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Construction of a mathematical model for tuberculosis transmission in highly endemic regions of the Asia-pacific

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HIGHLIGHTS

- We present a model for simulation of programmatic responses to tuberculosis in highly endemic countries of the Asia-Pacific.
- The model presented cannot be calibrated to estimated incidence rates without allowing for reinfection during latency.
- Even in the presence of a moderate fitness cost, MDR-TB dominates at equilibrium.
- Improved treatment of drug-susceptible TB does not result in decreased rates of MDR-TB through prevention of *de novo* resistance.
- Community transmission to MDR-TB incidence contributes markedly more to MDR-TB burden than resistance amplification under our model structure.

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ABSTRACT

We present a mathematical model to simulate tuberculosis (TB) transmission in highly endemic regions of the Asia-Pacific, where epidemiology does not appear to be primarily driven by HIV-coinfection. The ten-compartment deterministic model captures many of the observed phenomena important to disease dynamics, including partial and temporary vaccine efficacy, declining risk of active disease following infection, the possibility of reinfection both during the infection latent period and after treatment, multidrug resistant TB (MDR-TB) and *de novo* resistance during treatment. We found that the model could not be calibrated to the estimated incidence rate without allowing for reinfection during latency, and that even in the presence of a moderate fitness cost and a lower value of R_0, MDR-TB becomes the dominant strain at equilibrium. Of the modifiable programmatic parameters, the rate of detection and treatment commencement was the most important determinant of disease rates with each respective strain, while vaccination rates were less important. Improved treatment of drug-susceptible TB did not result in decreased rates of MDR-TB through prevention of *de novo* resistance, but rather resulted in a modest increase in MDR-TB through strain replacement. This was due to the considerably greater relative contribution of community transmission to MDR-TB incidence, by comparison to *de novo* amplification of resistance in previously susceptible strains.

1. Introduction

Although progress is being made in control of tuberculosis (TB), the global burden of disease remains enormous, several high burden countries are not on track to achieve Millennium Development Goal targets and multidrug-resistant TB (MDR-TB) has emerged as a major threat to control measures (World Health Organization, 2013c). In the Asia-Pacific region, here defined as countries within the World Health Organisation South East Asia Region (SEARO) and Western Pacific Region (WPRO) jurisdictions, seven countries have an incidence of greater than 300 per 100,000 per year (World Health Organization, 2013c).

MDR-TB is defined as TB resistant to both of the two most effective first line anti-tuberculous agents; rifampicin and isoniazid. Such strains require treatment that is substantially more difficult, in relation to patient tolerance, duration of therapy and expense. In the Asia-Pacific region, MDR-TB is a serious problem, representing a significant proportion of incident cases, despite probable under-reporting (Gilpin et al., 2008). By contrast, although the burden of HIV in some such countries is also significant, the large majority of

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TB cases occurs in HIV-negative persons. Unlike sub-Saharan Africa, the prevalence of HIV in adults aged 15–49 is generally less than 1% and so does not appear to be driving the regional TB epidemic (World Health Organization, 2013a).

Prolonged latency between infection and subsequent disease is characteristic of TB and has important implications for epidemiology (Blower et al., 1995). Therefore, from the earliest mathematical models of TB transmission, latent compartments have been incorporated (Waaler et al., 1962). Such studies typically model the incidence of active cases as proportional to the number of persons latently infected, and represent the force of infection as a function of the number of persons with active infection (ReVelle et al., 1967), usually assuming frequency-dependent transmission (Feng et al., 2001).

Most previously developed models aim to answer specific questions about the likely impact of individual interventions on the burden of TB in a hypothetical population. While models have been developed to estimate the global impact of a bundled intervention such as DOTS (Dye et al., 1998), the practical impact of implementation of multifactorial programmatic strategies at a local or regional level is less frequently modelled. In this study, we aimed to create a model structure that would be applicable to countries highly endemic for TB and MDR-TB, but with low HIV prevalence, and to describe its basic behaviour. We developed a compartmental deterministic model with frequency-dependent transmission that aims to incorporate the most current understanding of TB epidemiology to use as a realistic base for modelling of programmatic interventions in highly endemic countries of our region. The model allows for the incorporation of multiple aspects of a programmatic response to TB, in order to compare a number of scenarios simulating such responses.

The paper is organised as follows. Section 2 describes each aspect of the model construction in detail, while Section 3 describes the behaviour of the model and presents a sensitivity analysis for modifiable parameters.

2. Model construction

2.1. Immunisation

BCG is known to provide partial protection against infection with TB (Colditz et al., 1994). Past models for TB transmission in developed countries have represented this partial immunity as a compartment of fully immune individuals, with the flow entering the compartment proportional to the product of vaccine efficacy and vaccine coverage (Vynnycky and Fine, 1997). BCG may have particular efficacy in preventing disease in the years following vaccination (Medical Research Council, 1972), although this immunity may be overwhelmed by repeated exposure in a highly endemic setting. Therefore, representing vaccination as complete and permanent immunity for a proportion of the population may not be applicable to highly endemic developing countries. We represent BCG effect as a proportional reduction in the force of infection for those vaccinated, and as providing no further protective effect after infection has occurred. As BCG is administered as a neonatal vaccine, birth cohorts are split between vaccinated and fully susceptible compartments.

2.2. Latency

Markedly different rates of progression to active infection are observed in the years following infection with TB, by comparison to subsequent years remote from infection. Over the first 23 months following infection by a smear-positive index case confirmed by positive interferon-gamma release assay, 12.9% of patients progressed to active disease (Diel et al., 2011). By contrast, the rate at which active disease develops once this high risk period has ended is generally modelled at a much lower rate, e.g. 5–10% over 20 years (Blower et al., 1995).

To represent this clinical observation, past models have included both fast and slow pathways from susceptible to actively infected, with a proportion of exposed susceptibles progressing immediately to active infection (Basu and Galvani, 2008; Blower et al., 1995; Rodrigues et al., 2007). This approach allows slight modification of the standard exponential function governing sojourn time in the exposed, non-infectious compartment. Other models have utilised alternative distributions of the latent period, including a stepwise reduction in the rate of progression occurring five years after exposure (Vynnycky and Fine, 1997), and an arbitrary distribution of the latent period, which was demonstrated to retain important model properties (Feng et al., 2001). However, dual latent compartments linked by constant flow rates are increasingly utilised to represent the high and low risk periods following infection. These compartments may either be included as a sequential progression from early to late latent (Aparicio et al., 2002; Dowdy et al., 2013; Wu et al., 2010; Ziv et al., 2001) or allow for bypass of the early latent compartment with immediate entry into the late latent compartment after infection (Abu-Raddad et al., 2009; Dye and Williams, 2008).

We included two sequential latent compartments in our model to simulate the increased risk of progression to active disease in the years immediately following initial infection.

2.3. Diagnosis and commencement on treatment

The process of actively infected patients commencing on effective treatment can be divided into multiple compartments, and previous models have separated patient-related pre-health system delays from health system delays (Dye, 2012), or have distinguished pre-diagnosis delays from delays to treatment after diagnosis (Hickson et al., 2012). However, provided that 'patients yet to present to hospital', 'patients yet to be diagnosed after presentation', and 'patients diagnosed but yet to start treatment' are all considered to have the same mortality and infectiousness, representing all delays to treatment commencement within one model pathway is the most parsimonious approach. Pre-health system delays and post-diagnosis, pre-treatment delays can still be quantified by dividing the proportion who ever receive treatment by the typical period of delay to treatment, while missed diagnosis leading to undertreatment could be incorporated by multiplying the rate of movement from infectious to susceptible by the sensitivity of the test used. Therefore, consistent with the approach of several previous models (Abu-Raddad et al., 2009; Blower et al., 1996; Dowdy et al., 2013; Dye and Williams, 2008), we incorporated all stages from onset of symptoms to commencement on treatment within the same model compartment.

2.4. Recovery

Most previous models present a separate compartment for previously treated and spontaneously recovered individuals from the compartments representing individuals who are fully susceptible or previously vaccinated, allowing these individuals to be conferred a different rate of infection. The different approaches to quantifying this modified rate of infection include; assuming no further risk of infection after recovery (Blower et al., 1996; Dye and Williams, 2008), assuming all recurrent cases are due to relapse, (Blower et al., 1995) assuming the same risk modification as for latent infection (Dowdy et al., 2013), assuming the same rate of reinfection as for susceptible individuals (Castillo-Chavez and Feng, 1997), and allowing for both reinfection and relapse after