Guiding pragmatic treatment choices for rifampicin-resistant tuberculosis in the absence of second-line drug susceptibility testing

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Second line antimicrobial susceptibility test results are frequently unavailable for people with tuberculosis. We propose a method for comparing risks and benefits of different treatment regimens for rifampicin-resistant tuberculosis when accurate results are unavailable.

With recent expansion in the use of bedaquiline and limited access to accurate antimicrobial susceptibility testing (AST), we read with concern of examples of the high prevalence of bedaquiline resistance detected in *Mycobacterium tuberculosis* isolates(1). Choosing the most effective regimen for treatment of drug-resistant tuberculosis (TB) is crucially important(2) and requires accurate and timely AST. In the last decade there has been wide roll-out of rapid molecular tests that can identify *M.tuberculosis*, and mutations conferring rifampicin resistance (RR). However, for potent second-line drugs such as fluoroquinolones(3), bedaquiline, pretomanid and linezolid, AST is either unavailable, has poor coverage or generates delayed results. To support clinicians, policymakers must provide pragmatic treatment recommendations for situations where a patient is diagnosed with RR-TB but where additional AST results for second-line drugs are delayed or unavailable.

Worldwide, approximately half of patients with RR-TB do not have access to rapid fluoroquinolone AST(3). The detection of fluoroquinolone resistance in those with RR-TB has historically necessitated longer and more toxic treatment regimens. Although recent global policy updates permit the programmatic use of a 6-month regimen regardless of fluoroquinolone susceptibility(4), fluoroquinolones remain a key drug group in the treatment of drug-resistant TB. While access to newer regimens remains limited, policymakers are faced with two choices where fluoroquinolone susceptibility is unknown. They could recommend starting a treatment regimen that assumes fluoroquinolone susceptibility, or a regimen that assumes fluoroquinolone resistance. Either regimen could be adjusted if AST results became available. Both options have risks that vary according to individual and population characteristics, particularly the prevailing fluoroquinolone resistance prevalence. These risks include treatment failure and onward transmission (when a regimen is given assuming fluoroquinolone-susceptibility to a patient with a fluoroquinolone-resistant organism) or unnecessary adverse events (AEs) and increased costs (when a regimen is given assuming fluoroquinolone-resistance to a patient with a fluoroquinolone-susceptible organism). Policymakers must choose strategies, incorporating individual and population factors, that minimise risk on a population level. Here we propose an approach to assist in this decision-making, allowing for a quantitative comparison of the

risk and benefit between two regimens, to support treatment guideline development for when key AST information is unavailable.

We developed a model to estimate the effects of empirically prescribing a regimen for fluoroquinolone-resistant TB in patients with RR-TB, compared to a regimen for RR-TB without fluoroquinolone resistance. Our model takes estimates of regimen performance and calculates the difference in mortality and severe AEs (grades 3/4) between regimens across different anticipated levels of drug-resistance prevalence. To describe the relative difference between regimen choices, we use the number of severe AEs per death prevented. This would allow policymakers to quantitatively compare the risks and benefits of two regimens in their setting, and to make a choice based on the risk they are willing to accept (tolerance threshold). For example, would one additional severe AE for every additional death that the use of a particular regimen prevented be acceptable? What about ten severe AEs per death prevented, or 100 severe AEs? From a patient's perspective, would a higher likelihood of suffering a debilitating SAE be acceptable if the risk of death declined?

The mean population-level mortality risk on RR-TB treatment (M_i^P) for a given setting with prevalence of fluoroquinolone resistance (*P*) in RR-TB when treated with regimen *i* is calculated by interpolating the mortality risk for the regimen amongst people with fluoroquinolone-susceptible RR-TB (S_i), and the mortality risk for the regimen amongst those with fluoroquinolone-resistant RR-TB (R_i):

$$M_i^P = S_i\,(1 - P) + R_i\,(P)$$

We denote the risk of severe AEs on regimen i by T_i. We then calculate the AEs incurred per death prevented at the population-level (C) in moving all patients from a regimen for fluoroquinolone-susceptible RR-TB (s) to a regimen for fluoroquinolone-resistant RR-TB (f):

$$\text{AEs incurred per death prevented (C)} = (T_f - T_s) \,/\, (M_s^P - M_f^P)$$

This indicator quantifies the trade-off between safety and efficacy that is incurred, for a given prevalence of resistance, by switching from a regimen designed for susceptible disease to one designed for resistant disease.

The treatment strategy recommended by a policymaker is dependent on the tolerance threshold for severe AEs incurred per death prevented and the characteristics of the regimens:

- If regimen population-level mortality risk $M_s^P - M_f^P < 0$ and toxicity $T_f - T_s > 0$, the optimal regimen is *s*
- If $M_s^P - M_f^P > 0$ and $T_f - T_s < 0$, the optimal regimen is *f*
- If $M_s^P - M_f^P > 0$ and $T_f - T_s > 0$, the optimal regimen is *f* when C is above the threshold, otherwise *s*
- If $M_s^P - M_f^P < 0$ and $T_f - T_s < 0$, the optimal regimen is *s* when C is above the threshold, otherwise *f*

To allow interactive exploration of predictions, including the effect on costs, we deployed a web application (https://jay-achar.shinyapps.io/fqmodelr/). This allows characteristics of both regimens to be defined and estimates AEs incurred per death averted over a range of drug resistance prevalence scenarios and tolerance. We demonstrate below how this approach might be used in practice.

During 2018-19, the South African National TB Programme updated their treatment recommendations for RR-TB(5, 6) in response to changes in global guidance to deprioritise injectable drugs in favour of newer and repurposed drugs(7). Eligible patients with new, non-severe, fluoroquinolone-susceptible RR-TB could be treated with a 9–11-month all-oral regimen (bedaquiline, levofloxacin, clofazimine, ethambutol, pyrazinamide, high-dose isoniazid and at least 2 months of linezolid; Regimen 1), while patients with fluoroquinolone-resistant RR-TB strains would be treated with a longer, individualised regimen, typically including bedaquiline, linezolid, clofazimine, terizidone and delamanid (Regimen 2). Amongst South Africans diagnosed with RR -TB, fluoroquinolone resistance is detected in approximately 11%(8).

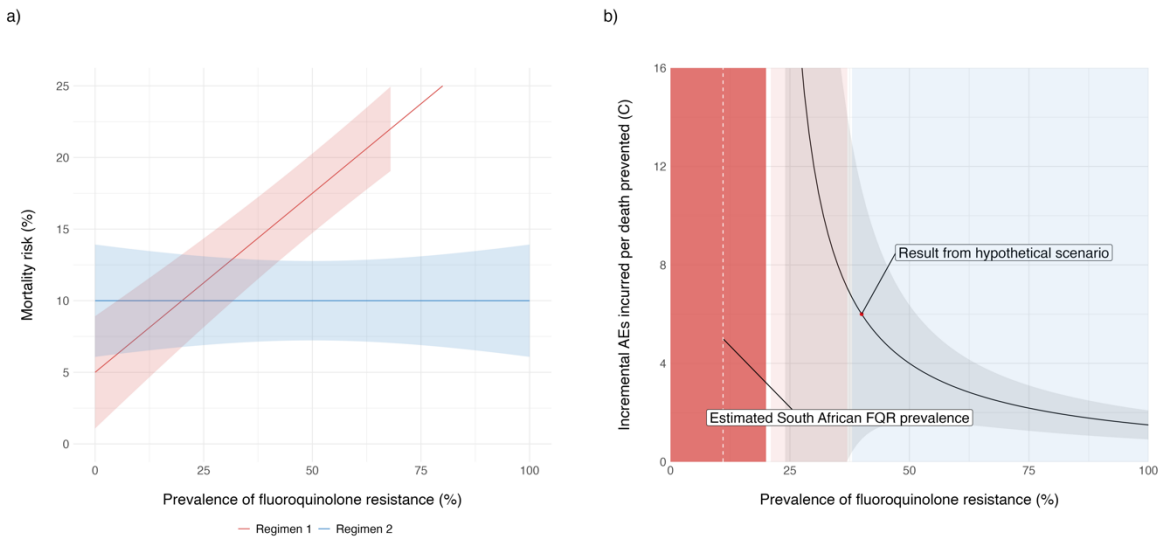

Figure 1 a) Regimen mortality risk by prevalence of fluoroquinolone resistance for Regimen 1 (red) and Regimen 2 (blue) with 95% uncertainty intervals; b) Incremental adverse events incurred per death prevented when switching from Regimen 1 to Regimen 2 with 95% uncertainty intervals; Colour key: Regimen 1 optimal (solid red area), Regimen 1 preferred in light of policymaker tolerance of 7 severe AEs per death prevented (light red area), Regimen 2 preferred in light of policymaker tolerance of 7 severe AEs per death prevented (light blue area). Since information on the efficacy and toxicity of these two regimens in different populations is limited, we make assumptions to illustrate the point. In our hypothetical scenario, suppose the mortality risk of Regimens 1 and 2 is 5%/10% in fluoroquinolone-susceptible RR-TB cases and 30%/10% in fluoroquinolone-resistant RR-TB cases respectively, and that the risk of severe AEs is 20%/50% respectively. Uncertainty boundaries for mortality risk have been set to 2% and 3% for severe AE risk. Finally, we include 7 severe AEs per death prevented as the policymaker tolerance.

Using illustrative regimen characteristics(Figure 1), mortality associated with Regimen 1 is lower than Regimen 2 when drug resistance prevalence is less than 20% but increases above that. The expected AEs incurred per death prevented by using Regimen 2 over Regimen 1 decrease as resistance prevalence increases (Figure 1B). At South Africa's current prevalence of fluoroquinolone resistance (dashed line), population-level mortality and toxicity from Regimen 1 is less than Regimen 2, so the former would be recommended (Figure 1B). However, in a setting where prevalent fluoroquinolone resistance is higher - e.g. Pakistan (40% (8)), policymakers faced with the same regimen choice and tolerance threshold would recommend Regimen 2.

We developed this model to demonstrate the utility of a quantitative approach to support national policymakers in recommending RR-TB treatment regimen choices for when second-line AST is unavailable. To make this approach a useful tool for policymakers, we envisage a body of work (including model validation) to explore key elements of the decision(9), integrating feedback from national policymakers to consider other measures such as resistance amplification, loss to follow-up and treatment failure, and treatment costs for healthcare systems and patients.

With baseline resistance to bedaquiline detected in 3.8% of patients in one South African cohort(10) and resistance-conferring mutations emerging in 15.3% of patients receiving treatment(1), tools to compare regimens where emerging resistance to other key drugs is anticipated are essential. Our proposal for a quantitative, comparative approach could support policymakers as new regimens targeting bedaquiline- or linezolid-resistant phenotypes are studied, and could also have applications beyond TB to any scenario where antibiotics are used.

National TB Programmes must prioritize access to second-line AST to allow regimens to be tailored to individuals with RR -TB. Where AST remains inaccessible, national recommendations should provide support for clinicians in choosing the most appropriate empirical treatment regimens. By simultaneously considering the role of toxicity and efficacy, we highlight the trade-offs that must be balanced in this difficult situation.

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