are estimated using data from countries with similar epidemiology. Hierarchical generalized linear modelling is used.</td>
<td></td>
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</tr>
<tr>
<td>Proportions of new and previously treated cases with RR-TB among bacteriologically confirmed cases are assumed to be the same as those among clinically diagnosed cases.</td>
<td>For example, is there a better assumption that could be used?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(p_r) is approximated using data that are for relapse and non-relapse retreatment cases combined. This may underestimate the true value of the proportion of non-relapse retreatment cases that have RR-TB.</td>
<td></td>
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</tbody>
</table>

\(^1\) Of note, the proportion of non-notified cases (out of all estimated incident TB cases) has varied considerably among countries for many years. The proportion increased significantly in many countries during the COVID-19 pandemic (see also Background document 1).
2. **Formula to estimate RR-TB incidence in a single year (continued)**

\[ I_{RR} = I[(1 - f)p_n((1 - r) + r\rho) + fp_r] \]

<table>
<thead>
<tr>
<th>Current method</th>
<th>Is there a better approach that is both necessary and feasible to implement in the next 2 months? (Yes, No)</th>
<th>If Yes: Alternative approach suggested</th>
<th>If Yes: Reasons why the alternative approach would be an improvement</th>
<th>If No: Suggestions (if any) for improvements that could be explored in coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r ) (the proportion of people with a new episode of TB who are relapse cases i.e. people previously treated for TB who were cured) is estimated using national notification data averaged over the most recent 5 years. These data are available for almost all countries.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>( f ) (risk that incident cases of TB return for retreatment following failure or loss to follow-up) is approximated as the proportion of all notified TB cases (new + relapse + non-relapse retreatment) that were reregistered for treatment following treatment failure or loss-to-follow-up. National notification data for the last 5 years are used to estimate this proportion.</td>
<td></td>
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</tr>
<tr>
<td>( \rho ) (relative risk of RR-TB in relapse compared with new cases) is estimated using measurements (mostly from surveys) in 35 countries that have data about the prevalence of resistance in subcategories of previously treated cases. Values are imputed for other countries using the pooled value from countries with data; if the pooled value of ( \rho ) times ( p_n ) is greater than ( p_r ) then ( p_r ) is used instead of the product ( \rho p_n ).</td>
<td></td>
<td></td>
<td></td>
<td>Other: pls add if there are other aspects of the formula for which the group would like to propose improvements</td>
</tr>
<tr>
<td>Other: pls add if there are other aspects of the formula for which the group would like to propose improvements</td>
<td></td>
<td></td>
<td></td>
<td>Other: pls add if there are other aspects of the formula for which the group would like to propose improvements</td>
</tr>
</tbody>
</table>
3. New analytical approach proposed for production of time-series of estimates of the proportion of new and previously treated cases with RR-TB, which will then be used in combination with the formula (see 2. above) to produce time series of estimates for 2015-2021

<table>
<thead>
<tr>
<th>Proposed method</th>
<th>Is there a better approach that is both necessary and feasible to implement in the next 2 months? (Yes, No)</th>
<th>If Yes: Alternative approach suggested</th>
<th>If Yes: Reasons why the alternative approach would be an improvement</th>
<th>If No: Suggestions (if any) for improvements that could be explored in the coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models structured with two categories of drug resistance only versus models with four categories of drug resistance</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The latter can use more data and generate estimates of both isoniazid resistance and MDR-TB. However, they are more complex, harder to fit, and do not necessarily provide the best fit to data on rifampicin resistance alone.</td>
<td></td>
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<tr>
<td>WHO regions used as covariates (the six WHO regions plus a grouping of the former republics of the Soviet Union, totaling 7 categories).</td>
<td></td>
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</tr>
<tr>
<td>Separate versus joint modelling of new and previously treated patient groups</td>
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<tr>
<td>Model variants jointly modelling proportions in each group typically have better performance metrics.</td>
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<tr>
<td>Modelling approach to random effects (RE):</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• RE for intercepts and slopes, each with shared distributions to specialise to individual countries;</td>
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</tr>
<tr>
<td>• regionally-dependent RE distributions;</td>
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<tr>
<td>• spatially-dependent RE distributions (via a Leroux conditional autoregressive areal prior);</td>
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<tr>
<td>• Gaussian process type models for temporal correlations; and</td>
<td></td>
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<td></td>
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<tr>
<td>• other (to be defined).</td>
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<tr>
<td>Simpler models are easier to communicate and fit, but may have less good predictive ability</td>
<td></td>
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</tr>
</tbody>
</table>
### 3. New analytical approach proposed for production of time-series of estimates of the proportion of new and previously treated cases with RR-TB, which will then be used in combination with the formula (see 2. above) to produce time series of estimates for 2015-2021 (continued)

<table>
<thead>
<tr>
<th>Proposed method</th>
<th>Is there a better approach that is both necessary and feasible to implement in the next 2 months? (Yes, No)</th>
<th>If Yes: Alternative approach suggested</th>
<th>If Yes: Reasons why the alternative approach would be an improvement</th>
<th>If No: Suggestions (if any) for improvements that could be explored in the coming year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion of space-time interaction random effects? Models with these interactions are more locally responsive and predictions are as good as without, but also have a more 'noisy' appearance and are more computationally intensive.</td>
<td></td>
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<tr>
<td>Choice of experiment/metric to evaluate models. Experiments have included:</td>
<td></td>
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<tr>
<td>- <strong>Approximate</strong> ELPD (via PSIS-LOO)</td>
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<tr>
<td>- <strong>Explicit</strong> leave-one-country out (LOO)</td>
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<tr>
<td>- <strong>Explicit</strong> country-wise omit-2020</td>
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<tr>
<td>- <strong>Explicit</strong> 4 year data roll-back</td>
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<tr>
<td>Metrics for explicit LOO experiments have included:</td>
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<tr>
<td>- Cross-entropy</td>
<td></td>
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<tr>
<td>- MAE &amp; MAPE</td>
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<tr>
<td>- Coverage &amp; precision (IQR)</td>
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<tr>
<td>Limited countries included in LOO experiments were selected prioritized by number of data points.</td>
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<tr>
<td>Only 3 models included in explicit experiments.</td>
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</tbody>
</table>