A Flexible Dynamic Transmission Model Framework for Evaluating Tuberculosis Treatments: Methodological Challenges and Applications

Hema K. Gandhi[1], Maia Mileva Lopez[2], Norbert Hittel[2], Karam Diaby[1], Onn Kon[3], Rosanna C. Barnard[4], Vasily Lukyanov[4], David Bointon[4], Richard Pitman[4]
[1]Otsuka Pharmaceutical Development & Commercialization, Inc.,[2]Otsuka Novel Products GmbH, [3]Imperial College Healthcare NHS Trust, [4]ICON PLC

Otsuka Pharmaceutical Development & Commercialization, Inc.

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Background and Objectives

Burden of TB

- Despite being preventable and curable, tuberculosis (TB) continues to be a major public health concern worldwide.
- The latest World Health Organization (WHO) Global TB report[1] estimates that in 2023, 10.8 million people fell ill with TB and 1.25 million people died from TB, and suggests that TB may have replaced COVID-19 as the world's leading cause of death from a single infectious agent.

Need for new TB treatments

- TB treatment plays a significant role in disease control by minimising the burden of existing infections, preventing onwards transmission, and reducing the risk of drug resistance.
- Historically, TB treatments have been lengthy, toxic, and poorly tolerated, particularly for MDR-TB.
- To improve patient outcomes and reduce the burden of TB on society, improved treatment options must be developed and then assessed to determine if they are cost-effective relative to existing treatments in use.

We present a dynamic transmission model (DTM) framework for evaluating different TB treatment regimens

Burden of TB

The need for a dynamic transmission model

- A novel combination therapy may reduce the duration of infectiousness of TB, thereby having an impact beyond just the individual being treated
- By reducing the potential to transmit TB, treatment will influence the bacteria's transmission dynamics

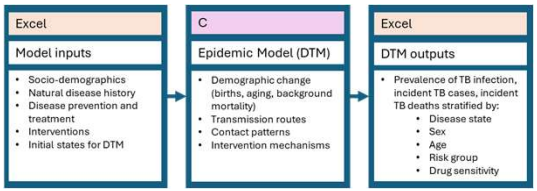
Dynamic transmission modelling is therefore required to capture the full value of such an intervention and to facilitate sound decision making

Methods

DTM model and user interface

- The DTM is an adaptable framework designed to simulate the impact of treatment and its effects on TB transmission.
- The model is calibrated to England and Wales as an exemplar, using TB notifications and mortality data from 1950-2021, and annual net migration estimates between 1991 and 2019.
- The front-end user interface (UI) is built in Microsoft Excel, where inputs and assumptions are user-specified. The DTM is run from Excel via a console executable coded in C, and results are returned to the UI for further analysis and visualization (Figure 1).

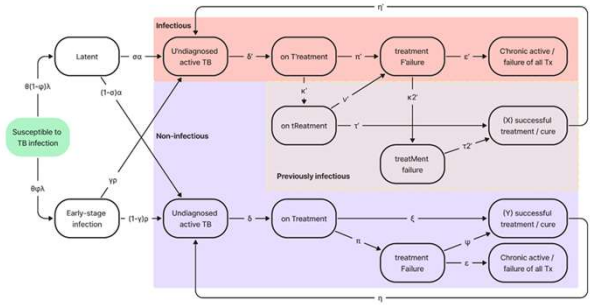
Figure 1 Schematic representation of the DTM model and Excel user interface



Modelling transmission and treatment of TB

- Building on existing published models[2-5], a compartmental DTM is used to describe TB transmission, with the population divided into applicable disease states (Figure 2).
- Susceptible individuals become infected and progress to active TB via infections and non-infectious pathways.
- Active infectious TB cases progress through diagnosis and treatment, reaching a cured or a chronic TB/ failure of all treatments state. Cured individuals may return to an active TB state, either through a relapse or through a reinfection with a de novo MTB strain.
- Clinical trial data for TB treatments such as time to sputum culture conversion, tolerability, toxicity of drug therapies (QALY loss resulting from TB morbidity and toxicity of drugs will be estimated by applying utility decrements to person years of time in specific states) and final treatment outcomes can be incorporated within this structure.
- Active TB states are stratified by drug sensitivity, e.g., DS-TB and multi-drug resistant (MDR).

Figure 2 Structure of dynamic transmission model (DTM) for TB



Other structural assumptions and processes

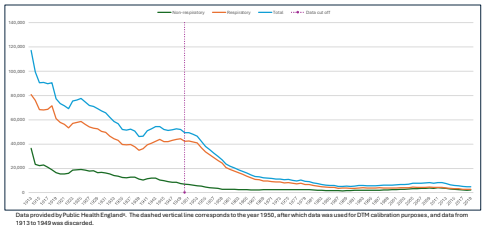
- The population is also stratified by: age (5-year age groups from 0-4 to 95-99), gender (male, female) and risk (low-risk, high risk).
- The model is integrated using a fourth order Runge-Kutta routine with adaptive timestep control and outputs results at the end of year.
- Demographic processes are implemented annually: births, aging, background mortality, and net migration.
- Net migration is introduced to the high-risk strata, which contributes to community transmission based on the assumption that migrant individuals are classified as susceptible. A small proportion of these individuals are assumed to have latent TB, which was acquired overseas that remain undetected by traveler screening and subsequently develop into active TB.

Methodological Challenges

Calibration to data

- For individuals infected with TB, the risk of progression to active TB is highest within the first 2 years following infection[6]. However, it is possible for a latent infection to activate many years after the initial infection occurred[7].
- Due to latency, the full impact of an intervention that impacts transmission will play out over a long timescale. There will be a rapid impact, but also additional effects over decades (Figure 3).
- We followed a multi-stage calibration process, fitting model parameter values of interest using TB notifications data between 1950 and 2019 and TB mortality data between 2006 and 2023.

Figure 3. Number of TB notifications by site of disease, England and Wales, 1913-2019.



Data provided by Public Health England. The dashed vertical line corresponds to the year 1950, after which data was used for DTM calibration purposes, and data from 1913 to 1949 was discarded.

Results – Demonstrating Selected Model Capabilities

- **Historical replication:** The framework can be calibrated to long time-series data and can reproduce observed TB incidence and mortality trends (e.g. England & Wales, 1950-2021), illustrating its ability to fit complex, multi-decadal epidemics (Figure 4). This allows the model to forecast the impact of treatment interventions and their effect on transmission thereby more accurately estimating the results of applicable interventions in TB management and the benefits they bring.
- **Scenario-based exploration:** The impact of key structural drivers can be assessed. For example:
  - Specific characteristics of novel treatments or interventions (standard of care vs. innovative treatment modalities) can be used to perform comparative analyses to demonstrate the impact of introducing a novel treatment or intervention on the transmission dynamics of TB.
  - *For example, if 50% reduction in time to sputum culture conversion was achieved in the United Kingdom (UK), we achieve a 30% net reduction in the number of incident cases over 100 years (Table 1).*
- **Interactive output visualization:** All simulation outputs (incidence curves, resistance breakdown, cumulative cases averted) are automatically returned to the Excel UI for an on-the-fly charting and tabulation, supporting rapid interventional, policy or economic appraisals.

Figure 4 Annual incidence of newly diagnosed TB cases (pulmonary and non-pulmonary), for calibrated model (green, 1951 to 2050), for historic TB notifications data (orange, 1950 to 2019), and for contemporary TB notifications data (blue, 2001 to 2022.

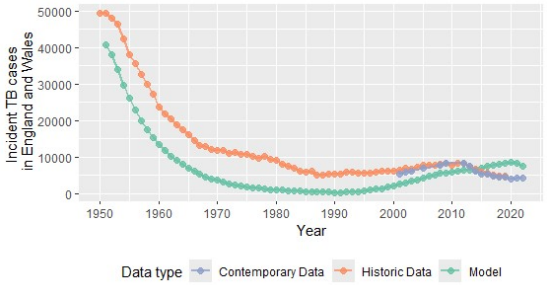


Table 1. A comparison of cumulative incident MDR-TB cases with different rates of sputum conversion for individuals on TB treatment

Rate of sputum conversion (year^{-1})	Interpretation	Cumulative incident MDR-TB cases (100-year timescale)
6.5	Average duration on treatment prior to sputum conversion is 1/6.5 = 0.15 year	104,549
13	Average duration on treatment prior to sputum conversion is 1/13 = 0.077 year	75,135
Percentage reduction in MDR-TB cases		28%

Conclusions

- The DTM offers a flexible framework for evaluating TB treatments in dynamic settings, accounting for both localized and global transmission drivers as well as the impact of a novel treatment on the dynamics of TB transmission.
- The model has been parametrized and calibrated to data from England and Wales as an example but can be easily adapted to consider TB in low- and middle-income countries (as long as similar historical data sets or detailed prevalence data exist).
- Assessing the direct and indirect effects of novel TB treatments on the treatment of TB and TB transmission is of crucial importance to overall public health and to budget-holders, policymakers and health economists.

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Contact: For more information, please contact Hema Gandhi: Hema.Gandhi@otsuka-us.com