

## Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'

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### SUMMARY

Infectious disease models are important tools for understanding epidemiology and supporting policy decisions for disease control. In the case of tuberculosis (TB), such models have informed our understanding and control strategies for over 40 years, but the primary assumptions of these models—and their most urgent data needs—remain obscure to many TB researchers and control officers. The structure and parameter values of TB models are informed by observational studies and experiments, but the evidence base in support of these models remains incomplete. Speaking from the perspective of infectious

disease modelers addressing the broader TB research and control communities, we describe the basic structure common to most TB models and present a 'wish list' that would improve the evidence foundation upon which these models are built. As a comprehensive TB research agenda is formulated, we argue that the data needs of infectious disease models—our primary long-term decision-making tools—should figure prominently.

**KEY WORDS:** tuberculosis; infectious disease transmission; theoretical models

TUBERCULOSIS (TB) is a curable disease, yet it kills 1.7 million people every year.<sup>1</sup> In response to this unacceptable disease burden, leaders of the TB research community are formulating a coordinated research agenda.<sup>2,3</sup> Meanwhile, policy makers and health officials at all levels must make decisions about how best to develop, implement and scale up TB control measures. These individuals often rely on mathematical models that estimate the population-level impact of interventions on TB transmission.<sup>4</sup> The first models to use assumptions about the natural history and transmission dynamics of TB to project the population-level impact of control strategies were developed in the 1960s.<sup>5–7</sup> Since then, TB models have provided support for the implementation of many policies such as the DOTS strategy,<sup>8</sup> and have informed the research agenda for new interventions, including drugs, diagnostics and vaccines.<sup>9</sup>

Global disease control programs face the task of identifying which interventional strategies offer the highest probability of improving population health. For example, in the coming 5 years, many national policy makers will decide whether to scale up novel TB diagnostics (such as Xpert® MTB/RIF, Cepheid, Sunnyvale, CA, USA) that have demonstrated impressive operational characteristics (e.g., sensitivity/

specificity), but are not known to reduce TB incidence or mortality at the population level. Studies of such population-level outcomes (e.g., cluster-randomized trials) are expensive and time-consuming, they can address only a limited number of questions and they are often difficult to generalize. When such experimental evidence is not feasible or not yet available, infectious disease models provide a quantitative framework to project population-level effects (e.g., reduced TB incidence) from evidence at the individual level (e.g., operating characteristics of a diagnostic test).

Published descriptions of infectious disease models typically describe the impact of various assumptions encoded in the model. These analyses (e.g., sensitivity and uncertainty analyses<sup>10</sup>) are often described in technical language and, due to space limitations, are placed in supplementary appendices. As such, readers may not be fully aware of which modeling assumptions most strongly influence model behavior. Many assumptions shared across TB models are both highly influential to model behavior and based on limited empirical data.

Our goal here is to highlight these assumptions as priority areas where additional research can directly lead to improved models, and thereby to better decision making for TB control.

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To advance this goal, we first provide an introduction to the basic structure and simplifying assumptions of many TB models. We then present a simple infectious disease model, calibrated to global estimates of TB incidence and prevalence, that we use to identify the most influential modeling assumptions and the corresponding gaps in evidence. Finally, we use this model to generate a 'wish list' of data elements that would bridge these gaps and increase both the usefulness of TB models and our confidence in their results.

## TUBERCULOSIS MODELS: BASIC STRUCTURE

As infectious disease models are developed to answer specific questions, each model's structure will reflect unique aspects of the question posed. For example, a model focusing on drug-resistant TB must consider processes related to the acquisition and transmission of drug resistance and may therefore address TB-HIV (human immunodeficiency virus) in simplistic fashion, whereas a model of TB-HIV co-dynamics may do the opposite. Nevertheless, most TB models share common structural elements, which form the basis of our discussion here.

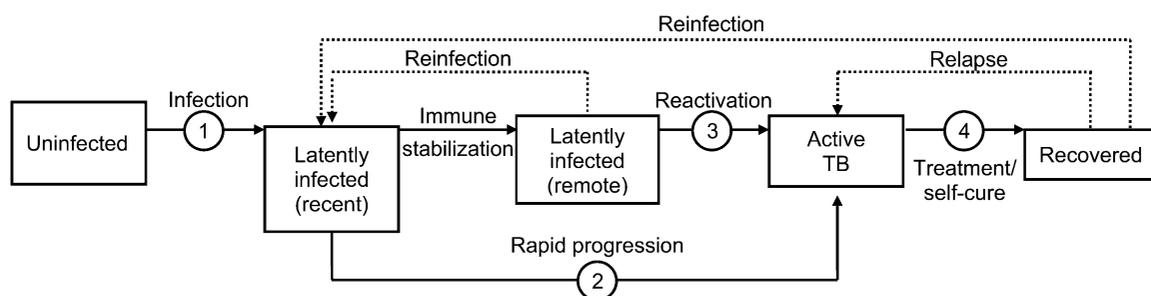
A common and relatively simple modeling approach is the compartmental model, which describes a population divided into mutually exclusive health states (compartments) and uses differential equations to represent the mechanisms of transition between these health states. A prototypical TB model might include five compartments with respect to TB disease status: non-infected, latently infected (recent), latently infected (remote), active TB and recovered (Figure 1). Such a model could be used to simulate a TB epidemic under different sets of assumptions to project the effects of alternative decisions (e.g., TB control interventions).<sup>11</sup> An advantage of infectious disease models for decision making is that the current state of the model (e.g., size of the 'active TB' compartment) influences rates of flow between compartments (e.g., size of the 'infection' arrow in Figure 1). This allows infectious disease models to capture the feedback loops and non-linear dynamics typical of infectious

disease epidemics, such as immediate reductions in disease duration leading to future reductions in transmission. While other dynamic modeling approaches (e.g., individual-based models<sup>12</sup>) also exist, we focus here on compartmental models, as they have been used most commonly to guide policy decisions.

## TUBERCULOSIS MODELS: ASSUMPTIONS

When building infectious disease models, modelers should typically make two different types of choices.<sup>4</sup> First, they must specify the model structure: the number of compartments and how they relate to each other. Additional complexity can be built around a simple structure (e.g., the five compartments in Figure 1) to answer policy questions of interest. However, increased model complexity comes at a substantial cost. For example, dividing the model population into two sub-populations (e.g., HIV-positive vs. HIV-negative) may double the number of compartments and thus the number of parameters required. Unnecessarily complex models often lack the transparency and interpretability needed to inform appropriate decision making by policy makers. As a result, the simplest model that can adequately represent relevant phenomena is generally preferred.<sup>13</sup> Testing the effects of adding model complexity (i.e., structural assumptions) is difficult, often requiring the construction of parallel models with different structures<sup>14–16</sup> or incorporating more advanced modeling techniques (e.g., Bayesian networks<sup>17</sup>). To date, such analyses have been infrequently performed, and there is no standardized way to include them in traditional sensitivity analyses; thus, while addressing 'structural' uncertainty is an important consideration for building better TB models, we do not discuss this challenge in further detail here.

Once the compartmental structure of a model is developed, modelers must specify the parameters that determine the flows between model compartments. For example, the rate at which infected individuals develop active TB depends on a rate of progression during latency; this rate must be introduced as a



**Figure 1** Simplified TB model: the basic structure that is common to many compartmental transmission models of TB. Health states are represented by boxes and transitions are indicated by arrows. We highlight assumptions necessary to estimate rates associated with four basic processes (in circles): infection, rapid progression, reactivation, and treatment/recovery. Mortality (not shown) also occurs from each box. TB = tuberculosis.

**Table 1** Simplified model of TB transmission

We used differential equations to develop a simplified model of TB transmission, as shown in Figure 1. The differential equations used were:

- 1 Susceptible, S:  

$$dS/dt = (\text{birth}) - (\text{infection}) * S - (\text{mortality}) * S$$
- 2 Latently infected (recent), L1:  

$$dL1/dt = (\text{infection}) * [S + (1 - \text{protection}) * (L2 + R)] - (\text{progression} + \text{stabilization} + \text{mortality}) * L1$$
- 3 Latently infected (remote), L2:  

$$dL2/dt = (\text{stabilization}) * L1 - [\text{reactivation} + (1 - \text{protection}) * (\text{infection}) + \text{mortality}] * L2$$
- 4 Actively infected, A:  

$$dA/dt = (\text{progression}) * L1 + (\text{reactivation}) * L2 + (\text{relapse}) * R - (\text{treatment} + \text{self-cure} + \text{mortality} + \text{TB mortality}) * A$$
- 5 Recovered, R:  

$$dR/dt = (\text{treatment} + \text{self-cure}) * A - [\text{relapse} + (1 - \text{protection}) * (\text{infection}) + \text{mortality}] * R$$

For these equations, each capital letter represents the number of people in the compartment (per 100 000), and  $dX/dt$  denotes the change in compartment size X per unit time. We used the following quantities:

- birth = sum of all mortality (to maintain a stable population)
- infection = (transmission rate)\*A  
 —The transmission rate is calibrated to give an annual steady-state TB incidence of 128/100 000/year, the global average.<sup>1</sup>
- mortality = 1/70 (life expectancy of 70 years)
- protection = 0.50 (50% efficacy against reinfection if latently infected or recovered)<sup>18,19</sup>
- progression = 0.03 per year (primary progression after recent infection)<sup>19</sup>
- stabilization = 0.2 per year ('recent' infection period of 5 years)<sup>19</sup>
- reactivation = 0.0005 per year (reactivation after remote infection)<sup>20</sup>
- relapse = rate of relapse after recovery, calibrated such that 11% of incident TB is retreatment<sup>1</sup> (final value = 0.0034/year)
- treatment = rate of successful diagnosis and treatment, calibrated to give steady-state TB prevalence of 178 per 100 000, the global average<sup>1</sup>
- self-cure = 0.167 per year (spontaneous recovery without treatment, 50% case fatality)<sup>21</sup>
- TB mortality = 0.167 per year (mortality rate of untreated TB)<sup>21</sup>

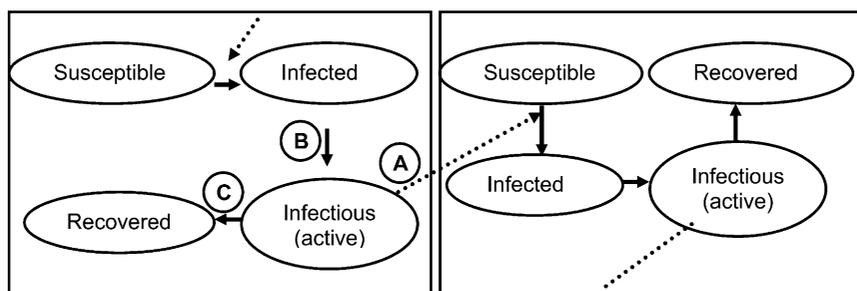
TB = tuberculosis.

parameter in the model. Where possible, parameter values should be well supported by data obtained through observation or experimental study. This is

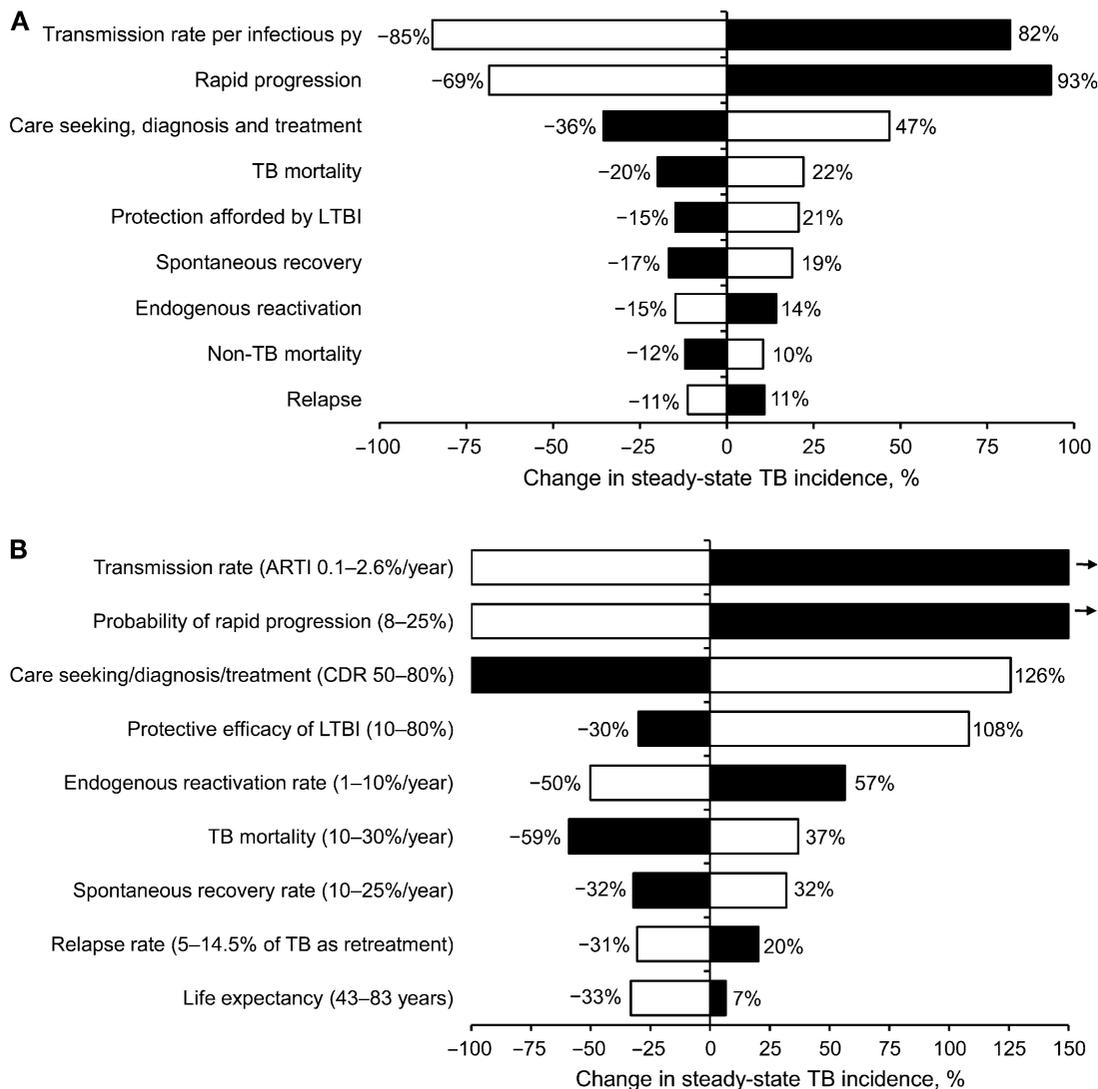
most important for parameters with strong effects on model behavior. To identify the most pressing data needs for building better TB models, therefore, we created a simple model (see basic structure in Figure 1 and mathematical description in Table 1) to identify and quantify parameters that 1) strongly influence model behavior, and 2) carry substantial uncertainty as to their appropriate contemporary value.

## REPRODUCTION NUMBERS AND THE TUBERCULOSIS TRANSMISSION CHAIN

As a framework for identifying target parameters, we used a key composite measure that governs the spread of a pathogen in a population: the basic reproduction number ( $R_0$ ).  $R_0$  is defined as 'the average number of secondary (cases) produced when one (active case) is introduced into a host population where everyone is susceptible',<sup>22</sup> and it provides a threshold effectiveness of disease control needed to achieve elimination (i.e.,  $R_0 < 1$ ). For an endemic disease such as TB, where entirely uninfected populations are not encountered, the effective reproduction number  $R_e$  describes the expected number of secondary cases generated by each infectious source case in an existing population. Both  $R_0$  and  $R_e$  depend on three quantities: the average number of secondary infections caused per unit of infectious time, the source case's duration of infectiousness, and the probability that a secondary infection will progress to active, infectious TB. These quantities can be envisioned as processes in a TB transmission chain (Figure 2). Parameters that directly influence one of these three processes will modify the reproduction number and thereby affect TB transmission. We therefore classify parameters according to their effects on these three processes. We designed the model to be globally representative, but also to fit a low-incidence scenario (incidence 5 per 100 000 per year) to evaluate differences based on underlying incidence. For each parameter, we describe the relevant process, detail existing data (and limitations) for informing its value and quantify the degree



**Figure 2**  $R_e$  and the transmission chain of TB. Each box represents a person in the TB transmission chain. Parameters that have the greatest influence on  $R_e$ , and thus on projected TB incidence and mortality, in mathematical models typically affect either A = the rate of TB transmission per infectious person-year; B = the probability of developing infectious TB; or C = duration of infectiousness.  $R_e$  = effective reproduction number; TB = tuberculosis.



**Figure 3** Sensitivity and uncertainty of model outcomes with parameter variation. Bars represent the change in steady-state TB incidence in a simplified model of TB transmission (Figure 1) that would occur with specified increases (black bars) and decreases (white bars) in model parameters. The model is calibrated to globally represent TB incidence and prevalence rates (Table 1); **A**) sensitivity of the model to a one-way 25% change in each parameter value given in Table 1; **B**) corresponding changes in steady-state incidence when parameters are varied across a reasonable uncertainty range, as specified (100% reduction corresponds to  $R_e < 1$  or eventual elimination, and rightward-pointing arrows denote changes  $> 150\%$ ). In both analyses, the seven most influential parameters describe the probability of progression to active TB, the rate of TB transmission per infectious person-year, or the duration of TB infectiousness. In a low-incidence scenario (incidence 5/100 000/year), the rate of endogenous reactivation was proportionally more important (ranked fourth in panel **B**), and the degree of protection afforded by LTBI was less important (ranked last), but other findings were similar. Within existing levels of uncertainty or heterogeneity, the TB transmission rate, probability of rapid progression and diagnosis/treatment rate could each generate steady-state TB incidence rates across all reasonable values, demonstrating the importance of appropriately specifying these parameters in setting-specific models. The two least influential parameters describe non-TB mortality and relapse, and were not included in the 'wish list' (Table 2). py = person-year; TB = tuberculosis; LTBI = latent TB infection; ARTI = annual risk of TB infection; CDR = case detection rate (defined as the proportion of all patients with TB who are detected);  $R_e$  = effective reproduction number.

to which changes in that value alter the parent model's estimate of TB incidence (Figure 3).

### TUBERCULOSIS MODELER'S 'WISH LIST'

#### *Parameters affecting the rate of transmission per infectious person-year*

**DESCRIPTION.** The rate of TB transmission depends on the frequency of infectious contacts and the prob-

ability of transmission during each contact event (Figure 1, Process 1).<sup>23</sup>

**EXISTING APPROACHES AND LIMITATIONS.** Classically, based on analysis of data from the Netherlands and India between 1920 and 1970, individuals with smear-positive TB were assumed to generate 8–12 secondary infections per year;<sup>24</sup> most models that fit TB incidence to transmission rates in high-burden settings have obtained similar results;<sup>25,26</sup> however, more

recent data suggest that this estimate may be 50% (or more) too high.<sup>27,28</sup> However, TB transmission is quite heterogeneous:<sup>29</sup> areas with hyperendemic transmission, such as South African townships,<sup>30,31</sup> likely have per-case transmission rates over 10 times as high as in modern industrialized countries,<sup>32</sup> although similar transmission rates were seen historically.<sup>33</sup> Rates of TB transmission may also differ by strain<sup>16,34,35</sup> and prevalence of social or other determinants of risk.<sup>36</sup> The TB transmission rate is among the most important determinants of epidemic severity,<sup>37</sup> and by extension, effectiveness of control interventions (e.g., active case finding, improved diagnostics) that aim to reduce the duration of transmission. Appropriate estimation of TB transmission rates across different geographic settings and times is thus as critical as it is difficult.

Another important consideration is the rate of TB transmission at different times in an individual's course of disease. Largely because the primary existing diagnostic test (sputum smear microscopy) correlates with infectiousness, most TB models assume that transmission is constant over a given individual's disease course. In other words, TB is assumed to be either infectious/smear-positive pulmonary or non-infectious,<sup>8</sup> with some models incorporating smear-negative pulmonary TB at a lower infectiousness, usually 20–25% that of smear-positive TB, based on molecular epidemiology tracing of patients with known smear status.<sup>38,39</sup> However, all smear-positive TB develops through a period of smear negativity, and smear status is itself dependent on laboratory characteristics.<sup>40</sup> If symptoms, infectiousness, health-seeking behavior and smear positivity (or ability to diagnose TB with other tests) all occur simultaneously, then passive smear microscopy is expected to have substantial impact on TB transmission. However, to the extent that TB transmission occurs before development of symptoms or sputum smear positivity, or cases remain persistently smear-negative, alternative diagnostic strategies, such as active case finding with culture or molecular methods, would be necessary to curb transmission.

#### *Parameters affecting the probability of progression to active/infectious tuberculosis*

##### *Rapid progression*

**DESCRIPTION.** Although it is undisputed that individuals can develop active TB many years after their initial infection, the physiology of latent TB infection (LTBI) remains a poorly understood process at the cellular level, likely representing a spectrum of persistent immune responses.<sup>41,42</sup> The risk of progression to active infectious disease declines with time since infection, but as the pattern of this decline is not precisely known, TB models often simplify LTBI into a set of compartments based on time since infection. Since 1969, a cut-off of 5 years has frequently been used to distinguish 'rapidly progressive' TB from

'endogenous reactivation,'<sup>18,43,44</sup> although other cut-offs may be equally reasonable from a biological perspective. As rapid progression and endogenous reactivation are clinically similar, it is impossible to directly measure the proportion of incident TB that results from these two respective processes. Furthermore, as time of infection is generally unknown, it is likewise difficult to assess the time from infection to disease (Figure 1, Process 2).

**EXISTING APPROACHES AND LIMITATIONS.** We currently rely primarily on modeling studies that fit population-level data to the annual risk of TB infection over time in historical data sets (e.g., the Netherlands<sup>8,18</sup> and England and Wales<sup>19</sup>), results from large population-based trials of interventions (e.g., bacille Calmette-Guérin vaccine<sup>45</sup>), and molecular epidemiology studies that attempt to determine the proportion of incident TB that can be linked to other recent cases.<sup>46–48</sup> These studies suggest that the risk of rapid TB progression is greater in adults than in children and declines over a period of 5 years after infection,<sup>19</sup> with up to 45% of all disease occurring in the first year after infection.<sup>49</sup> No study to our knowledge has comprehensively evaluated the risk of rapid progression after infection in modern high-burden settings, which may differ dramatically from historical cohorts<sup>50–52</sup> in intensity of exposure, degree of natural protection against progressive disease in the host, and propensity of the pathogen to induce rapid progression.<sup>53,54</sup> Furthermore, these dynamics remain almost completely unspecified among people living with HIV, limited mostly to small outbreak investigations before the availability of antiretroviral therapy (ART).<sup>23,55–58</sup> These studies suggest that 75% or more of TB infections progress rapidly to active disease among people living with HIV, but this proportion is likely much lower in individuals on ART<sup>59</sup> or with higher CD4 T-cell counts.<sup>58,60</sup> Other determinants of susceptibility,<sup>61</sup> including diabetes mellitus,<sup>62,63</sup> nutritional status<sup>64</sup> and smoking,<sup>65</sup> also affect progression from infection to active TB, although it remains unknown whether this is better modeled as a change in the proportion of individuals progressing rapidly after initial infection or the rate at which that progression occurs. These effects may have important implications for the effectiveness of TB control interventions such as isoniazid preventive therapy (IPT)<sup>66,67</sup> and contact investigation,<sup>68</sup> which depend on detecting TB infection before progression to active disease.

##### *Endogenous reactivation*

**DESCRIPTION.** Individuals with LTBI remain at risk for reactivation for prolonged periods of time; TB models must incorporate a rate of progression to active TB that persists for extended periods from the time of infection (Figure 1, Process 3).

**EXISTING APPROACHES AND LIMITATIONS.** Compared to rates of progression from recent infection,

rates of reactivation after remote infection are relatively well characterized—through population-based studies where reinfection rates are low—and have less influence on model projections. Although estimates of the reactivation rate vary by almost one order of magnitude, from 0.03<sup>19</sup> to 0.16<sup>69</sup> per 100 person-years (py), the most recent population-based estimate (0.05/100 py)<sup>20</sup> falls in the middle of this range. However, far more important than the background rate of reactivation is the influence of other TB determinants<sup>36</sup> on this rate. For example, while the rate of TB reactivation among people living with HIV—a primary driver of TB epidemics in HIV-endemic settings<sup>70</sup>—is frequently quoted as 10% per year,<sup>32,71,72</sup> many empiric studies have estimated a lower rate.<sup>73,74</sup> TB reactivation rates vary with degree of immunosuppression, such as CD4 count,<sup>60,75</sup> and ART dramatically reduces reactivation rates.<sup>23,75</sup> The relative influence of other TB risk factors on reactivation and reinfection is even less well-characterized. Age is of particular importance; if reactivation rates increase with age,<sup>76–78</sup> TB may become harder to eliminate as populations become older. Such considerations are also relevant when projecting the impact of interventions that differentially affect reactivation and recent infection, such as IPT for TB-HIV co-infected patients.<sup>79</sup>

#### *Protection afforded by latent tuberculosis infection*

**DESCRIPTION.** LTBI likely provides some protection against developing primary progressive TB after a subsequent infectious contact, whether by prevention of reinfection or prevention of disease progression after reinfection.

**EXISTING APPROACHES AND LIMITATIONS.** The relative contributions of ('endogenous') reactivation of remote LTBI vs. ('exogenous') reinfection in propagating TB epidemics have been discussed for decades<sup>80–82</sup> and have been investigated using numerous TB models.<sup>18,19,83</sup> Reinfection with a second strain after remote infection with a first has been clearly demonstrated,<sup>84,85</sup> and multiple strains have even been found in the same sputum.<sup>86</sup> The relative proportion of active TB among remotely infected individuals caused by reinfection vs. reactivation depends on the community risk of TB infection, which is often geographically heterogeneous.<sup>87</sup> Thus, in areas with higher annual risk of TB infection, the contribution of reinfection is expected to be greater.<sup>88–90</sup> However, this balance between reinfection and reactivation is also influenced by the degree of protection against progressive disease afforded by prior TB infection—a parameter value that is poorly understood.<sup>82</sup> Estimates of this 'protective efficacy' are based on modeling studies that fit historical European data to alternative assumptions about the effect of LTBI; estimated values range from 16%<sup>19</sup> to 81%.<sup>18</sup> A recent review using data from pre-isoniazid studies estimated this value at 79% (95% confidence interval [CI] 70–86).<sup>91</sup>

Neither the impact of HIV infection on this parameter value nor the mechanism of protection (i.e., prevention of reinfection vs. prevention of rapid progression after reinfection<sup>19</sup>) are completely understood. Protection afforded by infection with one TB strain against either reinfection or progressive disease with another affects the projected impact of IPT, which may be more effective if protection is high and long-lasting,<sup>66</sup> and vaccines, which seek to evoke similar immunologic phenomena,<sup>16</sup> as well as the rate of decline of TB over time.<sup>92</sup>

#### *Parameters affecting the duration of infectiousness*

##### *Care seeking, diagnosis, and successful treatment*

**DESCRIPTION.** TB programs are often assessed in terms of the proportion of TB cases detected and successfully treated, with goals of respectively 70% and 85%.<sup>93</sup> These proportions depend on the overall rate of care seeking, appropriate diagnosis and successful treatment (Figure 1, Process 4).

**EXISTING APPROACHES AND LIMITATIONS.** As the number of incident TB cases (including undiagnosed cases) is not directly measurable, case detection is difficult to specify accurately.<sup>94,95</sup> More importantly, impact on TB transmission depends on the speed at which cases are detected and treated, as detecting the same number of cases, but earlier in their infectious course, can dramatically reduce TB incidence,<sup>96,97</sup> However, the rate of detection and treatment depends on delays in diagnosis and treatment, which are difficult to measure and vary widely according to such factors as access to care and comorbid conditions.<sup>98</sup> Unknown relationships between onset of symptoms and infectivity are also important considerations. For example, the impact of improved clinic-based diagnosis in areas where a substantial fraction of the population lacks any access to care<sup>99</sup> will be smaller than in areas where most people with active TB do access care but whose diagnosis is missed or simply too late, as suggested by autopsy studies in South Africa.<sup>100–102</sup> Furthermore, diagnostic sensitivity of existing algorithms may be the most important determinant of the incremental impact or cost-effectiveness of new diagnostics.<sup>103</sup>

##### *Spontaneous recovery*

**DESCRIPTION.** A poorly characterized but often critical parameter in TB models is the rate of spontaneous recovery or 'self-cure'. This parameter corresponds to a transition from active, infectious TB to a non-infectious, asymptomatic state in the absence of treatment.

**EXISTING APPROACHES AND LIMITATIONS.** Studies from the pre-antibiotic era demonstrate that the 10-year case-fatality rate of untreated, smear-positive TB is about 70%, while that of culture-positive smear-negative TB may have been as low as 20%.<sup>21</sup> Thus, a substantial proportion of patients with active TB will

not die, even in the absence of treatment. These individuals' average duration of infectiousness has been estimated at 3 years<sup>21</sup> but may be very heterogeneous, and the generalizability of this estimate to modern TB epidemics is unknown. Furthermore, most models assume that mortality, spontaneous recovery and treatment operate as competing and constant rates. If diagnosis and treatment occur preferentially among those who would otherwise have recovered spontaneously, or toward the end of the infectious period in those who would otherwise have died, the impact of these interventions on TB mortality or transmission, respectively, may be blunted. Mortality continues for between 5 and 10 years in these studies,<sup>21</sup> suggesting the existence of 'superspreaders'<sup>104</sup> who remain persistently (or intermittently) infectious without experiencing spontaneous recovery. The relative importance of such 'chronic' cases in modern TB epidemics requires further study.

### *Tuberculosis mortality*

**DESCRIPTION.** Individuals with active TB who are not detected either die or recover spontaneously. Mortality rates of people with untreated, active TB in modern epidemics remain uncertain.

**EXISTING APPROACHES AND LIMITATIONS.** TB mortality rates are exceedingly high, in excess of 5% per month, early in the course of anti-tuberculosis treatment<sup>105</sup> and, among TB-HIV co-infected patients, on initiation of ART,<sup>106</sup> suggesting that mortality rates are not constant over time, but rather peak around the time of diagnosis and treatment initiation. Reducing time to diagnosis by 1 or 2 months may thus have a disproportionate impact on TB mortality. Mortality rates of untreated TB-HIV co-infected patients are particularly poorly characterized, as no data from the pre-antibiotic era exist to inform these estimates. Most empirical observations suggest a case-fatality ratio of around 1.0,<sup>107,108</sup> but the duration of disease has not been measured. Prior analyses<sup>32</sup> have used nosocomial outbreaks of multidrug-resistant TB<sup>109</sup> to assume a disease duration of 0.5 years, whereas a combined incidence/prevalence survey of South African gold miners estimated this duration at 0.8 years (95%CI 0.42–1.35),<sup>110</sup> an estimate that is replicated in models fit to population-level mortality data.<sup>23,26</sup>

### *Tuberculosis control interventions*

As described above, most TB models evaluate specific aspects of natural history or disease control; a single model is unlikely to be appropriate for answering all questions. As a wide array of TB control interventions, such as improved diagnosis, shorter treatment courses, active case finding, IPT, and novel vaccines, are available or under development, and most TB models will not include all available interventions, we have not included specific TB control interventions on our 'wish list' of parameters for TB models

in general. However, it is important to recognize that, for any specific model of TB control, the parameters governing the modeled intervention(s) will be critical to the duration of infectiousness (or probability of progression, in the case of preventive treatment), and will thus have strong effects on  $R_0$  and projected incidence.

## DISCUSSION AND SYNTHESIS

Combining this knowledge with an understanding of the gaps in the existing literature, we have created an extensive 'wish list' of 11 data elements that would help inform the development of better TB models (Table 2). We do not intend this list to be exhaustive. Specifically, we have not addressed structural model uncertainty or assumptions relevant to several other key issues, such as drug-resistant TB or TB-HIV. Nevertheless, our analysis provides an empirical basis for prioritizing those data elements that are most influential to model output (Figure 3). We found that 1) the transmission rate, 2) the risk of rapid progression to TB disease after infection, and 3) the duration of disease prior to diagnosis and treatment, in that order, are the parameters for which better specification could most reduce uncertainty in our model's projections. These three priority parameters most influence our model outcomes from a statistical basis; the process of setting actual research priorities should also consider the generalizability of parameter values across epidemiological conditions and the feasibility of collecting data that would inform each parameter. The relative importance of individual parameters will also vary depending on the epidemiological setting and the particular intervention being studied. Nevertheless, where better specification of these three priority parameters is feasible, such data will almost certainly improve the predictive value of TB models for decision making. In attempting to better specify these three parameters, three broad focus areas emerge.

### *Understanding heterogeneity*

We need to better understand heterogeneity (wish list items 1, 4, 9, 10, 11), i.e., the diverse patterns of TB infection, progression and diagnosis/treatment across both space and time. Many of our existing model assumptions derive from studies undertaken in the pre-chemotherapy era. While the underlying organism is the same, the settings in which *Mycobacterium tuberculosis* causes human disease are dramatically different. Population-based prevalence surveys,<sup>110–114</sup> coupled with detailed care-seeking questionnaires and long-term individual follow-up of clinical outcomes in a variety of locations, could provide data of tremendous value to future models. As existing TB prevalence surveys are carried out, additional data (e.g., household structure, geocoding, duration of symptoms) or samples (e.g., for molecular

**Table 2** A TB modeler's 'wish list': data needs for TB transmission models

<b>A</b> Rate of TB transmission per infectious person-year (Process 1, Figure 1)	
1	TB transmission rate in geographically diverse settings <ul style="list-style-type: none"> <li>• Comprehensive population-based surveillance, description of geographic heterogeneity</li> </ul>
2	TB transmission rate according to TB risk factors/social determinants <ul style="list-style-type: none"> <li>• Understanding of the individual and joint effects of key risk factors on the transmission of TB and acquisition of TB infection</li> </ul>
3	TB transmission rate at different times during the course of TB disease <ul style="list-style-type: none"> <li>• Description of when, during an infectious individual's course of disease, transmission events occur, including development of an assay for recent TB transmission</li> </ul>
<b>B</b> Probability of developing active TB following infection	
Rapid progression (Process 2, Figure 1)	
4	Rate of rapid progression in modern, high-burden settings <ul style="list-style-type: none"> <li>• Extension of existing knowledge about progression rates in historical and low-burden settings to the epidemiology and microbiology typical of high-burden settings</li> </ul>
5	Rate of rapid progression among people with TB risk factors/social determinants <ul style="list-style-type: none"> <li>• Evaluation of progression rates according to HIV and other determinants of susceptibility (age, smoking, nutritional status, diabetes, alcohol, etc.)</li> </ul>
Reactivation (Process 3, Figure 1)	
6	Rate of reactivation among people with TB risk factors, particularly HIV and age <ul style="list-style-type: none"> <li>• More complete characterization of the risk of progression to active TB, according to time since infection</li> </ul>
7	Population-level correlation between prevalence of LTBI and TB risk factors <ul style="list-style-type: none"> <li>• Description of the degree to which populations with high prevalence of TB risk factors also carry high prevalence of LTBI</li> </ul>
Protection afforded by LTBI	
8	Degree of protection afforded by remote TB infection <ul style="list-style-type: none"> <li>• Understanding of the mechanism of protection (i.e., prevention of reinfection, rapid progression, or reactivation)</li> </ul>
<b>C</b> Duration of infectiousness (Process 4, Figure 1)	
9	Care seeking: relationship to infectiousness and heterogeneity across risk groups <ul style="list-style-type: none"> <li>• Characterization of when, in the natural course of disease, diagnosis is sought and treatment administered; understanding of how care-seeking patterns vary across populations</li> </ul>
10	Diagnostic sensitivity and treatment success in geographically diverse settings <ul style="list-style-type: none"> <li>• Description of actual and achievable speed and effectiveness in diagnosing infectious individuals and placing them on treatment</li> </ul>
11	Rate (or probability) of spontaneous recovery in modern high-burden settings <ul style="list-style-type: none"> <li>• Understanding the natural history of untreated TB in the post-chemotherapy era</li> </ul>

TB = tuberculosis; HIV = human immunodeficiency virus; LTBI = latent TB infection.

epidemiology) could be simultaneously collected that could greatly inform our understanding of TB dynamics, even in the absence of long-term follow-up.

#### *Specifying modulators of tuberculosis disease*

We also need to learn more about key modulators (wish list items 2, 5, 6, 7, 9), including biological risk

factors (e.g., HIV), social determinants (e.g., crowding) and latent infection (i.e., protective efficacy). This understanding should include both the strength of each association and the point(s) in the TB disease cycle (infection, progression, and/or transmission) at which each modulator acts. Furthermore, we should not limit our thinking about disease modulation to host factors; heterogeneity across different strains of *M. tuberculosis*, including drug-resistant strains, is also a key consideration.<sup>30,115</sup> In vitro and animal models can provide some insight into strain fitness and within-host dynamics. Population-based studies (e.g., prevalence surveys) that include prospective follow-up of close contacts to identified TB cases<sup>116,117</sup> may facilitate better understanding about the disease stage and strength at which each modulator exerts its primary effect.

#### *Describing time courses of tuberculosis progression and transmission*

Third, we need to know when in a patient's disease course the burden of TB transmission occurs (wish list items 3, 8, 9, 11). The relationships between duration of disease, symptom burden, contact networks, diagnosis/treatment and patient infectiousness remain obscure. Numerous studies have demonstrated that positive TB cultures can be obtained from asymptomatic individuals, particularly those with immune suppression,<sup>118,119</sup> and while most studies of diagnostic delay suggest that patients seek treatment within weeks to months of developing symptoms,<sup>98,120</sup> global estimates based on the prevalence/incidence ratio suggest an infectious period of more than 1 year.<sup>1</sup> As the TB transmission rate from a given individual depends not only on intrinsic infectiousness (bacillary burden) but also on the frequency of contacts and structure of transmission networks,<sup>83,121</sup> understanding how these vary over the infectious period is key. As individuals with active TB are identified in community-based prevalence surveys, assessing the duration and severity of these individuals' symptoms, patterns of seeking care and infectiousness, through contact investigation with molecular epidemiology or using experimental designs (e.g., guinea pig infection<sup>122,123</sup>), could be very informative. Ultimately, we are limited in our ability to characterize TB time courses by the fact that current diagnostics can only identify TB disease, and not transmission events. Successful development of a diagnostic assay that could identify recent infection or superinfection would truly revolutionize our understanding of these complex interactions.

As with any priority-setting exercise, our approach has limitations. As mentioned above, in trying to capture data needs relevant to virtually all TB models in a simple framework, we ignore complex interactions that, while appropriately ignored by some transmission models, is nonetheless critical to TB control as a whole. Prime examples include TB-HIV co-infection

and drug-resistant TB. We do not intend to suggest that these topic areas should be de-prioritized; rather, we argue that it is important to understand each of the above concepts—heterogeneity, modulators and transmission timing—across different strata of immune suppression and TB drug resistance. In this analysis, we have focused on population-level (epidemiological) models of TB; similar models of within-host dynamics, such as those studied by Alavez-Ramirez et al.,<sup>124</sup> also play an important role in our understanding of TB and may provide additional insights. We acknowledge that our broad-based approach using a simple model may not appropriately capture priorities for unique epidemiological situations (for example, Eastern European prisons<sup>125</sup>). Finally, our ‘wish list’ is admittedly long and does not seek to rank-order items within the list; we intend this exercise as a method for bringing modeling concerns into a broader discussion of research priorities, rather than suggesting that specific parameters should be prioritized based only on their potential influence over model outputs.

## CONCLUSION

Infectious disease models simplify complex dynamics to inform decision making when data on population-level effects are otherwise unavailable. We have described the use of infectious disease modeling in TB and have developed a model to identify the following:

- An 11-item ‘wish list’ of data needs for TB transmission models (Table 2)
- Three priority parameters whose specification would improve the predictive ability of virtually all TB models: TB transmission rate, risk of rapid progression and duration of disease
- Three focus areas that will inform these priority parameters: spatial/temporal heterogeneity in TB dynamics, modulators of TB natural history and timing of secondary infections.

Success in the fight against TB depends on the quality of our decisions about which interventions to implement and how to implement them—and models are essential tools in that decision-making process. By targeting research to better inform those models’ assumptions, we can ensure that future decisions result in better health, not just for individual patients, but for populations as a whole.

*Conflict of interest:* none declared.

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## R É S U M É

Les modèles de maladie infectieuse sont des outils importants pour comprendre l'épidémiologie et aider aux décisions de politique en matière de lutte contre les maladies. Dans le cas de la tuberculose (TB), de tels modèles ont servi d'information à notre compréhension et à nos stratégies de lutte depuis >40 ans, mais les suppositions primaires de ces modèles et leurs besoins les plus urgents de données restent peu connus par de nombreux chercheurs en matière de TB et par les agents de lutte contre la maladie. La structure et les valeurs des paramètres pour les modèles TB proviennent d'études observationnelles et expérimentales, mais la base d'évidences soutenant

ces modèles reste incomplète. En nous plaçant dans la perspective des concepteurs de modèles des maladies infectieuses s'intéressant aux collectivités plus large de recherche de lutte contre la TB, nous décrivons la structure de base commune à la plupart des modèles TB et présentons une « liste de souhaits » qui améliorerait les fondements d'évidences sur lesquels ces modèles sont construits. Quand un agenda de recherche TB complet est formulé, nous plaidons pour la nécessité d'y introduire de manière prééminente les besoins de données des modèles de maladies infectieuses, nos outils principaux de prises de décision à long terme.

## R E S U M E N

Los modelos experimentales de las enfermedades infecciosas constituyen herramientas importantes en la comprensión de las situaciones epidemiológicas y en la documentación de las decisiones políticas orientadas al control de estas enfermedades. En el caso de la tuberculosis (TB), los modelos han contribuido a mejorar los conocimientos y a fundamentar las estrategias de control durante más de 40 años, pero muchos investigadores y encargados del control de la TB no tienen aun una idea clara sobre las hipótesis básicas de estos modelos y ni sobre sus necesidades más urgentes en materia de datos. Los estudios de observación y los experimentos documentan la estructura y los valores de referencia de los parámetros de los modelos de TB, pero la base fáctica que sustenta estos modelos sigue siendo incompleta. En

el presente artículo, desde la perspectiva de los diseñadores de modelos de enfermedades infecciosas y en dirección de las comunidades más amplias de investigación en TB y de control de la enfermedad, se describe una estructura básica que es común a la mayor parte de modelos experimentales de tuberculosis y se propone una 'lista de criterios deseables' que podrían hacer más sólidos los fundamentos sobre los cuales se construyen estos modelos. Se propone que en la medida en que se formule un programa exhaustivo de investigación en TB, es preciso que ocupen un lugar prominente las necesidades en materia de datos de los modelos de las enfermedades infecciosas, estos modelos constituyen las herramientas básicas de las decisiones políticas a largo plazo.