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Tuberculosis in Cape Town: An age-structured transmission model

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ABSTRACT

Background: Tuberculosis (TB) is the leading cause of death in South Africa. The burden of disease varies by age, with peaks in TB notification rates in the HIV-negative population at ages 0–5, 20–24, and 45–49 years. There is little variation between age groups in the rates in the HIV-positive population. The drivers of this age pattern remain unknown.
Methods: We developed an age-structured simulation model of *Mycobacterium tuberculosis* (Mtb) transmission in Cape Town, South Africa. We considered five states of TB progression: susceptible, infected (latent TB), active TB, treated TB, and treatment default. Latently infected individuals could be re-infected; a previous Mtb infection slowed progression to active disease. We further considered three states of HIV progression: HIV negative, HIV positive, on antiretroviral therapy. To parameterize the model, we analysed treatment outcomes from the Cape Town electronic TB register, social mixing patterns from a Cape Town community and used literature estimates for other parameters. To investigate the main drivers behind the age patterns, we conducted sensitivity analyses on all parameters related to the age structure.
Results: The model replicated the age patterns in HIV-negative TB notification rates of Cape Town in 2009. Simulated TB notification rate in HIV-negative patients was 1000/100,000 person-years (pyrs) in children aged <5 years and decreased to 51/100,000 in children 5–15 years. The peak in early adulthood occurred at 25–29 years (463/100,000 pyrs). After a subsequent decline, simulated TB notification rates gradually increased from the age of 30 years. Sensitivity analyses showed that the dip after the early adult peak was due to the protective effect of latent TB and that retreatment TB was mainly responsible for the rise in TB notification rates from the age of 30 years.
Conclusion: The protective effect of a first latent infection on subsequent infections and the faster progression in previously treated patients are the key determinants of the age-structure of TB notification rates in Cape Town.

1. Introduction

The HIV and Tuberculosis (TB) epidemics in South Africa (SA) are among the worst in the world. Tuberculosis (TB) is now the leading cause of natural death in South Africa (Statistics South Africa, 2014a). HIV positive individuals who are infected with *Mycobacterium tuberculosis* (Mtb) have a substantially higher risk of developing active TB than their HIV-negative peers (Corbett et al., 2003), whose lifetime risk following a single infection is about 10% (Styblo, 1991). Even though South Africa has implemented the World Health Organization (WHO) "Directly observed therapy, short course" (DOTS, WHO, 1996) strategy, the incidence of TB in South Africa has continued to rise steadily over the past 20 years, and reached a rate of 1000 cases per 100,000 person-years in 2012 (WHO, 2013). DOTS has been estimated to reduce TB incidence by 11% per year (Dye et al., 1998), but is failing in HIV endemic settings (De Cock and Chaisson, 1999). The HIV-associated TB epidemic partly explains the failure of DOTS to reduce the TB prevalence in SA (Wood et al., 2011b), since about 65% of TB patients in South Africa

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are co-infected with HIV (WHO, 2014a). Because Mtb infection is preventable and TB disease is curable, effective interventions hold the potential of drastically lowering infection and mortality rates.

In addition to DOTS, HIV-specific interventions have been implemented to control TB in this population, including scaling up the use of antiretroviral therapy (ART) and the "Three I's" strategy: Intensified case finding, Isoniazid preventive therapy (IPT) and infection control (IC) at all clinical encounters (WHO, 2004). Assessing the impact of ART on TB incidence is difficult because ART reduces the risk of TB diseases among HIV-positive individuals and at the same time increases the number of people living with HIV due to reduced HIV-related mortality, thereby increasing the population risk of TB (Bacaer et al., 2008; Bhunu et al., 2009). Mathematical models estimated that universal ART eligibility for all HIV-infected South Africans would reduce the risk of AIDS-related TB by 48% in 2015 (Williams et al., 2010) and reduce new TB cases by 28–37% by 2033 (Pretorius et al., 2014). In contrast, Dodd et al. (Dodd et al., 2013) estimated that TB incidence would initially decline, but rebound 20 years after widespread introduction of ART. Results of modeling studies of IPT are also contradictory. Bacaer et al. (Bacaer et al., 2008) showed that IPT in HIV-positive individuals could substantially reduce TB notification rates. But Mills et al. (Mills et al., 2011) concluded that the predicted effectiveness of IPT would be undermined by repeated re-infections, and Houben et al. (Houben et al., 2014) found that IPT did not cure latent Mtb infection in HIV-positive patients.

TB incidence rates are strongly associated with age (Wiker et al., 2010; Wood et al., 2011a). A study of data from the beginning of the 20th century showed that in the United Kingdom age and reinfection after a cured TB episode were important determinants of transmission (Vynnycky and Fine, 1997). The authors concluded that "the sharp peaks in mortality during young adult life were attributable to the combination of a high incidence of (re)infection and a rapid risk of developing disease in late adolescence". The same age pattern is also seen today in South Africa: a community-based study in Cape Town, showed that the highest burden of TB had shifted from the oldest (>60 years) age group to a younger population (20–39 year olds) (Lawn et al., 2006). In another study, a very distinct age pattern with three notification peaks at ages 0–5 (first peak), 20–24 (second peak), and 45–49 years (third peak) was observed in the HIV-negative population, whereas in the HIV-positive population the burden of TB mirrored age-stratified HIV prevalence (Wood et al., 2011a). The same study also found a high burden of TB in patients who were previously treated, with most patients having no history of treatment failure or default (Wood et al., 2011a).

Despite being of such importance in TB epidemiology, most South African TB models (Aparicio and Castillo-Chavez, 2009; Bacaer et al., 2008; Bhunu et al., 2009; Blower et al., 1995; Castillo-Chavez and Feng, 1997; Hickson et al., 2012; Mills et al., 2011; Ozcaglar et al., 2012; Rodrigues et al., 2007; Roeger et al., 2009; Williams et al., 2010) do not include age, or include age only for HIV incidence but not for rates of progression from latent Mtb infection to active disease or Mtb transmission. We chose to model Cape Town because of the high quality of TB notification data, and the high rates of HIV testing. We aimed to explore the drivers underlying the age-patterns in HIV-negative TB notification rates observed in Cape Town in a mathematical model that includes age-stratification and reinfection.

2. Methods

2.1. Setting

We modeled the TB dynamics in the city of Cape Town, where both TB and HIV are endemic. In 2009, the population of the Cape Town metropolitan area was approximately 3.5 million (Statistics South Africa, 2014b). HIV prevalence was estimated at around 5% of the population, and increasing over time (ASSA, 2011). Both HIV care and TB treatment are provided free of charge in government clinics across the city. ART was introduced in 2004 and has been scaled up since, reaching a coverage of 63% in 2013 (Hermans et al., 2015a). According to the 2009 National TB management guidelines, new TB cases are treated for 6 months and TB cases with a history of previous TB for 9 months (Department of Health, 2009). We used these guidelines in our model, because these were the guidelines that influenced the current TB incidence and age structure.

2.2. Model structure

We developed an individual-based TB transmission model stratified by five-year age groups. We used an individual-based stochastic simulation model because it allowed us to consider details about individual TB progression depending on age and time since infection and to capture the uncertainty of modeling outputs. Individuals were simulated from birth to death using the disease progression model implemented in the R package *gems* (Blaser et al., 2015). We considered the following stages of TB progression: susceptible; exposed (latent infection); active disease; treatment; treatment failure/default; and, recovered/susceptible (Figs. 1 and S1). Individuals latently infected with Mtb could be re-infected by another Mtb strain or progress to active disease. Active TB cases were initiated on treatment at a certain rate. After treatment initiation, patients were cured within six months (nine months in the case of retreatment TB) or they failed treatment. Cured individuals were considered susceptible to new Mtb infections (Marx et al., 2014). In case of reinfection, individuals progressed to active disease at twice the rate as previously uninfected individuals (Wood et al., 2011a).

We modeled HIV status of the patients as HIV-negative, HIV-positive not on ART, and HIV-positive on ART (Figs. 1, S2). We assumed HIV incidence was independent of TB progression, but TB progression depended on HIV status. ART initiation was also independent of the natural TB progression, but patients treated for TB were also initiated on ART. We first modeled HIV status over the entire lifespan and then Mtb infection and progression based on HIV status. We considered heterosexual transmission of HIV but ignored vertical transmission. We used separate HIV incidence rates for the pre-ART and ART eras (Table S1). In addition, each simulated individual had characteristics that changed over time: age, number of previous Mtb exposures, and number of previous active TB episodes.

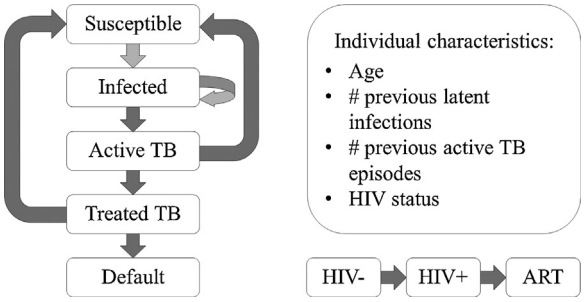

Fig. 1. Model structure. Individuals who start in the susceptible state can be exposed to tuberculosis. Exposed individuals can be exposed to a second strain or progress to active TB. Patients with active TB can recover spontaneously or receive treatment. Treated patients either recover and become susceptible again or they default. Throughout this TB progression, all individuals can also progress in their HIV status, by becoming infected and receiving antiretroviral therapy (ART). Even though it is not represented on the diagram, patients can die at any of the stages.