Outline of the Tuberculosis transmission model

Dr. Nimalan Arinaminpathy, Department of Infectious Disease Epidemiology, Imperial College London

Background

Tuberculosis (TB) is a leading cause of mortality from infectious disease [1]. Most cases of TB are curable with cost-effective antibiotics, involving 6-9 months of treatment and cure rates approaching 90% in well-implemented programmes [2]. However, TB control is being challenged by the emergence and continuing spread of multi-drug-resistant TB (MDR-TB).

MDR-TB presents real challenges that are disproportionate to its relative burden. Second-line treatment for MDR-TB can cost a hundred times as much as that of drug-sensitive TB, and lasts for upto two years, with drugs that can cause severe side effects [3,4]. With treatment outcomes being far poorer than those of drug-sensitive TB [5,6], there is an urgent need for second-line treatment that is more effective, more tolerable and more widely affordable than at present. Recent developments, such as the new WHO recommendation of a second-line TB regimen lasting 9-12 months, represent important steps in this direction [7].

The diagnosis of drug resistance also presents major challenges, with drug sensitivity testing (DST) typically being conducted through the growth of the organism in laboratory culture in the presence of drugs [8,9]. This method is costly, resource-intensive and can take weeks to provide a result: DST is therefore typically only provided to a small minority of patients [10,11]. The resulting delays in recognizing a patient's drug resistance mean missed opportunities for controlling the transmission of MDR-TB. Therefore, there is a need for new diagnostic tests that can detect drug resistance at the same time as providing a TB diagnosis (so-called 'upfront' DST), so that a patient can be initiated on the correct treatment from the outset.

New and emerging technology offers fresh prospects for addressing these needs. For example, GeneXpert is a rapid molecular diagnostic test that offers diagnosis for TB and for rifampicin-resistance (often a good correlate for MDR-TB) in a matter of hours [12,13]. Other emerging technologies are improving on the ability of GeneXpert to be deployed in secondary and even primary healthcare settings, as close to the patient as possible [14]. In future, with sufficiently lowered costs, such tests could make it feasible for most patients to know their drug resistance status at the point of TB diagnosis.

Improving our control of MDR-TB, then, requires not only better treatment outcomes, but also more efficient and timely diagnosis. Mathematical modelling of TB transmission offers a useful tool for assessing the potential impact of such improvements in future [15]. While there is limited data on MDR burden and trends across the world (particularly on the sizeable MDR burden that goes undetected each year), mathematical models – by capturing

the transmission dynamics of MDR-TB – can cast light on how improved diagnosis and treatment might alter the world's MDR-TB epidemic.

Overview of the analysis

Figure 1 illustrates the model structure, a simplified version of a model that has been described in detail elsewhere [16]. Briefly, a given population is divided into the different compartments shown in the figure, each compartment reflecting states of infection, diagnosis and treatment. Flows between compartments (including the transmission of TB and MDR-TB) are captured by a series of ordinary differential equations.

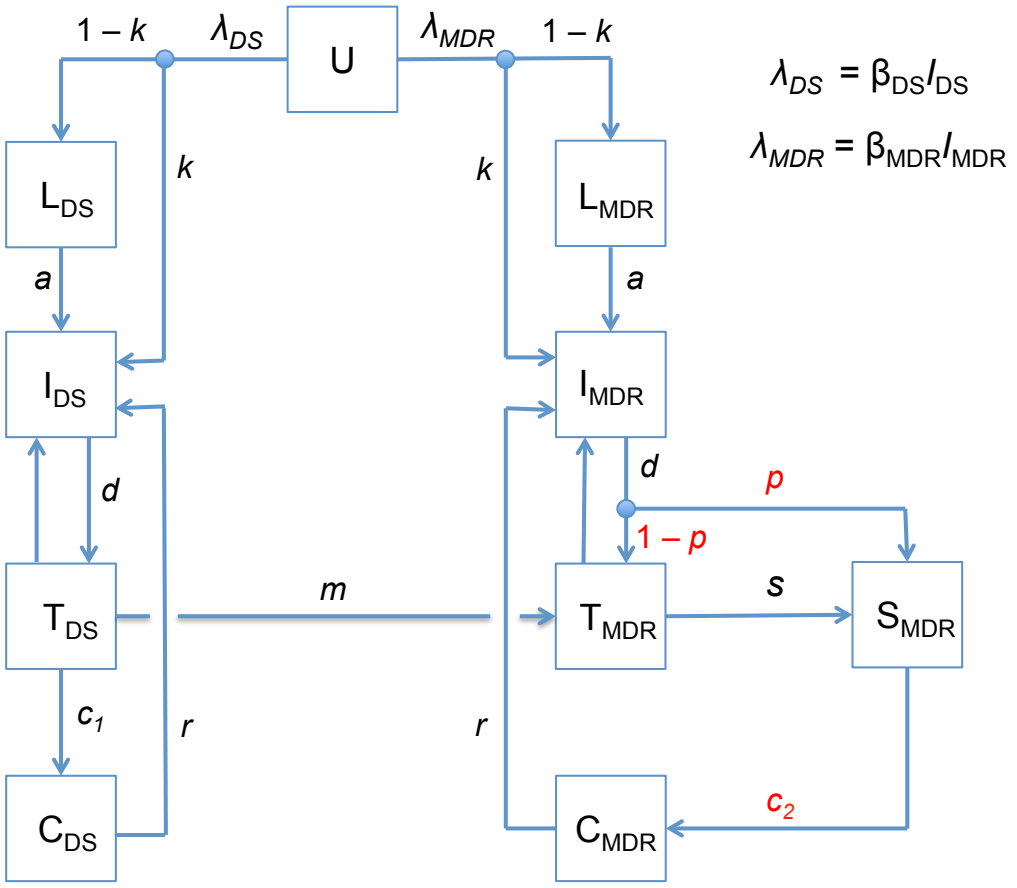

Figure 1. Illustration of the model structure. Shown in boxes are population compartments, with DS denoting drug-sensitive infections and MDR denoting MDR infections. For clarity, not shown on the figure are mortality rates from each compartment, and births into the population. See text for further description.

Compartments in Figure 1 are as follows: Uninfected individuals (U); latent infections (L); those with active, infectious disease (D); patients on first-line treatment (T); patients on second-line treatment (S); and those who are cured, whether spontaneously or through treatment (C).

Terms annotating arrows show the rates and proportions associated with flows between compartments. Terms in red relate to the interventions explored here, namely: the proportion of patients having DST at the point of TB diagnosis (*p*) and the rate of effective cure of MDR-TB with second-line TB drugs (c_2). Other coefficients are: the proportion of infections progressing 'rapidly' to active disease (*k*); the rate of breakdown to active disease (*a*); the rate at which active cases are diagnosed and initiated on treatment (*d*, calibrated to yield incidence and prevalence); the rate of acquisition of multi-drug-resistance while on first-line treatment (*m,* calibrated to yield WHO estimates for MDR amongst previously treated cases); the rate at which MDR cases on first-line treatment are switched empirically to second-line treatment (*s*); and the rate of relapse and reinfection amongst cured cases (*r*).

The nonlinear dynamics of transmission are captured through the force-of-infection terms (λ), defined in the upper-right corner of the figure, and depending on the prevalence of infectious cases, I_{DS} and I_{MDR}. Here, the infectiousness terms β_{DS} and β_{MDR} are calibrated against incidence, prevalence and the proportion of new cases having MDR-TB.

We modeled 'better diagnosis' as an increase in the proportion of patients having upfront DST, and initiating appropriate treatment as a result (thereby increasing the proportion p in Figure 1). We modeled 'better treatment' with the hypothetical scenario of a new, improved second-line regimen having the same duration and cure rates as first-line treatment (thereby increasing the rate c_2 in Figure 1).

Free parameters in the model are: (i) the infectiousness of drug-susceptible TB (infections per case per year), (ii) the infectiousness of MDR-TB, (iii) the average duration of infectiousness of a TB episode, and (iv) a patient's rate of acquisition of multi-drug resistance while on first-line treatment. We calibrated these model parameters to capture WHO estimates for TB and MDR-TB burden in different regions of the world, as described below.

Data inputs

We used World Health Organization (WHO) estimates for annual TB incidence and prevalence for 219 countries worldwide [1]. For MDR-TB burden we used available WHO estimates for the proportion of incident TB cases having MDR-TB (both amongst new cases and those with previous treatment history). The model was calibrated to simultaneously meet these targets for the years available. Model fitting was conducted by likelihood maximization, using the WHO uncertainty intervals to construct a joint likelihood function.

To accommodate regional differences in TB epidemiology in a simple way, we aggregated countries by WHO region, finding separate model calibrations for each region. These regions, identified in [17], are designated as: the Americas (AMR); European (EUR); Western Pacific (WPR); South-East Asian (SEA); Eastern Mediterranean (EMR); and African (AFR) regions. However, this grouping masks significant MDR variation within the European

region, including countries having some of the world's highest MDR-TB rates. Accordingly we defined 'Europe high-burden' as those countries in which over 10% of new cases are estimated to have MDR-TB: a grouping including the Russian Federation, Belarus, Kazakhstan, and other high-burden countries from the former Soviet Union.

HIV is another important factor, with HIV/TB coinfected patients having a much higher risk of developing active TB than HIV-negative patients [18,19]. In Sub-Saharan Africa, the emergence of HIV in the 1990s was a major driver in the expansion of the TB epidemic there [20]. Accordingly we used a modified version of the model to take into account TB/HIV dynamics for the AFR region alone, using WHO data for the proportion of TB cases that are HIV coinfected, together with UNAIDS projections for future HIV burden and coverage of antiretroviral therapy.

Results

Figure 2 shows the lives saved each year in each of the regions being simulated. In each shaded area the lower boundary, representing a 'low-MDR' scenario, is obtained by calibrating the model to the lower limits in WHO estimates for the proportion of new and previously treated cases that are MDR. Likewise, the upper boundary represents a 'high-MDR' scenario, drawn from the upper limits of WHO burden estimates. Bold curves running through the middle of each area arise from the midpoints of WHO estimates. Aggregating the latter over all regions yields the global estimates for lives saved that are presented in the main text. Table 1 below shows the cumulative lives saved from 2016 to 2025, under each of the interventions modeled here.

Region	**Better diagnosis**			**Better treatment**			**Better diagnosis and treatment**		
	Low	Mid	High	Low	Mid	High	Low	Mid	High
AFR	30.0	65.4	110.0	23.5	44.5	70.3	62.3	124.6	201.5
AMR	7.7	10.6	14.7	6.8	9.1	12.1	17.3	23.4	31.4
EMR	13.7	23.0	33.5	10.4	16.2	22.3	29.5	47.4	66.8
EUR	2.1	3.4	6.0	2.0	2.8	4.1	4.9	7.2	11.3
EUR high	73.6	95.8	130.5	63.8	83.9	120.5	150.9	191.8	250.2
SEA	81.0	104.0	133.7	58.8	79.5	103.7	167.0	220.7	286.0
WPR	68.8	89.2	111.7	35.1	46.2	59.2	118.7	155.0	196.2
Global	277.0	391.4	540.0	200.4	282.3	392.2	550.6	770.0	1043.4

Table 1. Cumulative lives (in thousands) saved by region and intervention, from 2016 – 2025. 'Low', 'Mid' and 'High' represent scenarios for MDR burden, corresponding to the shaded regions in Fig.2

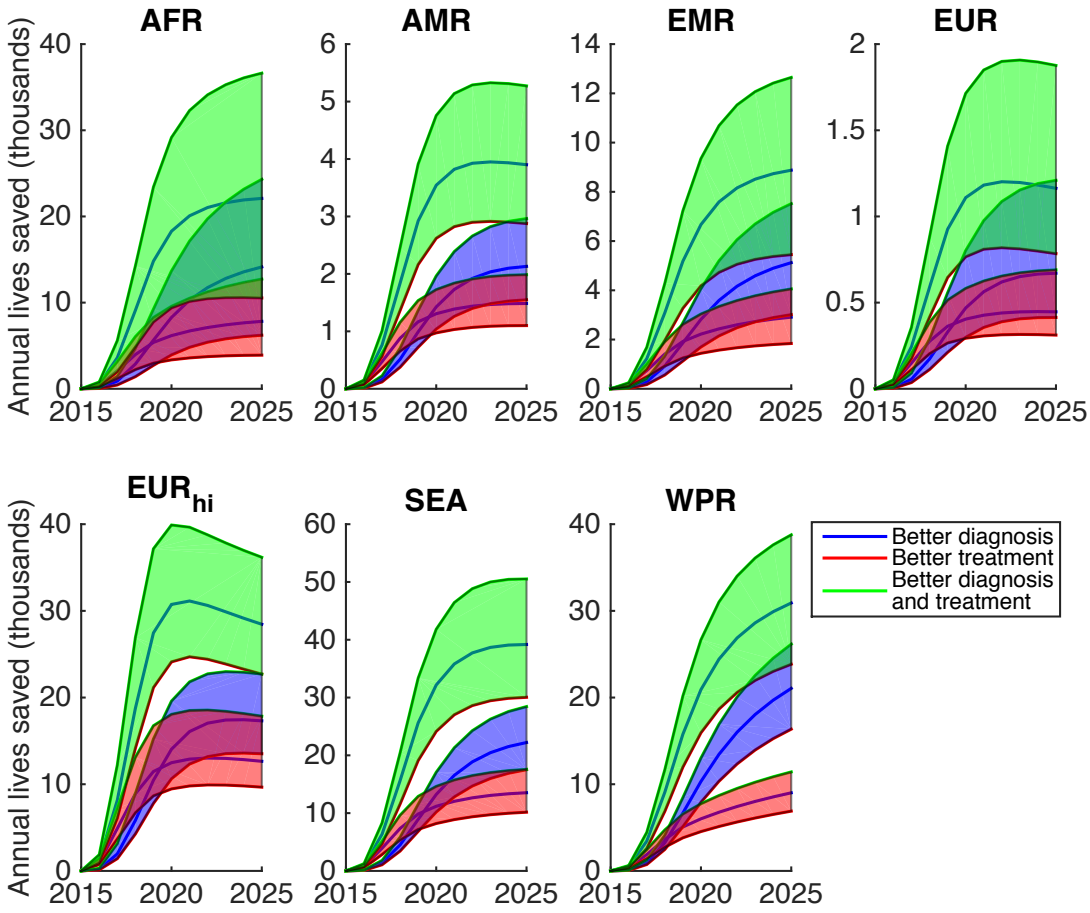

Figure 2. Model projections for annual lives saved under different interventions. Under 'better diagnosis', 80% of MDR-TB cases are initiated on appropriate (second-line) treatment at the point of TB diagnosis. 'Better treatment' refers to a hypothetical second-line regimen having the same duration and treatment outcomes as current, first-line treatment. The figure assumes a linear scale-up over the first three years shown. Shaded areas illustrate ranges of outcomes associated with the range in WHO estimates for MDR burden (see text).

Model limitations

Because of the gaps in our knowledge of the epidemiology of MDR-TB, the purpose of this model is to provide broadly illustrative, but not necessarily definitive, scenarios. For example, we have calibrated using WHO estimates for incidence and prevalence, which themselves arise from a model. We have also not taken account of the wide uncertainty intervals in WHO estimates of overall TB burden. Such uncertainty could translate to wide variation in the model findings. The model also adopts a much-simplified biology of MDR-TB. For example, the uncertainties around the natural history of TB apply also to MDR-TB [21]. Moreover, with MDR involving resistance to both first-line drugs isoniazid and rifampicin, the emergence of drug resistance may not be as simple as a single, per-capita rate applied to those on first-line treatment [22,23]. In light of these and other uncertainties, these results should be interpreted as being one set of futures (amongst several) that is consistent with our current understanding of TB and MDR TB burden.

References

1. World Health Organization (2015) Global tuberculosis report 2015.

2. Chaulk CP, Kazandjian VA (1998) Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. Vol. 279. pp. 943–948.

3. Caminero JA, World Health Organization, American Thoracic Society, British Thoracic Society (2006) Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis 10: 829–837.

4. Nachega JB, Chaisson RE (2003) Tuberculosis drug resistance: a global threat. Clin Infect Dis 36: S24–S30. doi:10.1086/344657.

5. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM (2009) Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS ONE 4: e6914. doi:10.1371/journal.pone.0006914.

6. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, et al. (2009) Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. The Lancet Infectious Diseases 9: 153–161. doi:10.1016/S1473-3099(09)70041-6.

7. World Health Organization (2016) Rapid diagnostic test and shorter, cheaper treatment signal new hope for multidrug-resistant tuberculosis patients. Available: http://www.who.int/mediacentre/news/releases/2016/multidrug-resistant-tuberculosis/en/. Accessed 17 May 2016.

8. Kim SJ (2005) Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J 25: 564–569. doi:10.1183/09031936.05.00111304.

9. Aziz M, Ryszewska K, Blanc L, Vincent V, Getahun H, et al. (2007) Expanding culture and drug susceptibility testing capacity in tuberculosis diagnostic services: the new challenge. Int J Tuberc Lung Dis 11: 247–250.

10. Chadha SS, Sharath BN, Reddy K, Jaju J, Vishnu PH, et al. (2011) Operational challenges in diagnosing multi-drug resistant TB and initiating treatment in Andhra Pradesh, India. PLoS ONE 6: e26659. doi:10.1371/journal.pone.0026659.

11. Zumla A, Abubakar I, Raviglione M, Hoelscher M, Ditiu L, et al. (2012) Drug-resistant tuberculosis--current dilemmas, unanswered questions, challenges, and priority needs. J Infect Dis 205 Suppl 2: S228–S240. doi:10.1093/infdis/jir858.

12. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, et al. (2014) Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 1: CD009593. doi:10.1002/14651858.CD009593.pub3.

13. Evans CA (2011) GeneXpert--a game-changer for tuberculosis control? Plos Med 8: e1001064. doi:10.1371/journal.pmed.1001064.

14. Drain PK, Garrett NJ (2015) The arrival of a true point-of-care molecular assay-ready for global implementation? The Lancet Global Health 3: e663–e664. doi:10.1016/S2214-109X(15)00186-2.

15. Dye C, Williams BG (2010) The Population Dynamics and Control of Tuberculosis.

Science 328: 856–861. doi:10.1126/science.1185449.

16. Sachdeva KS, Raizada N, Gupta RS, Nair SA, Denkinger C, et al. (2015) The Potential Impact of Up-Front Drug Sensitivity Testing on India's Epidemic of Multi-Drug Resistant Tuberculosis. PLoS ONE 10: e0131438. doi:10.1371/journal.pone.0131438.

17. World Health Organization: WHO regional offices. Available: http://www.who.int/about/regions/en/. Accessed 16 May 2016.

18. Kwan CK, Ernst JD (2011) HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev 24: 351–376. doi:10.1128/CMR.00042-10.

19. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G (2012) Tuberculosis and HIV co-infection. PLoS Pathog 8: e1002464. doi:10.1371/journal.ppat.1002464.

20. Lawn SD, Churchyard G (2009) Epidemiology of HIV-associated tuberculosis. Curr Opin HIV AIDS 4: 325–333. doi:10.1097/COH.0b013e32832c7d61.

21. Dowdy DW, Dye C, Cohen T (2013) Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list' [Review article]. Int J Tuberc Lung Dis 17: 866–877. doi:10.5588/ijtld.12.0573.

22. Cohen T, Murray M (2004) Modeling epidemics of multidrug-resistant M. tuberculosis of heterogeneous fitness. Nat Med 10: 1117–1121. doi:10.1038/nm1110.

23. Kendall EA, Fofana MO, Dowdy DW (2015) Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med 3: 963–972. doi:10.1016/S2213-2600(15)00458-0.