Published: September 2014

How can mathematical modelling advance TB control in high HIV prevalence settings?

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Existing approaches to TB control have been no more than partially successful in areas with high HIV prevalence. In the context of increasingly constrained resources, mathematical modelling can augment understanding and support policy for implementing strategies most likely to bring public health and economic benefits.

Recognising the urgency of TB control in high HIV prevalence settings and the potential contributions of modelling, the TB Modelling and Analysis Consortium (TB MAC, www.tb-mac.org) convened its first meeting between empirical scientists, policy makers and mathematical modellers in September 2012 in Johannesburg, South Africa.

Here we present a summary of results from these discussions, as well as progress made in South Africa. This is an abridged version of a paper published recently, and is presented on behalf of co-authors and meeting participants.

What are mathematical models?

Mathematical models are usually defined as mechanistic representations for how disease burden is established. They are useful tools for projecting the potential public health and economic impact of interventions when population-level empirical data (e.g. from cluster-randomized trials) are unavailable and too expensive, too time-consuming, or unethical to acquire (1). Models can also provide insight by simplifying complex systems into frameworks that are more easily understood. For example, the relationship between the scale up of antiretroviral therapy (ART) and the subsequent impact on population level TB incidence is difficult to predict, but can be understood using a combined model of HIV and TB transmission (2). In a time of limited resources, mathematical modelling, grounded in the available data, can be an important guide for the rational use of resources in TB control, development pipelines of new drugs, vaccines or diagnostics, and highlight what empirical data gaps need to be filled.

Contributions of modelling to understanding of TB natural history and control in high HIV prevalence settings

Some key findings from a systematic literature review about TB in high HIV prevalence settings are described here:

Natural history of TB in high HIV prevalence setting

Already in 1992 Schulzer et al. published the first model to quantify the potential disastrous consequences of the emerging association between HIV and TB (3). Later confirmed by others, her model predicted the steep rise in TB incidence which was to overwhelm many TB programmes in usually low to middle income settings (4).

Interventions to reduce TB in high HIV prevalence settings

Models have explored a variety of interventions that could reduce TB, including preventive therapy (e.g. isoniazid (INH) monotherapy), although the lack of data on the level and duration of protection offered by isoniazid prophylactic treatment (IPT) let to wide variations in assumptions, from a 34% (5) to 100% (6) reduction in the risk of TB during IPT, while the assumed duration of protection post-therapy varied between immediate loss of effect (7) to lifelong protection (6). Recent work following the meeting has focussed on addressing some of these data gaps (8).

Impact of additional interventions for HIV-associated TB

Mathematical models of TB-HIV have also been used to explore enhancements to DOTS-based programmes, including active case finding (9) and expanding access to culture-based diagnosis or drug sensitivity testing (10). These models usually found that such enhancements could provide substantial benefits. In 2010 World Health Organization (WHO) endorsed a new TB diagnostic test (Xpert MTB/RIF), generating a need for models that explored costs, benefits as well as operational aspects of integrating these novel devices into existing TB care and control infrastructures.

Implementations of interventions for TB

Models can look also inform policy questions on implementation of new interventions and tools. Often, such models will include an operational modelling component that explicitly captures key parts of the health system (11). While the importance of the operational modelling of combined TB-HIV interventions was recognised, little work has been done in this area with only one paper addressing this issue, which evaluated the impact of a novel diagnostic tool (11).

A modelling agenda to support TB control in high HIV prevalence settings

Based on past work and current needs, a modelling research agenda was outlined that identified five high priority areas for future modelling efforts including: 1) the difficult diagnosis and high mortality of TB-HIV; 2) the high risk of disease progression; 3) TB health systems in high HIV prevalence settings; 4) Uncertainty in the natural progression of HIV-associated TB; 5) Combined interventions for HIV-associated TB. Here we give some of the considerations, and potential contributions of modelling for three high priority areas.

Priority Area 1: Diagnosis and mortality of HIV-associated TB

Among people living with HIV (PLHIV), TB is both more difficult to diagnose than in HIV negative individuals, and a major cause of death if untreated (4). To reduce mortality, early diagnosis and the resulting access to lifesaving treatment for TB and often HIV is key. Therefore, it is likely that intensified case-finding strategies (12) (which aim to diagnose individuals at earlier stages of disease) and improved diagnosis (10) might have a disproportionate morbidity and mortality benefit among HIV positive individuals with active TB disease. However, given the likely much shorter duration of overall TB disease and higher probability of smear-negative (i.e. presumably less infectious) disease (4), the impact of such strategies on TB transmission and future TB disease incidence may be less pronounced.

Although the population-level benefits of intensified TB case finding and improved TB diagnosis among PLHIV have not been conclusively demonstrated (12), models can use the best available data to help identify the approaches to diagnosis (and case-finding that are likely to be most (cost-) effective if scaled up at the population level. For example, models that incorporate routes of care-seeking and diagnosis among individuals with HIV and TB can augment these findings by relating them to existing systems of care. Progress in this area is therefore clearly dependent on increasing the empirical evidence base related to organization of health systems for HIV and TB in resource-constrained settings (Priority Area 3) as well as the progression (Priority Area 2) and pathogenesis (Priority Area 4) of HIV-associated TB.

Priority Area 3: TB health systems in high HIV prevalence settings

TB requires intensive, often directly-observed, therapy with a short course of inexpensive drugs, whereas HIV requires lifelong, mostly unsupervised, therapy with expensive agents and regular therapeutic monitoring. However, in HIV-endemic regions, the patients taking these drugs are often the same, and synergistic efforts to link TB and HIV care can improve systems of diagnosis and treatment at relatively low costs (13).

Health systems in these settings must therefore adapt to this reality. Operational and economic models have great potential for informing decisions about how to structure health systems, in particularly to inform the optimal level of service integration. Such models can identify ways to resolve both allocative inefficiencies (e.g. by combining resources in optimal ways to provide services for those who are co-infected) and technical inefficiencies (e.g. by combining services in optimal ways to improve outcomes). They also can assist in understanding the delays and costs that service users face, and how to reduce them.

Combined health system and economic models could also help identify the corresponding health systems investments needed to support the efficient operation of both TB and HIV services. To date, such health system models have been underutilised (11); however, as resources for TB and HIV care become increasingly constrained, and new technologies continue to be scaled-up, health systems models will become increasingly important in helping to maximise value for money.

Priority Area 4: Uncertainty in the natural history of HIV-associated TB

All epidemiological models of infectious diseases are limited by the current state of knowledge of the natural history of the pathogen. In the case of HIV-associated TB we must consider not only two individual natural histories, but the interaction of these two (potentially) chronic infectious diseases as well. The need for a more thorough understanding of the natural history of HIV-associated TB is clear.

The natural history of untreated HIV is well-known from cohort studies of HIV-infected individuals before the availability of ART, and some insight exists into the natural history of TB from the pre-chemotherapy era (1950s). However, the availability of TB chemotherapy throughout the HIV era has meant that, for ethical and methodological reasons, studies to acquire this information for HIV positive TB patients are not possible – including the infectious duration of untreated TB (14) (and its relationship to CD4 count and/or ART), and TB mortality risk (15) and risk of reinfection and progression to disease relative to HIV-uninfected individuals (Priority Area 2).

In order to accurately project the impact of interventions for TB in HIV-endemic regions, it is essential to better understand these elements of natural history. For example, the impact of early diagnosis cannot be accurately estimated without knowing the duration of infectiousness likely to be averted.

Empirical studies that provide further insight into these areas are urgently needed; in the interim, models using existing data may be able to better define and communicate the bounds of our uncertainty.

Integrating modelling into policy

While we know the historical and potential future contributions of modelling, the most important step is how to ensure modelling results are used to guide and support the ongoing process of TB care and control strategy policy setting. Efficient and rapid progress towards completion of this modelling agenda will require co-ordination between the modelling community and key stakeholders, including advocates, health policymakers, donors, and national or regional finance officials. A continuing dialogue will ensure that new results are effectively communicated and new policy-relevant questions are addressed swiftly.

In South Africa, encouraging progress has been made to achieve this dialogue. As part of a newly set up National Department of Health 'TB Think Tank', which aims to link scientific evidence with policy, policy makers and modellers will meet quarterly to identify key questions as well as collate and use quantitative evidence to input into policy making. The synergy between policy and modelling will help South Africa to continue its progress to controlling the TB epidemic.

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