Can Australia eliminate TB? Modelling immigration strategies for reaching MDG targets in a low-transmission setting

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Abstract

Background: The 2050 Millennium Development Goals (MDG) for tuberculosis (TB) aim for elimination of TB as a public health issue. We used a mathematical modelling approach to evaluate the feasibility of this target in a low-prevalence setting with immigration-related strategies directed at latent tuberculosis.

Methods: We used a stochastic individual-based model to simulate tuberculosis disease among immigrants to Victoria, Australia; a representative low-transmission setting. A variety of screening and treatment approaches aimed at preventing reactivation of latent infection were applied to evaluate overall tuberculosis incidence reduction and rates of multidrug resistant disease.

Results: Without additional intervention, tuberculosis incidence was predicted to reach 34.5 cases/million by 2050. Strategies involving the introduction of an available screening/treatment combination reduced TB incidence to between 16.9-23.8 cases/million, and required screening of 136-427 new arrivals for each case of TB prevented. Limiting screening to higher incidence regions of origin was less effective but more efficient.

Conclusions: Public health strategies targeting latent tuberculosis infection in immigrants may substantially reduce tuberculosis incidence in a low prevalence region. However, immigration-focused strategies cannot achieve the 2050 MDG and alternative or complementary approaches are required.

Key words: latent tuberculosis infection, immigration, screening, mathematical model, public health

The Millennium Development Goals include the stated aim of eliminating tuberculosis as a public health issue by 2050, defined as an incidence of less than one case per million population.[1] While a combination of factors – including a current global incidence of about 1,280 cases per million and lack of an effective therapeutic vaccine – have led some to conclude this outcome is unlikely to be achieved, it remains plausible that such a target may be possible for selected low-prevalence areas.[2,3] Australia has a number of factors that may make it a more promising area for disease eradication, including geographic isolation and a 2010 national TB incidence of 68 per million.[4] Accordingly, the evaluation of the potential impact of public health policies aimed at tuberculosis incidence reduction in this region would be of interest.

International strategies for reducing tuberculosis incidence emphasise early effective treatment of active infection and interruption of transmission.[5] These are key strategies in high-transmission regions; however, in a low prevalence context such as Australia, the considerable bulk of new tuberculosis cases may arise from reactivation of latent tuberculosis infection (LTBI) rather than local transmission.[6,7] Accordingly, while maintenance of traditional public health approaches remains important, expanding public health efforts along these lines is unlikely to lead to further reduction in tuberculosis incidence in these settings. Increasing recognition of the importance of LTBI reactivation in low prevalence contexts has led a number of countries to consider or develop immigration screening programs for LTBI.[8,9] However, while strategies focused on the prevention of disease following latent reactivation have theoretic potential for significant impact, evaluation of the effectiveness of such programs on TB incidence reduction is limited.

Given the potentially lengthy latent periods prior to TB reactivation, even optimal strategies targeting treatment of active disease and interruption of transmission alone are unlikely to result in eradication within the World Health Organization (WHO) objectives, and expansion of strategies targeting LTBI require consideration.[8] We aimed, therefore, to use a mathematical modelling approach to evaluate the potential impact on TB incidence of immigration-related strategies targeting latent infection within a low prevalence, low transmission setting.

Methods

Setting

The State of Victoria, Australia, has about 5.5 million residents, 75% of whom live in the capital city of Melbourne. The use of

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an Australian setting for construction of a mathematical model of tuberculosis was considered optimal for several reasons. TB incidence in 2010 was 71 cases/million, similar to the Australian national average, with the considerable majority of TB diagnoses occurring in residents born outside of Australia (96% in 2010) and epidemiologic and genotypic data supportive of minimal local transmission of infection.[7,10] In addition, individual-level demographic data was available for both immigration and tuberculosis notification.

Mathematical model

An individual-based, stochastic model with discrete time intervals of tuberculosis reactivation in immigrants was developed using MATLAB (R2012a, The MathWorks, Nowick, MA, USA). Figure 1 demonstrates a model schematic. Individuals populating this model were derived initially from immigration records of permanent arrivals to Victoria, Australia between 1975 and 2007. Individual level data on age, year of arrival and region of origin were available for about 750,000 arrivals over this period, with additional characteristics (HIV status, diabetes mellitus, smoking status, sex) stochastically assigned according to an initial randomisation process weighted by regional risk estimates and adjusted by age and sex. Future arrivals were subsequently generated based on demographic profiles of current immigrant cohorts. Population incidence calculations used 2006 census data to provide a total population denominator, adjusted by +1.3% annually in accordance with historic population growth trend.

For each yearly time-step of the model, age and other time-dependent variables were updated and new arrival cohorts integrated, over 100 iterations. Summary risk estimates for tuberculosis reactivation were then generated through adjustment of regional risk by individual multiplicative modifiers. Regional risk of tuberculosis reactivation was taken from historical cohort-specific risk in the state of Victoria.[11] Region-specific risk was adjusted to account for a projected annual 3.4% proportional decline in global TB incidence.[4] Risk modification for the presence of HIV infection, smoking, diabetes and age were taken from published estimates. Details of model parameters, including risk modification associated with individual variables are provided in Supplementary file 1, available online. An age-specific risk of mortality was applied based on Australian life expectancy tables, with subjects removed from subsequent iterations following tuberculosis infection or death. Because of low TB-associated mortality in Australia, individuals with TB were assumed to recover and were removed from the model. Model outputs were fitted to current and historical tuberculosis notifications in Victoria, with the 2007–2012 data used to check model predictions (Supplementary file 3, available online). Baseline scenarios assumed that no transmission or secondary cases occurred following disease. Consistent with current local data, 0.5–2.4% of TB disease was expected to be multidrug resistant at baseline, with sensitivity analyses performed to consider future trends.[12]

Following consideration of baseline expectations for future tuberculosis incidence, a variety of strategies relating to latent tuberculosis infection were evaluated. Strategies focused on immigration interventions using combinations of tuberculin skin testing (TST)/interferon-gamma release assays (IGRA; both Quantiferon Gold and Tspot-TB) and/or treatment with isoniazid, rifampicin or isoniazid with rifapentine preventative therapies. All strategies were initiated in 2013 cohorts, and assume immediate application in relevant immigrant cohorts. Median treatment efficacy estimates were taken from published literature, and are detailed in Supplementary file 1 (available online). For all strategies, the primary outcome of interest was overall tuberculosis incidence in 2050, with secondary outcomes including proportion of multi-drug resistant disease and efficiency associated with various strategies.

Ethics statement

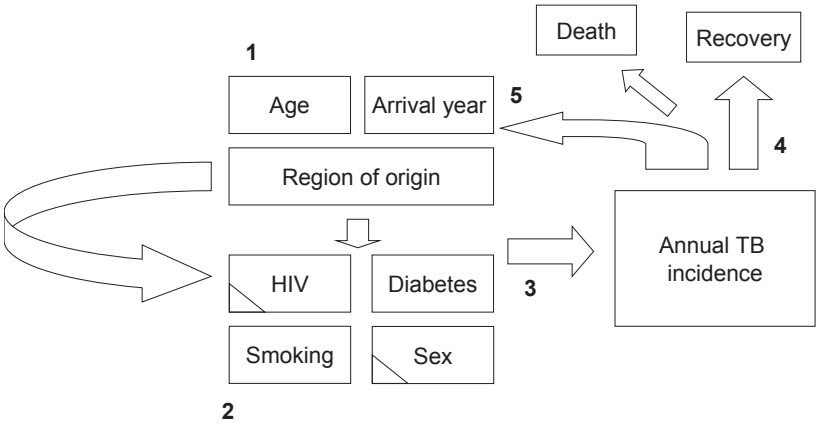
Data on immigrant demographics was obtained from the Australian Bureau of Statistics. Data on country-specific risk of was obtained from the TB Control Program of the Department of Health Victoria. All data used in this analysis was de-identified prior to extraction, with approval for use provided by relevant data managers. According to institutional policy, no review by Human Research Ethics Committee was required.

Results

Baseline scenario

Without additional intervention, the baseline scenario from this model predicts that about 14,700 cases of tuberculosis will occur in 1.5 million immigrants to Victoria during the period 2013–2050, with an expected 318 (95%CI 316-321) cases in 2050. Adjusting for expected population growth, this is equivalent to an incidence of 34.5 (95%CI 34.3-34.8) cases/million population in 2050. Figure 2 shows the baseline scenario incorporating variation in predicted global decline of tuberculosis incidence.

Figure 1: Schematic diagram of model operation.



1. Annual arrival cohorts initially developed, matched with historical cohorts for region of origin and age profiles.
2. Characteristics stochastically assigned in proportion to regions of origin, age and sex. (Sex randomly assigned, 1:1).
3. Proportionate risk reduction applied to those selected for immigration screening strategies at time of arrival
4. Progression to active tuberculosis stochastically determined, based on individual dynamic hazards.
5. Model updates each year with removal of those diagnosed with TB and death from non-TB related causes, and addition of new arrival cohort.

Sensitivity analyses

Sensitivity analyses were performed around several assumptions within this model. Varying annual global decline in tuberculosis incidence by +/-50% resulted in a range of expected incidence from 28–49 cases/million in 2050 (shown in Figure 2). Sensitivity analyses explored the impact of 1–5% annual increases in the MDR proportion of global TB cases. A 5% proportionate increase per year resulted in about 665 cumulative cases over this period, with a mean of 32 new cases of MDR TB in 2050.

Characteristics of diagnostic tests, particularly the specificity for detection of LTBI, were also explored. Model output was relatively insensitive to diagnostic test specificity, with a decline of an additional four cases per year in 2050 by varying the specificity of a diagnostic test from 80% to 100% (not shown).

Sensitivity analysis considering the impact of secondary transmission was also performed. A 1% risk of secondary case per index case resulted in 322 cases in 2050 (35.0 cases/million), while a 5% risk was consistent with 334 cases in 2050 (36.2 cases/million). A 5% risk would result in an additional 1,156 cases during the period 2013–2050.

Figure 2: Baseline scenario given current trends in tuberculosis global incidence reduction, +/- 50%. Graph displays expected number of annual TB cases (95%CI) in Victoria without additional intervention, 2011-2050.

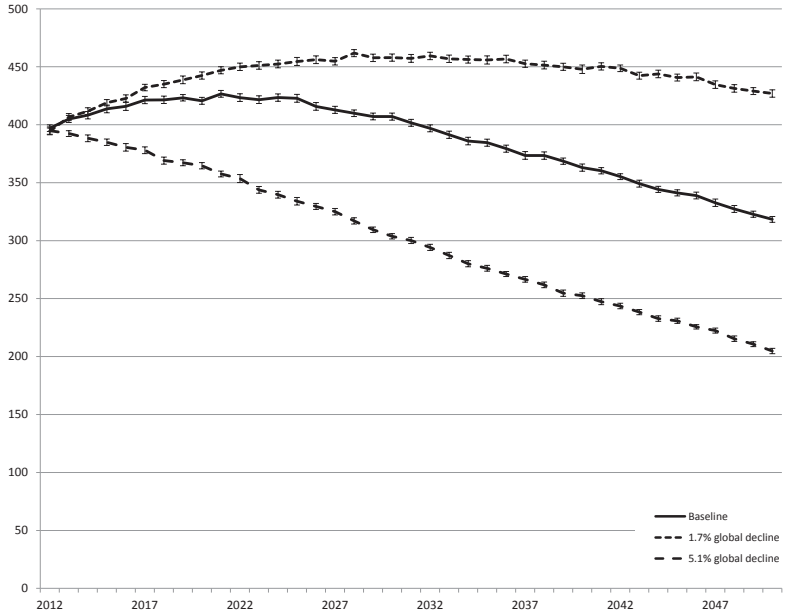


Table 1: Summary comparison of effectiveness and efficiency of various strategies for tuberculosis incidence reduction.

Strategy	Immigrants included in screening*	Number of TB cases prevented**	Number needed to screen (95%CI)	TB incidence in 2050***
Baseline	0	0	NA	34.5 (34.2-34.8)
Interventions for all new immigrants[a]				
TST+INH	1,561,545	3,657 (3,559-3,755)	427 (416-439)	23.8 (23.7-24.1)
QFT+INH	1,561,545	3,744 (3,648-3,840)	417 (407-428)	23.3 (23.1-23.5)
Tspot+INH	1,561,545	4,374 (4,279-4,469)	357 (349-365)	21.8 (21.6-22.0)
TST+INH/RPT	1,561,545	5,022 (4,931-5,113)	311 (305-317)	20 (19.9-20.1)
QFT+INH/RPT	1,561,545	5,219 (5,117-5,321)	299 (293-305)	19.4 (19.2-19.6)
Tspot+INH/RPT	1,561,545	6,055 (5,968-6,142)	258 (254-262)	16.9 (16.7-17.1)
Sub-populations				
Regions with incidence >1000/million	200,602	1,472 (1,363-1,581)	136 (127-147)	30.2 (29.8-30.4)
Regions with incidence >400/million	359,404	1,756 (1,649-1,863)	205 (193-218)	29.6 (29.4-29.8)
Regions with incidence >200/million	748,182	2,516 (2,400-2,632)	297 (284-312)	27.2 (27.0-27.4)

** Cumulative immigrants, 2013-2050*

*** Cumulative cases of TB prevented, 2013-2050. Mean model output values (95%CI) presented.*

**** Per million population/year (95%CI)*

a. Screening applied to all new arrivals after 1 Jan 2013, with treatment given if screening test positive.

INH=isoniazid, RPT=rifapentine. TST = tuberculin skin test, QFT = Quantiferon Gold, Tspot = Tspot TB.

Evaluation of strategies

Screening and chemopreventative therapy

The use of either tuberculin skin testing, Quantiferon or T-spot TB testing was evaluated in conjunction with the use of a nine-month course of isoniazid or a 12-dose (three-month) course of weekly isoniazid and rifapentine. Figure 3 shows a comparison of different screening and treatment strategies applied to all immigrants from 2013, while Table 1 presents the total number of cases and TB incidence for the target year 2050. These approaches would involve screening and/or treatment for the entire immigration cohorts, totalling about 1.5 million people during the period 2013–2050.

Based on available estimates of test characteristics, T-spot TB performed best, with 13–17 fewer cases of TB disease per year by 2050 than if screening had been performed with TST ($p<0.05$). Overall, however, the use of any screening test led to a significant reduction in TB incidence, while differences between the various screening tests for latent tuberculosis were relatively minor. The use of isoniazid and rifapentine combination therapy resulted in significant reduction in tuberculosis incidence, with 154–158 fewer cases per year by 2050 when used in conjunction with Tspot TB (versus baseline; $p<0.01$). The additional benefit from the use of isoniazid and rifapentine was about 25–30 cases/year by 2050, regardless of which diagnostic test for LTBI had been employed.

Various subpopulation of interest were also selected for screening and treatment. Strategies targeting personal risk factors for tuberculosis reactivation, such as diabetes and HIV infection, were not effective in reducing TB incidence, probably due to low proportions in arrival cohorts (not shown). Strategies targeting screening and treatment to those from high-prevalence regions of origin were also evaluated, with results shown in Table 1. Combinations of screening and chemopreventative therapy for all immigrants resulted overall in a reduction of about one-third to one-half of the number of TB cases in 2050.

Discussion

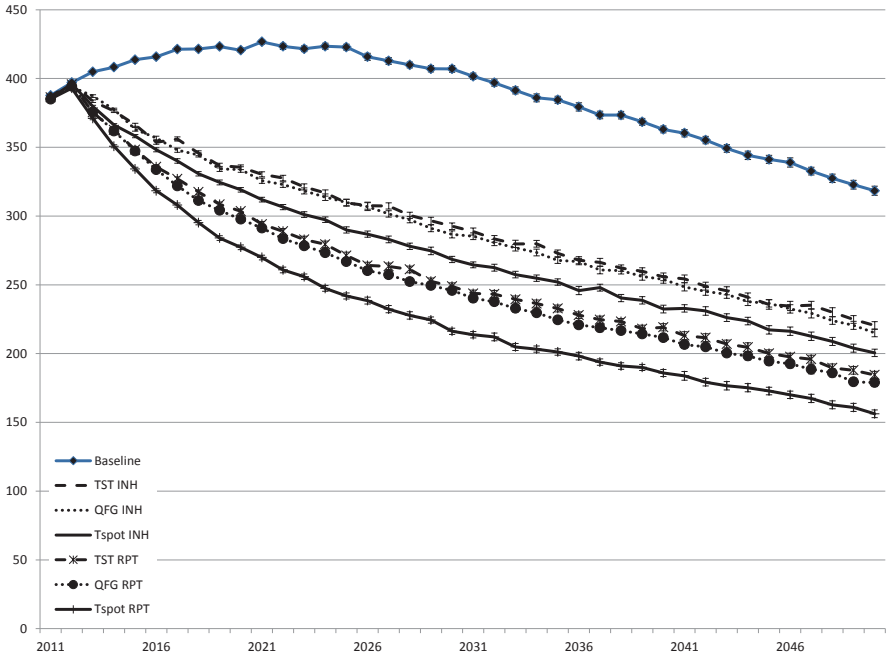
This model suggests that the use of public health strategies targeting latent tuberculosis infection may substantially reduce tuberculosis incidence in a low prevalence region. However, no strategy was considered likely to achieve the 2050 Millennium Development Goal by meeting the TB incidence target of less than one case per million population. While the greatest risk for tuberculosis reactivation occurs in the few years following arrival to a low-prevalence region, even if a completely effective intervention could be immediately incorporated into immigration practices, sufficient risk would persist in prior cohorts to make this target unachievable with such strategies. These conclusions are consistent with analyses from other low prevalence settings, and reinforce the need for contextualised approaches to tuberculosis control.[13]

Other mathematical models have highlighted the value of LTBI screening and treatment, and suggested that its impact may be further augmented by interaction with strategies to control active TB.[14,15] Our findings are consistent with these models, however, they are based on the assumption of significant local TB transmission that limits their applicability in countries such as Australia. In addition, our approach includes the capacity to include a high degree of individual risk characteristics, including age-structure, country of origin and risk factors such as diabetes and smoking history, which have not generally been incorporated into other models.

Predictions arising from this model are dependent on a number of underlying assumptions, particularly relating to future trends in population growth, immigration demographics and international TB control. Individual risk modifiers, such as smoking and diabetes, have also been assumed to be independent and multiplicative, which has limited available data for empiric evaluation. This model is dominated by reactivation of previously latent disease, rather than reinfection or local transmission. However, our intention was to evaluate whether optimised immigration-related strategies may achieve sufficient TB incidence reduction towards the 2050 MDG, and as such, these exclusions are conservative.

Numbers needed to screen in order to prevent one case of tuberculosis ranged from 136 to 395. Such values need to be considered in the context of other public health interventions. The use of faecal occult blood test as a screen for colon cancer has been estimated to prevent one death for every 1,173 people including in screening, while screening with mammography has been estimated to prevent one breast cancer associated death for every 100–2,000 women included, depending on age.[16,17] Similarly, a large randomised-controlled trial of prostate-specific antigen screening for prostate cancer reported that 1,410 men were screened for each death prevented.[18] While TB-associated deaths have not been directly considered in this analysis, previously published data in this region reported 1.2% mortality associated with incident TB cases.[19] Using this figure, more than 10,000 immigrants would need to be screened for each TB-associated death prevented; however, a range of other outcomes, including cost-effectiveness and reduction in risk of secondary transmission would need to be considered in evaluating whether some immigration-related strategy should be adopted. Several countries, including the United Kingdom, have considered that immigration screening programs for latent tuberculosis infection are cost-effective and continue with expansion of existing policies.[20]

Figure 3: Expected number (95%CI) of annual tuberculosis cases in Victoria, 2011-2050, following introduction of various screening and treatment interventions for all new permanent arrivals. INH = 9 months of isoniazid, RPT = 3 months of isoniazid+rifapentine, TST = tuberculin skin test, QFG= Quantiferon Gold, Tspot = Tspot TB.



In order to accomplish the 2050 MDG for TB, a strategy targeting latent-phase infection would need to be expanded beyond immigration cohorts, and may potentially include intervention directed at other high risk groups already resident in Australia. While such approaches have not been considered here, it would appear likely that such programs would involve impracticably large cohorts to accomplish sufficient population-level impact. Alternative approaches, including strategies aimed at reducing tuberculosis disease among those most likely to experience poor outcomes, could be considered. We would highlight that such strategies have considerable potential ethical implications, which have been considered elsewhere.[21]

Sensitivity analyses highlighted the substantial reduction in Australian TB incidence that would result from accelerated global decline in TB disease. When considered in conjunction with the potentially similar magnitude of the impact from targeted screening and treatment demonstrated here, one conclusion may be that Australian efforts in reducing TB incidence could more profitably be directed towards high incidence countries from which immigration originates. This is particularly so given the well-established approaches to reducing active disease incidence already in operation,

and the additional benefit in reducing TB morbidity and mortality globally. While comparative cost-effectiveness analyses have not been considered here, accelerating TB incidence decline in countries such as India, Vietnam and China would be expected to lead to subsequent reduction in Australian incidence also, and are worth exploring in future analysis.

Conclusions

Overall, this model suggests that broad immigration-related strategies targeting LTBI would be effective for reducing TB incidence, but are likely to be too inefficient for introduction as an 'across-the-board' public health measure. Strategies targeting immigrants from high-prevalence regions may be an effective and efficient public health intervention, which could be considered for TB incidence reduction in Australia. This model also highlights the potential value of novel diagnostic and therapeutic approaches, which could further reduce TB incidence in low prevalence contexts in future if appropriately targeted. Strategies concentrating on improved identification of individual immigrants at high risk for TB disease may be more efficient and realistic; however, no immigration-related strategy is likely to meet the 2050 MDG of eliminating TB as a public health issue.

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Supporting information

Additional supprting information may be found in the online version of this article:

Appendix 1: MATLAB code.