
Modelling tuberculosis trends in the USA

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SUMMARY

We present a mathematical transmission model of tuberculosis in the USA. The model is calibrated to recent trends of declining incidence in the US-born and foreign-born populations and is used in assessing relative impacts of treatment of latently infected individuals on elimination time, where elimination is defined as annual incidence < 1 case/million. Provided current control efforts are maintained, elimination in the US-born population can be achieved before the end of this century. However, elimination in the foreign-born population is unlikely in this timeframe even with higher rates of targeted testing and treatment of residents of and immigrants to the USA with latent tuberculosis infection. Cutting transmission of disease as an interim step would shorten the time to elimination in the US-born population but foreign-born rates would remain above the elimination target.

Key words: Incidence, mathematical modelling, tuberculosis.

INTRODUCTION

The incidence of *Mycobacterium tuberculosis* cases in the USA has declined for most of the twentieth century, particularly after the introduction of successful drug regimens mid-century, and has continued to decline so far in the twenty-first century. In 1989, the United States Centers for Disease Control and Prevention (CDC) and the Advisory Council for the Elimination of Tuberculosis published a policy document which established a national goal of tuberculosis (TB) elimination, defined as an annual incidence of < 1 case/million population, by 2010 with an interim annual rate of 35 cases/million by 2000 [1]. However,

the incidence rates in 2000 and 2008 were 58 and 42 cases/million, respectively. Incidence rates over this period of time declined 3·8% annually. Were this rate of decline to persist, elimination of TB in the USA would occur in 2107.

In 2008, 59% of all cases were in the foreign-born population [2]. The arrival each year of people with latent tuberculosis infection (LTBI) contributes to high incidence rates in the foreign-born population. In the US-born population, incidence rates from 2002 to 2008 declined 5·9% annually, with 20 cases/million in 2008. In the foreign-born population, incidence rates from 1993 until 2008 declined 3·8% annually, with 202 cases/million in 2008.

Mathematical modelling offers a means of identifying potentially effective strategies for disease control [3]. Recent TB models are described in [4, 5] of which there are several instances [6–18]. With a few exceptions [13, 16, 17], there has been very little work, to

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our knowledge, on the specific question of modelling TB transmission in industrialized countries when a subpopulation (foreign-born) has a high incidence that slows the overall rate of decline.

We developed a model for the USA similar to the model in [15] and examined the relative impacts of various intervention strategies on the time to elimination: treatment for disease of active TB cases; treatment of latent infection; reduction of the proportion of foreign-born individuals arriving in the USA with LTBI; stopping transmission of disease, which has been suggested as an interim step towards the goal of elimination.

METHODS

Surveillance of newly reported TB cases in the USA is conducted by the CDC's Division of Tuberculosis Elimination in cooperation with state and local health departments. Each individual case is reported electronically and is verified according to case definitions. Reporting areas comprise the 50 states, District of Columbia, New York City, Puerto Rico and other US jurisdictions. Annual counts are recorded and stratified by categories such as location of case, country of origin or birth, gender, site of disease, sputum smear and sputum culture results, drug resistance, HIV co-infection. Annual reports are publically available on the CDC's website [2].

Our model comprises a system of differential equations and was fitted to 2000–2008 TB incidence data [2]. The population is partitioned into US and foreign-born, each divided into compartments intended to capture the epidemiological mechanisms of TB infection (Fig. 1). Each subpopulation has a proportion of preferred contacts with its own members and the remaining proportion mixes randomly in the whole population. The proportion of preferred contacts within the foreign-born population was assumed to be higher than that within the US-born population. There are two compartments for latent infection, one consisting of primary infections, defined as those who develop active disease within approximately 2 years, the other comprising chronic infections progressing to disease at a much slower rate. Individuals with chronic LTBI may be exogenously re-infected and move into the primary infection compartment with some partial immunity acquired by their initial infection. We distinguish between infectious and non-infectious TB. Diseased individuals may self-cure naturally and both infected and diseased individuals

may be treated. Treatment of infection blocks progression to disease; treatment of disease reduces transmission. In all cases, treatment is completed and individuals revert to the susceptible state. New individuals enter the population either by birth or arrival from other countries. All newborns are susceptible. Arrivals are either susceptible or latently infected. All individuals die eventually, those with TB at a higher rate.

Parameter ranges were drawn from the TB literature wherever possible (Table 1), otherwise they were assumed. We used U.S. Census Bureau data for 2000–2008 to estimate birth and arrival rates in each of the US-born and foreign-born populations [19, 20]. These calculations rest on an assumption of a higher natural mortality rate for the foreign-born population whose individuals enter the USA as young adults on average.

We assumed that the proportions of new cases in each subpopulation arising from endogenous reactivation of chronic latent infection ranged from 60% to 70% for US-born and from 75% to 85% for foreign-born. We imputed the reactivation progression rates to disease of each subpopulation by fitting to 2000 incidence data and using estimates of LTBI prevalence for 2000 [21].

Other parameter values are given in Table 1. Initial conditions were derived for 2000 and all simulations run for 100 years. A full description of the model, including the system of differential equations and details about parameter estimation, is available in the online Supplementary material.

To account for uncertainty in parameter estimation and to explore fully the possibility of fitting our model to surveillance data for 2000–2008, we randomly drew parameter values from pre-specified distributions whose ranges reflect epidemiological knowledge, using Latin hypercube sampling [22, 23]. We kept parameter combinations which fit well, as gauged by the following scoring criterion,

$$\text{score} = \|\text{model.inc} - \text{reported.inc}\|,$$

where *model.inc* and *reported.inc* are the time-sequential vectors of model calculated and reported incidence, respectively, for each subpopulation for 2000–2008, $\|\cdot\|$ denotes the square root of the sum of squares, and the total score was calculated as the sum of the scores for each subpopulation. We generated a Latin hypercube sample of size one million for 16 parameters, retaining the best 5000 in terms of fit. Partial rank correlation coefficients were used to

Table 1. Model parameter values and probability distributions

Parameter	Distribution or single value	2·5, 50, 97·5 percentiles (best-fit)	Source
Natural mortality rate	1/78 (USB) 1/53 (FB)	—	[19, 20]
Birth rate USB	0·018	—	Natural mortality and 2000–2008 population data [19]
Arrival rate FB	0·005	—	Natural mortality and 2000–2008 population data [19]
Fraction new infections that are acute	Tri(0·010, 0·056, 0·150)	0·053, 0·092, 0·137 (0·103)	[9]
Acute infection progression rate	1·5	—	95% progression in 2 years
LTBI prevalence USB 2000	Tri(0·014, 0·018, 0·021)	0·015, 0·018, 0·020 (0·015)	[21]
LTBI prevalence FB 2000	Tri(0·135, 0·187, 0·252)	0·158, 0·202, 0·242 (0·211)	[21]
USB fraction of cases from reactivation	Tri(0·60, 0·65, 0·70)	0·623, 0·663, 0·694 (0·667)	Assumed
FB fraction of cases from reactivation	Tri(0·75, 0·80, 0·85)	0·759, 0·793, 0·831 (0·780)	Assumed, based on [29]
USB reactivation rate	imputed	0·0011, 0·0013 0·0015 (0·0014)	2000 incidence [2] and proportion of cases from reactivation
FB reactivation rate	imputed	0·0009, 0·0011, 0·0014 (0·0010)	2000 incidence [2] and proportion of cases from reactivation
Fraction LTBI progressing to infectious TB	Tri(0·50, 0·75, 0·85)	0·569, 0·731, 0·825 (0·708)	[7, 8]
TB mortality rate	Tri(0·06, 0·14, 0·28)	0·071, 0·133, 0·231 (0·115)	[7, 8]
Fraction of re-infections moving to acute infection	U(0, 1)	0·088, 0·394, 0·860 (0·111)	[15], assumes 0·35
Fraction of FB LTBI arrivals	U(0·15, 0·25)	0·157 0·190, 0·232 (0·187)	Assumed
USB annual risk of infection in 2000	U(0·02, 0·03)/100	(0·021, 0·026, 0·030)/100 (0·030/100)	[37]
Effective contact rate	imputed	5·06, 10·22, 21·44 (10·39)	USB ARI and 2000 incidence [2]
Fraction preferred contacts within USB	U(0·85, 1)	0·853, 0·914, 0·995 (0·965)	Assumed
Fraction preferred contacts within FB	Uniform	0·877, 0·960, 0·999 (0·985)	Assumed greater than corresponding fraction for USB
Fraction FB LTBI arrivals progressing within 2 years due to acute infection	Uniform	0·0008, 0·0201, 0·0815 (0·0047)	Assumed less than fraction of new infections that are acute
Cumulative fraction self-cure + treatment active disease	Tri(0·85, 0·90, 0·95)	0·861, 0·898, 0·938 (0·897)	Assumed
Cumulative fraction treatment for acute infection	Tri(0·40, 0·50, 0·60)	0·419, 0·495, 0·574 (0·461)	Assumed
Treatment rate for chronic LTBI	U(0·01, 0·1)	0·015, 0·044, 0·086 (0·057)	[38]

USB, US-born; FB, foreign-born; ARI, annual risk of infection; LTBI, latent tuberculosis infection.

Units for all *per capita* rates are per year. U(x, y) refers to the uniform distribution on the interval (x, y). Tri(x, y, z) refers to the triangular distribution on the interval (x, z) with mode at y . Percentiles refer to samples retained from the Latin hypercube sample according to the score criterion described in the text. Values in parentheses refer to the single set of parameters giving the best fit.

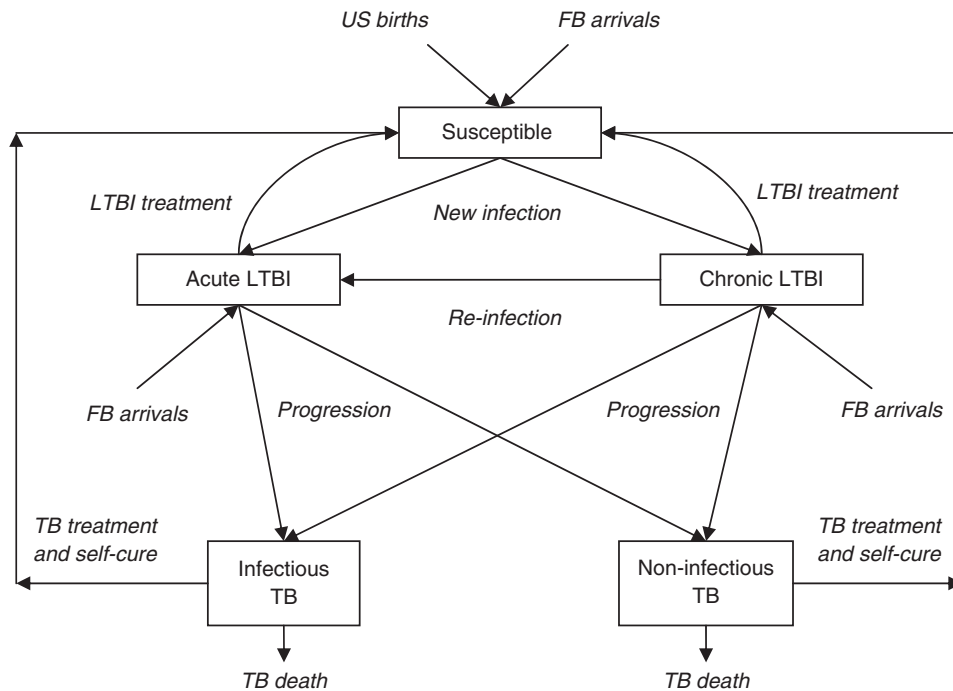


Fig. 1. Schematic diagram of the compartmental TB model. The template applies to the US-born and foreign-born models with arrows shown to distinguish between US births and foreign-born arrivals. Individuals in all compartments are subject to death from natural causes but these arrows are omitted. FB, foreign-born; LTBI, latent tuberculosis infection; TB, tuberculosis.

assess the relative influence of model parameters on outcomes of interest [22, 23].

All simulations were performed with the open source statistical software R, version 2.10.0 [24]. Differential equations were solved by implementation of the 'lsoda' routine [25] with a time-step of 0.02 years.

RESULTS

Elimination of TB was projected to occur by 2100 in the US-born population in 3860/5000 simulations retained for best fit. The median year for elimination was 2063 (Fig. 2*a*, Table 2). Elimination was not achieved by 2100 in either the overall population or the foreign-born population in any of the best-fit simulations (Fig. 2*b*, Table 2). The median annual incidence rate/million for the overall population was 21.3 and for the foreign-born population it was 119.1. Summary statistics of these distributions are given in Table 2.

If transmission of disease is stopped in 2008, all samples project the elimination of TB in the US-born population by 2100 with median year 2048 (Fig. 2*c*, Table 2). While long-term incidence is also reduced in the overall and foreign-born populations, it is insufficient to achieve elimination. The median annual

incidence rate/million for the overall population was 15.5 and for the foreign-born population it was 88.8 (Fig. 2*d*, Table 2). Cutting transmission initially speeds up the rate of decline in incidence for the first few years but is followed by an abrupt slowing down (Fig. 3*a*).

The elimination year for the US-born population may be reduced by as much as 20 years if the treatment rate for chronic LTBI is doubled (Table 2). For the best-fit set of parameters, the elimination year for the US-born population is brought forward from 2056 at baseline to 2033 if the treatment rate of chronic LTBI is doubled and to 2021 if it is quadrupled (Fig. 3*b*). The treatment rate of chronic LTBI is also influential on the foreign-born incidence rate. The annual incidence rate in 2100 for the foreign-born (respectively, overall) population decreases from 103.5 (respectively, 17.7/million) at baseline to 34.7 (respectively, 5.7/million) when the treatment rate is quadrupled (Fig. 3*b*).

The fraction of foreign-born arrivals with LTBI influences the foreign-born incidence rate. However, combinations of doubling the treatment rate and reducing the fraction of foreign-born arrivals to 50% or 25% of its baseline value, while considerably reducing long-term incidence rates, are

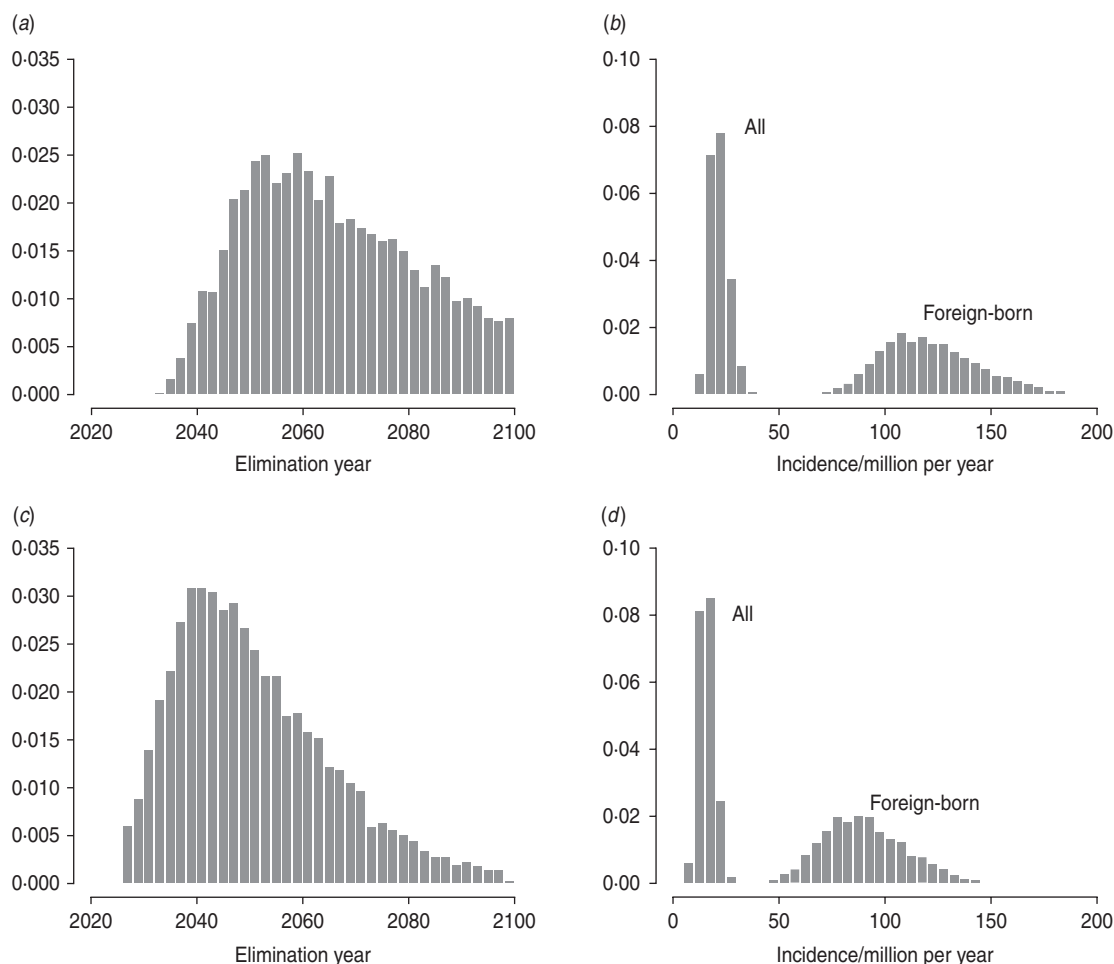


Fig. 2. Effect of cutting transmission in 2008 on densities for overall and foreign-born incidence in 2100 and elimination years for US-born incidence corresponding to best-fit parameter sets in Table 1. (a) US-born elimination times assuming transmission persists. (b) Overall and foreign-born incidence in 2100 assuming transmission persists. (c) US-born elimination times assuming transmission is cut. (d) Overall and foreign-born incidence in 2100 assuming transmission is cut.

insufficient to achieve elimination in either the foreign-born or overall population (Table 2). For the best-fit set of parameters, quadrupling the treatment rate of chronic LTBI and reducing the fraction of foreign-born arrivals to 50% or 25% of its baseline value comes close to achieving the elimination target in the overall population but is insufficient to do so in the foreign-born population (Fig. 3*c, d*).

Medians and 2.5 and 97.5 percentiles for the best-fit parameter combinations are reported in Table 1 as are the specific parameter values corresponding to the overall best fit.

Partial rank correlation coefficients for the US-born year of elimination and long-term incidence rates for the foreign-born and overall populations are given in Supplementary Table S1 (online).

DISCUSSION

Barring major breakthroughs in the ability to markedly accelerate the decline of TB, elimination in the foreign-born, and therefore in the overall, population of the USA is unlikely to be achieved before the end of this century. Incidence rates could be reduced with targeted testing and treatment of LTBI, possibly in conjunction with cutting of transmission, yet these will probably be insufficient to achieve elimination by 2100 or even beyond (Table 2).

Exponential extrapolation of current trends in foreign-born incidence rates implicitly ignores the effect of ongoing arrival into that population of latently infected individuals and therefore projects the possibility of, and earlier times to, elimination of TB in that subpopulation than is likely. However, assuming

Table 2. Summary statistics for projections of US-born elimination year and foreign-born and overall annual incidence per million in 2100 from best-fit parameter samples assuming different intervention scenarios

	2·5 percentile	Lower quartile	Median	Upper quartile	97·5 percentile
Baseline: USB	2039	2052	2063	2077	2096
Baseline: all	14·7	18·6	21·3	24·5	31·4
Baseline: FB	82·6	104·5	119·1	136·4	171·9
USB: A	2029	2039	2048	2059	2085
Overall: A	9·7	13·3	15·5	18·2	23·5
FB: A	55·7	76·1	88·8	103·6	132·4
USB: B	2025	2032	2039	2051	2083
Overall: B	8·9	11·6	13·5	15·9	22·3
FB: B	49·8	65·5	76·2	90·0	124·4
Overall: B+C	4·5	5·8	6·8	8·0	11·5
FB: B+C	25·0	32·9	38·3	45·3	63·6
Overall, A+B+C	3·0	4·3	5·0	6·1	8·6
FB: A+B+C	17·0	24·2	28·8	34·7	48·8

USB, US-born; FB, foreign-born; A, transmission cut in 2008; B, double the baseline treatment rate of chronic latent tuberculosis infection (LTBI) in 2008; C, half the proportion of arrivals with LTBI into the foreign-born population in 2008.

mostly preferred mixing between the two subpopulations, such extrapolations may be reasonable for the US-born population.

High level of treatment of disease distinguishes our study from many infectious disease models which are concerned with outbreaks of epidemics. Early identification of cases and treatment rates for active TB disease are already very high in the USA. Further increase of disease treatment yields small gains in our model. Such high levels of treatment of active disease are a precondition for elimination and the model is consistent with this in that relaxation of treatment rates will eventually result in a resurgence of disease (projections not shown).

Treatment of active disease directly reduces prevalence of infectious TB and hence brings down transmission, which eventually has the effect of lowering incidence. By contrast, treatment of latent infection does not reduce transmission although it does confer that as a secondary benefit over time. Instead, it prevents progression to disease and directly reduces incidence. It has been noted that treatment of latent infection and active disease act synergistically in concert to reduce incidence [15]. However, as treatment levels of disease in the USA are already high (85–95% when added to self-cure, Table 1), a similar payoff accrues by stepping up treatment of chronic LTBI alone.

Reduction in transmission of disease has been suggested as an interim goal towards elimination of TB.

This could be achieved by early identification and treatment of cases before they infect others. Although complete prevention of transmission is unrealistic, we modelled it to examine the impact on incidence rates by setting the parameter governing transmission to zero (Supplementary material). Cases continue to develop via progression of latent infection but now only the foreign-born pool of infection is replenished (by people arriving from outside the USA). After an initial period, cases are predominantly due to progression from the more populous chronic LTBI compartment.

Cutting transmission acts along the same aetiological route as treatment of active disease does, by reducing the force of infection. As the model shows, insufficient benefit is gained from this approach to TB elimination as it does not block progression to disease (Figs 2*c*, *d*, 3*a*). Furthermore, the continued importation into the foreign-born population of latent infection ensures persistent levels of incidence due to reactivation of chronic infection (and due, to a much lesser extent, to recent infection, because of its smaller contribution to incidence, particularly in the foreign-born population).

Sensitivity analysis indicates that increases in current high levels of active TB treatment do little to accelerate the decline in incidence (Supplementary material). By contrast, targeting LTBI would focus on the large pool of individuals whose presence ensures that TB incidence persists via reactivation. Our results

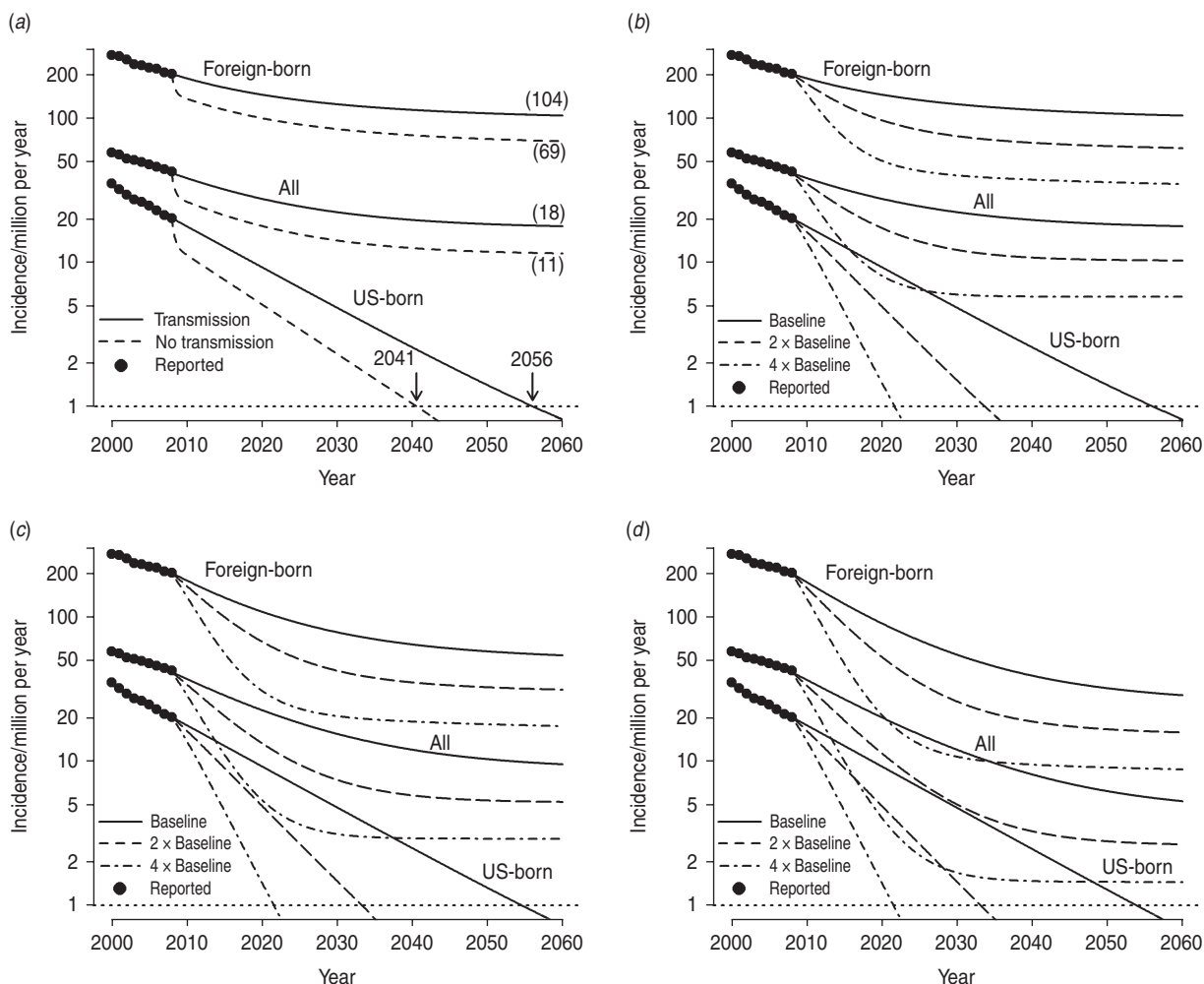


Fig. 3. Incidence projections to 2060 for the best-fit parameter set in Table 1 assuming transmission is cut, or treatment of chronic latent tuberculosis infection (LTBI) increased, or the proportion of foreign-born arrivals with LTBI reduced in 2008. Reported incidence is shown for 2000–2008. (a) Solid curves show projections assuming transmission persists; dashed curves show projections assuming transmission is cut in 2008. Elimination years for US-born are indicated by arrows. Long-term overall and foreign-born incidence levels are shown in parentheses. (b) Incidence projections assuming the treatment rate of chronic LTBI is doubled or quadrupled in 2008. (c) Incidence projections assuming that the proportion of foreign-born arrivals with LTBI is reduced to 50% of the baseline value. The treatment rate of chronic LTBI is doubled or quadrupled in 2008. (d) Incidence projections assuming that the proportion of foreign-born arrivals with LTBI is reduced to 25% of the baseline value. The treatment rate of chronic LTBI is doubled or quadrupled in 2008.

suggest that slowing rates of decline in incidence among the foreign-born population can be expected and the currently observed 3.8% annual decline may not continue in the long term, even with improved treatment interventions or cutting of transmission (Fig. 3).

Parameter ranges for the foreign-born population in Table 1 project long-term incidence rates well above the elimination target (Fig. 2b). By contrast, the outlook is better for the US-born population with elimination likely in the third quarter of this century at current trends (Fig. 2a). Elimination times can be hastened by increasing treatment of LTBI (Fig. 3b).

The foreign-born model differs from the US-born model, where all newborns are uninfected, because it allows for recruitment of individuals with LTBI. This reflects the fact that a substantial proportion of foreign-born individuals arriving in the USA each year are latently infected. The World Health Organization estimates that one third of the world’s population is infected with TB [26]. We allowed the proportion of foreign-born arrivals with LTBI to vary between 15% and 25%, an assumption based on discussions with experts in TB control in the USA and supported by the previously published estimate of 18.7% LTBI prevalence in the foreign-born population in 2000,

since most infection is acquired prior to arrival [21]. Due to the continued flow of latently infected persons into the foreign-born population, progression to disease ensures an ongoing supply of new cases and the incidence rate predicted by the model approaches a fixed value above zero [27]. Cross-infection implies the same for the US-born incidence projections but these long-term values are generally close to or below the elimination goal of one new case annually per one million population. This is seen in Fig. 3*c, d* where the percentage of foreign-born individuals arriving with LTBI was taken as 0.5 and 0.25, respectively, of the baseline best-fit value of 18.72% (Table 1). In Figure 3*d*, the percentage of LTBI arrivals is 4.7% yet elimination does not occur in the foreign-born population. Allowing the fraction of imported LTBI to decrease over time did not qualitatively change our conclusions.

Genotyping studies indicate that most cases in the USA are a result of reactivation of LTBI as opposed to recent infection [28]. The proportion of foreign-born cases developing disease within 2 years of arriving in the USA has been estimated as 28% for the period 2001–2006 [29]. As many of these individuals would have acquired infection more than 2 years before entering the USA, this number represents an upper bound for the proportion of foreign-born cases due to recent infection. Consequently, the proportion of cases due to reactivation of long-term LTBI is at least 72%. We assumed the proportion of foreign-born cases due to reactivation of chronic latent infection ranged between 75% and 85%. Comparison of reported cases for US-born and foreign-born populations in 2000, combined with estimates of the prevalence of LTBI for that year [21], suggest that the proportion of US-born cases due to reactivation are somewhat lower than the corresponding fraction for the foreign-born. A genotyping study conducted in San Francisco estimated that approximately 80% of US-born cases resulted from reactivation [28]. As this study pertained to a highly urbanized area, we conservatively assumed that the national proportion of US-born cases due to reactivation ranged between 60% and 70%. This caused the imputed reactivation rates for the US-born population to be slightly higher than those for the foreign-born population, but not appreciably so (Table 1). Details of calculations of reactivation rates are given in the Supplementary material.

Overall elimination of TB in the USA is possible without elimination in the foreign-born population. For the parameters in Table 1, the foreign-born

population constitutes nearly one-fifth (18%) of the total population long-term. Assuming elimination is achieved in the US-born population, this implies overall elimination is possible while the foreign-born incidence rate remains at around 5 per million. This number depends on the ultimate fraction of foreign-born in the whole population but, as this fraction decreases, the foreign-born rate corresponding to overall elimination increases. This underscores the further effort required to eliminate TB in the foreign-born population.

We calibrated our model by fitting parameter draws to reported incidence data for the US-born and foreign-born populations from 2000 to 2008. Reported incidence in the USA for 2009 showed an unexpected decline in incidence rates. The 2010 rates continued at the same trend detected before 2009 but from the decreased 2009 baseline [30]. We therefore chose to omit these years for fitting.

Caution should be exercised when fitting to a short span of time and projecting over a much longer one as we have done here. We have attempted to control for this by using Latin hypercube sampling and allowing parameters to vary within their epidemiological ranges, reporting summary statistics and showing histograms of projections.

All models are subject to simplifying assumptions in the interests of parsimony and tractability of analysis. Progression rates are known to vary with age. We explored an age-structured model and tested it with a range of possible age-specific progression rates but without cross-infection between the two subpopulations. The results agree qualitatively with those presented here, as do results from a simpler model without either age structure or cross-infection. However, in the absence of reliable published data for the USA on age-specific progression rates and with the difficulties we encountered in modelling both age structure and cross-infection with unknown associated age-specific contact rates, we did not develop an age-structured model incorporating cross-infection. We did, however, account for the difference in lifespans between the two subpopulations by taking the average age of entry of foreign-born as 25 years [20] and increasing the corresponding mortality rate (Supplementary material).

It has been argued that there is no epidemiological evidence of substantial cross-infection between the US-born and foreign-born groups in the USA [28, 31]. We included cross-contact, which leads to cross-infection, by allowing for a high proportion of

preferred mixing within one's own population, assuming this proportion was higher for the foreign-born than for the US-born groups. Sensitivity analysis showed that these parameters have no effect on long-term incidence projections for the foreign-born, but the levels of contact made by foreign-born with US-born individuals do have some effect on prolonging elimination time for the latter subpopulation. This implies that the higher the assumption of preferred mixing of foreign-born with foreign-born individuals, the less the influence on US-born incidence. In the simulations we explored, dropping the assumption of cross-infection tended to result in virtually all good-fit parameter combinations projecting elimination this century, and projections tend to move closer to simple exponential extrapolations of the 5.9% annual decline in the US-born population.

It is generally thought that low-prevalence settings, such as the USA, preclude the opportunity for re-infection in the native-born population [32]. However, some modelling studies indicate that re-infection can play an important role in these situations due to heterogeneity in contacts [14] and also due to the arrival of foreign-born individuals from high-burden countries. We therefore included re-infection and allowed the immunity conferred by prior infection range anywhere from none to full immunity. Sensitivity analysis showed that re-infection is not influential on model projections and accordingly, we believe re-infection is unlikely to play a significant role in incidence at overall levels.

The simple model presented here accounts for overall national trends as reported annually in the CDC Tuberculosis Surveillance Reports. Any adaptation of this model to individual states or territories would need to take into account appropriate changes in incidence patterns and parameters, such as state-specific proportions of all cases occurring among the foreign-born population. In some instances, the need to include HIV co-infection or multidrug-resistant (MDR) TB would dictate a different model structure.

We deliberately ignored HIV co-infection as it is not a major determinant in the USA transmission dynamics of TB at the overall population level. Following the resurgence of TB in the USA between 1985 and 1992, HIV prevalence has steadily decreased in reported TB cases to 6% in 2008 [2].

Neither did we model MDR TB. In 2008, 0.6% of US-born and 1.2% of foreign-born cases were due to

MDR TB [2]. We examined the effect of including MDR TB as a separate compartment in the model and we assumed that it increases over time to 20% of new cases in the foreign-born population by 2100. This did not substantively affect our conclusions (see Supplementary material). Therefore, while our model projections do not accommodate diminished effectiveness of treatment due to ongoing development of drug resistance, our results are cautiously optimistic. It has been suggested that MDR TB may not be self-sustaining in many countries where it is currently on the rise, although the time to elimination is likely to remain long [33].

A very significant challenge is to set in place conditions such that the long-term foreign-born incidence level is <1 case/million annually. One way of approaching this goal could be for the USA to assist efforts in enhancing TB control programmes in those high-burden countries from which many individuals come to the USA to live. This would reduce the fraction of people arriving with LTBI which our sensitivity analyses indicate is an influential model parameter. Such scenarios have been shown to be cost-effective in the case of persons coming to the USA from Mexico [34]. Moreover, assistance in improvements in population health in high-burden countries promises to further reduce TB outcomes in those countries and therefore may be another important avenue for consideration [35, 36].

New treatments for LTBI with shorter completion times could allow for increased treatment rates which could reduce the long-term incidence levels within the foreign-born and overall populations. It seems reasonable to assume that targeted testing and treatment of LTBI will be necessary given the large numbers of individuals involved and high rates of treatment required for our model to achieve levels close to elimination in an acceptable time-frame. This is a public health undertaking whose direction might be assisted by a more sophisticated model, building on the basic premises presented here. Without such interventions, it seems likely that long time periods to elimination would persist or that an annual incidence level of 1 case/million may not be possible. Thus, TB elimination within the twenty-first century will necessitate new tools for diagnosis of LTBI and shorter and safer treatment regimens, or even an effective vaccine, particularly among the foreign-born population, both newly arriving and currently residing in the USA.

NOTE

Supplementary material accompanies this paper on the Journal's website (<http://journals.cambridge.org/hyg>).

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DECLARATION OF INTEREST

None.

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