Model-based methods for estimating effects of COVID-19 on TB incidence and mortality

Meeting of the WHO Task Force for TB Impact Measurement,
11 May 2022
Preceding work

• Early modelling work in 2020:
  • McQuaid, McCreeesh et al, ERJ 2020
  • Glaziou, 2020
  • Cilloni, Fu et al, EClinicalMedicine 2020

• Prospective modelling on potential impacts that may unfold

• Region-level support: WHO South-East Asian Region

Led by Sandip Mandal, Carel Pretorius (with funding support from TB-Mac)
Outline

• Notifications as evidence of disruptions to TB services
• Technical details:
  • Priority countries and the different models used
  • Model calibrations
  • TB service disruptions and future projections
  • TB transmission reductions: assumptions and uncertainties
• Overview of results, 2021 report
• Ongoing work: streamlining the modelling approach
• Some outstanding questions
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Notifications as evidence of disruptions

Drops in notifications could arise from a range of different factors:

• Symptomatic patients not being able to access care

• Even once symptomatic patients present for care, healthcare facilities do not have capacity to diagnose/manage TB
  • Diagnostic facilities are diverted to COVID
  • Any available HR capacity is diverted to COVID
  • Some primary care providers simply closed their facilities

• Temporary decrease in TB burden

• Programmatic delays in reporting TB
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Model delays to diagnosis and treatment initiation, to match notifications

Model lockdown-related reductions in transmission

[ Likely to have resolved once reports stabilised ]
Other possible effects of COVID-19 on TB

• ‘Direct’ effects: e.g. evidence from India, that co-disease with COVID-19 and TB carried substantially higher mortality risk than either disease alone

• Other ‘indirect’ effects: possibility for disruptions in other parts of the care cascade than just diagnosis, e.g. treatment continuity or provision of DST
  • No systematic data for these outcomes
  • Previous analysis suggests that these types of disruptions may have only minor effects on TB incidence and mortality, compared to diagnosis (Cilloni et al, EClinicalMedicine 2020)

• ‘Distal’ effects acting on TB determinants, e.g. impoverishment
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Notifications as evidence of disruptions

Uninfected $\lambda$ Latent, ‘fast’ progression $\rightarrow$ Latent, ‘slow’ progression $\xrightarrow{\text{Breakdown}}$ Active, infectious disease $\xleftarrow{\text{Diagnosis and treatment initiation rate}}$ Recovered

$
\begin{array}{l}
\lambda: \text{Diagnosis and treatment initiation rate} \\
\text{COVID-19-related disruptions}
\end{array}$

Public notifications

Monthly notifications per 100k

- Jan 19, May 19, Sep 19, Jan 20, May 20, Sep 20, Jan 21, May 21
- National lockdown
- Second wave

Private notifications

Monthly notifications per 100k

- Jan 19, May 19, Sep 19, Jan 20, May 20, Sep 20, Jan 21, May 21
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Priority countries

• Concentrated on 16 countries accounting for >95% of ‘missed notifications’ in 2020
• Statistical extrapolation to other countries

<table>
<thead>
<tr>
<th>Countries with strong role of private sector in TB management</th>
<th>Countries with ≥ 10% of TB incidence being HIV-coinfected</th>
<th>Countries with ≥ 10% of TB incidence being RR-TB</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Public/private model</th>
<th>TB/HIV model</th>
<th>DS/DR-TB model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>Angola</td>
<td>Peru</td>
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<tr>
<td>China</td>
<td>Brazil</td>
<td>Russian Federation</td>
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<tr>
<td>India</td>
<td>Kenya</td>
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<td>Philippines</td>
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<td>Viet Nam</td>
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WHO Global TB report, 2021
Public/private healthcare systems

• In working with notification data, need to account for under-reporting by private healthcare providers

• Notification data typically isn’t available separately for the private sector:
  • **Assume** that disruptions affected public and private sectors equally

• **Exception:** India, whose Nikshay data shows public and private separately
  • ‘Private’ reflects only ‘engaged private’: **Assume** that disruptions apply to all private providers equally
TB/HIV model

• Dynamics of HIV not explicitly modelled
  • Taken as external input

• Stratify all TB compartments into three HIV strata:
  • HIV negative; HIV positive not on ART; on ART

• HIV confers increased risk of progression to active disease from all latent compartments; ART reduces this risk

• Transitions between strata informed by Thembisa model estimates for:
  • HIV incidence and prevalence; and ART coverage
RR-TB model structure

- Incorporated prior to current discussion around separate methods for RR-TB estimation (see also ongoing model updates)
  - Rationale: diagnostic delays (underpinning transmission effects) are likely to be *multimodal* when combining DS- and RR-TB
    - Modelling separately will allow us to untangle these different delays
- Model stratified to capture multistrain dynamics: DS- and RR-TB
- Assumed that levels of DST, and treatment outcomes, were unaffected by pandemic (conservative)

*Also including:* Multistrain reinfection; Inappropriate first-line treatment; second-line treatment
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## Model calibrations: targets and parameters

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<tr>
<th></th>
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<th>Public/private only</th>
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<th>RR-TB only</th>
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<tbody>
<tr>
<td><strong>Calibration targets</strong></td>
<td>Incidence rates, 2019</td>
<td>--</td>
<td>Proportion of TB incidence that was HIV-coinfected, 2019</td>
<td>Overall proportion of incident TB that was RR-TB, 2019</td>
</tr>
<tr>
<td></td>
<td>Mortality rates, 2019</td>
<td></td>
<td>Mortality rates amongst HIV +ve TB, 2019</td>
<td>(aggregated over new &amp; previous Tx)</td>
</tr>
<tr>
<td><strong>Free parameters</strong></td>
<td>Average onward infections per case per year</td>
<td>Upon careseeking, proportion of patients visiting public vs private sector</td>
<td>Relative hazard of developing TB given latent infection, HIV +ve vs HIV –ve</td>
<td>Relative infectivity, RR- vs DS-TB</td>
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<tr>
<td></td>
<td>Mortality hazard, untreated TB</td>
<td></td>
<td>Relative hazard of mortality for untreated TB, HIV +ve vs HIV –ve</td>
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</table>

Model calibrations: technical approach

- Bayesian MCMC to systematically propagate uncertainty from input parameters to model projections
- For each country: 3 independent MCMC chains to ensure convergence
- Ran for 100,000 iterations, then ‘thinned’ to extract 250 samples
- Uncertainty intervals on model projections quantified as 2.5th, 50th and 97.5th percentiles
- See additional info for further outputs on calibration results
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Modelling disruptions

- **All model structures** have a parameter $k(t)$, denoting COVID-induced effects on TB careseeking and diagnosis.

- For each country, take monthly (or quarterly) data from Jan 2020 onwards.

- **Modelled** notifications in a given month:
  \[
  \int_{t_0}^{t_0+12} k(t) d I(t) \, dt
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- Adjust $k(t)$ on a monthly/quarterly basis so that the timeseries for modelled notifications matches the data.
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Forward projections to 2025

• For countries that haven’t yet fully recovered, we don’t know how long they may take to do so

• Possible approach: make a uniform assumption for gradual recovery from the last available datapoint, e.g. 6 months
  • Will be over-optimistic for some countries (e.g. Indonesia), over-pessimistic for others (e.g. Pakistan)

• Another approach: services return to normal ($k = 1$) immediately after last available data point
  • Deliberately wrong: all countries will be biased in the same direction
  • Forward projections aren’t ‘predictions’, but merely isolate the long-term impact of disruptions that have already occurred
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TB transmission reductions

• Much as restrictions have affected SARS-CoV-2 transmission, they are likely to have done the same to TB

• We don’t yet have direct evidence for effects on TB transmission during lockdowns

• For purpose of modelling: assume that TB transmission was reduced by a constant factor $c$ during periods of restrictions
  • Draw $c$ from a uniform distribution from 25% - 75%
  • Where restrictions acted only at the subnational level, scale $c$ by the size of the population affected

• Assume that TB transmission returned to pre-pandemic levels after restrictions were lifted...
• ...Although see later discussion of outstanding questions!!
Putting it all together...

(With thanks to Nick Menzies and Hsien-Ho Lin for rapid review)
Overall mortality projections

(Global TB Report, 2021)
Overall incidence projections

(Global TB Report, 2021)
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Ongoing model updates

• Dropping the RR-TB model
  • To avoid duplication/circularity with parallel efforts (Pete Dodd) to estimate RR-TB burden

• Combining the HIV/TB and public/private models into a single framework
  • Can now avoid artificial categorisations for e.g. Ukraine, Thailand, Kenya

• Data extraction and calibration being increasingly automated
  • Although matching to notifications timeseries remains manual

• Using this framework, extending to an additional 16 countries based on contribution to ‘missed notifications’ since 2020

• Once codebase has stabilized: post in public repository
Some outstanding questions

• What is the role of reductions in TB transmission?
  • Currently: assuming it applied only during periods of restrictions
  • Might ‘COVID-appropriate behaviours’ have affected TB transmission for much longer?

• Some early indications of possible decreases in TB prevalence
  • Ongoing discussions on India prevalence survey
  • Kampala, Uganda [confidential]: Dowdy and colleagues observe >40% reduction in prevalence in study sites

• What are the potential roles of persistent reductions in TB transmission vs COVID-induced increases in TB mortality?