Comparing the health and economic outcomes of multi-drug resistant tuberculosis empirical treatment choices

Background

Multidrug-resistant (rifampicin and isoniazid resistance) or rifampicin-resistant tuberculosis (MDR/RR-TB) is one of the main causes of antimicrobial resistant related deaths, accounting for around 0.18 million deaths each year (1). Even though TB can be treated with drugs with a high cure rate, the emergence and spread of resistant strains made TB more difficult to treat. Fluoroquinolones or second-line injectable drugs are essential to treat multidrug-resistant tuberculosis. Resistance to these drugs, called extensively drug-resistant tuberculosis (XDRTB), results in decreased treatment success rates (85% in drug-susceptible TB, 56% in MDRTB, 36% in XDR-TB) (2).

The World Health Organization recommends empirical treatment options with different drugs and regimen periods depending on resistant status (3). Drug susceptibility test (DST) would be required to know the most effective regimen. However, the coverage of second-line DST is still low in many countries. Therefore, MDR/RR-TB patients are often treated empirically either assuming resistance to second-line drugs or not. Consequently, sub-optimal treatment choices can result in onward transmission (when ineffective treatment regimens are given) or additional costs and a greater chance of adverse events (when resistance was assumed unnecessarily) (4). Making decisions between different treatment regimens without proper knowledge of their second-line resistant profile may depend on different characteristics at individual and population levels. Evidence is needed to inform treatment guidelines and to help policymakers to adopt optimal strategies in respective settings.

Aim

My aim is to generate evidence to guide decision-making for empirical treatment choices for MDR/RR-TB. I will accomplish my aim through the following objectives:

1. Conduct a systematic review to summarise the available evidence on empirical treatment outcomes of different regimens
2. Develop a dynamic model to estimate health outcomes of different regimens
3. Conduct a cost-effective analysis of different regimens

Significance

The TB treatment guidelines from the World Health Organization added new regimens that include fluoroquinolone. For instance, it suggested the 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen to treat MDR/RR-TB (3). Timely DST for fluoroquinolones may guide the choices of regimen where in this case it would guide whether moxifloxacin should be retained or dropped from the regimen. This research can close the evidence gaps not only in gauging the potential impact of the newly recommended regimens, but also in understanding the complex interactions between diagnostics and antibiotic usage. Furthermore, previous research shows that proportion of fluoroquinolone resistance among MDR/RR TB patients varies across countries (5). By comparing outcomes in different settings, this research can also inform other low and middle-income country settings how to empirically treat MDR/RR TB patients.

Innovation

Available tuberculosis models tend to focus on drug-susceptible and multidrug-resistant tuberculosis and do not consider the emergence of XDR-TB cases. In addition, previous TB models were not used to guide empiric prescribing. This research will uniquely focus on the treatment of MDR/RR-TB patients to guide empirical decisions. Empiric prescribing is also common for other bacteria/diseases. Therefore, lessons from this research on how to use population and patient level factors to improve empirical treatment choices of TB would provide a modelling framework and valuable implications for other resistant pathogens.

Research Plan

Objective 1: Conduct a systematic review to summarise the available evidence on empirical treatment outcomes of different regimens on MDR/RR-TB patients

I will systematically search for peer-reviewed papers estimating the potential values of the treatment regimens on MDR/RR-TB in the Web of Science, Medline (PubMed) and Embase. The primary outcomes will be the evidence of the effectiveness of the treatments in cure rates, mortality, adverse events, and amplification of resistance. The extracted data on the outcomes will be grouped by second-line resistance status to compare the potential benefits and harms of different regimens used against second-line resistant or susceptible TB. To determine the eligibility of the studies, the study population should include MDR/RR-TB patients or the resistant TB compartment in the model. The included studies would be observational studies (cohort, case-control, cross-sectional), randomised controlled trials, modelling studies, and economic evaluation studies. The methodology and perspectives used in the modelling studies will also be explored.

Objective 2: Develop a dynamic model to estimate health outcomes of different regimens when fluoroquinolone resistance status is not known

I will develop a MDR-TB compartmental dynamic model to estimate and compare the potential outcomes of using different regimens on MDR-TB in the absence of the DST results on the second-line drugs. I will extend the traditional SEIS TB model to take into account the MDR+F TB (fluoroquinolone resistance in MDR-TB patients) and the important traits of TB treatment. Dynamic model will allow the capturing of the indirect impact in that infected individuals who receive ineffective treatment go on transmitting the infections.

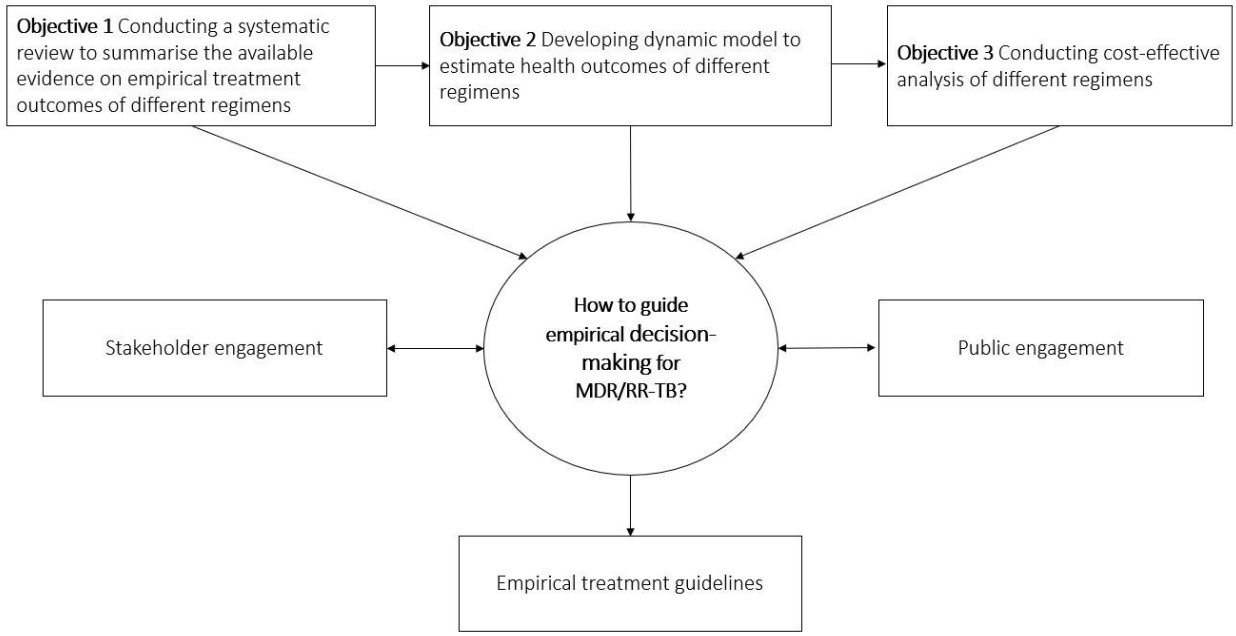
The model will start with susceptible individuals S(t). Upon infection, the susceptible individuals could be infected with drug-susceptible TB, MDR-TB or MDR+F TB depending on the exposed disease types. The exposed individuals (E_{DS}, E_{MDR} or E_{MDR+F}) will progress to I_{DS}, I_{MDR} or I_{MDR+F} when the disease becomes activated. The individuals with active infections would be treated according to the probabilities of cure of the treatment regimens. In addition to TB transmission, an important feature of TB treatment such as treatment failure, acquisition of resistance during treatment, and the incursion of adverse events will also be added into the model to effectively compare outcomes of different treatment regimens.

The model will be simulated with different scenarios of different treatment regimen choices using DST coverage for fluoroquinolone resistance in the respective settings. For individuals entering the model without DST results, estimates will be calculated using two different scenarios; (1) treated in a shortened regimen with fluoroquinolones in both MDR and MDR+F cases (2) treated with XDR-TB regimen with longer treatment duration in both MDR and MDR+F cases. Individuals entering the model with DST results will be assumed to obtain the correct treatment. The development and calibration of the model will be done in different country settings where variance in fluoroquinolone resistance prevalence exists (5). Health outcomes will be measured in deaths and adverse events in each scenario and checked how it varies by different population characteristics (e.g., fluoroquinolone resistance prevalence, smoking rate, and prevalence of diabetes).

Objective 3: Conduct a cost-effective analysis of different treatment regimens when fluoroquinolone resistance status is not known

I will conduct the cost-effective analysis (CEA) of MDR-TB using dynamic models developed in objective 2. Using a health system perspective, the incremental cost per disability-adjusted lifeyear (DALY) averted will be estimated between the different regimens identified. Likewise objective 2, the model will reflect the DST coverage for fluoroquinolone resistance in the respective settings. Based on epidemiology (e.g., fluoroquinolone resistance prevalence) and the existing relationship of these countries with the supervisory group, South Africa and Pakistan may be considered for the study settings. Further building cooperative relationships with country stakeholders and involving them in structuring the research questions of their interests will also be key part of the objective 3. Parameter values on costs will be identified in objective 1 and through searches in relevant TB data repositories. Probabilistic sensitivity analysis will be conducted using a Monte Carlo simulation.

Figure 1 Conceptual framework that links research objectives to guide decision-making



Impact

Based on findings from the available literature and findings from this research, I will develop a policy brief to guide policy decisions. In addition, I will develop web-based interactive decision support tools using an R package (Shiny) for policymakers to use and apply the research output in their relevant settings. I will also seek stakeholder and public engagement throughout the research process.

Potential limitations and challenges to the research plan

There could be insufficient evidence on some of the parameters in the model (e.g., possibility of acquisition of resistance during treatment or treatment outcomes for MDR+F TB). These potential challenges can be mitigated by simplifying the model or by making assumptions based on the most relevant evidence. In addition, a decision tree and/or Markov model can be used instead of dynamic model if I face major challenges in model fitting or find this model better to reflect multiple stages of the treatment process. Lastly, South Africa and Pakistan are proposed as study settings, but this is subject to change after further discussion with country stakeholders depending on the availability of data and their interests to collaborate.

Investigator

PhD applicant [name deleted]: I graduated from [institution deleted] with a master's degree in [programme deleted]. I have been working in [deleted] as a [deleted] and for [deleted] as a [deleted]. My recent research experience includes [applicant-specific employment history and skills development deleted].

Supervisory team: *Dr Finn McQuaid* is a mathematical modeller and will be the primary supervisor from LSHTM. He is the TB Modelling and Analysis Consortium (TB MAC) Secretariat Epidemiologist and co-director of the TB centre. He has experience in TB modelling at the country level and researching drug-resistant TB. *Dr Gwen Knight* is a co-director of the AMR centre at LSHTM and has been appointed to the WHO's advisory group on the bacterial priority pathogen list. Her current research explores the prevalence of resistance to infection by age. I will add country stakeholders in my advisory committee.

Environment

The research environment at LSHTM, especially TB Centers, Centre for Mathematical Modelling of Infectious Diseases, Global Health Economics Centre, and Antimicrobial Resistance Centre will provide an optimal environment to conduct my proposed research as well as gain a broader scientific knowledge in tuberculosis, antimicrobial resistance, economics, and modelling.

Budget

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Timeline

Task	Year 1	Year 2	Year 3

Activity 1: Conduct a systematic review to summarise the available evidence on empirical treatment outcomes of different regimens on MDR/RR-TB patients	x		
Activity 2: Develop a dynamic model to estimate health outcomes of different regimens	x	x	
Activity 3: Conduct a cost-effective analysis of different regimens		x	x
Stakeholder/public engagement	x	x	x
Conference presentations and peer-reviewed journal publications		x	x
Decision-support tool & making the modelling code publicly available and collect feedback for model improvements		x	x
Communicate the major findings with national stakeholders to translate evidence into technical policy guidelines			x

References

1. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. apo.org.au; 2016.

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3. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update [Internet]. 2022 [cited 2023 Jan 10]. Available from: https://www.who.int/publications/i/item/9789240063129

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5. Monedero-Recuero I, Gegia M, Wares DF, Chadha SS, Mirzayev F. Situational analysis of 10 countries with a high burden of drug-resistant tuberculosis 2 years post-UNHLM declaration: progress and setbacks in a changing landscape. Int J Infect Dis. 2021 Jul;108:557–67.

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