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Background. *Simulation models are useful in policy planning for tuberculosis (TB) control. To accurately assess interventions, important modifiers of the epidemic should be accounted for in evaluative models. Improvements in population health were associated with the declining TB epidemic in the pre–antibiotic era and may be relevant today. The objective of this study was to develop and validate a TB transmission model that accounted for changes in population health.* ***Methods.*** *We developed a deterministic TB transmission model, using reported data from the pre–antibiotic era in England. Change in adjusted life expectancy, used as a proxy for general health, was used to determine the rate of change of key epidemiological parameters. Predicted outcomes included risk of TB infection and TB mortality. The model was validated in the setting of the Netherlands and then applied to modern Peru.* ***Results.*** *The model, developed in the setting of England, predicted TB trends in the Netherlands very accurately. The* R_2 value for correlation between observed and predicted data was 0.97 and 0.95 for TB infection and mortality, respectively. In Peru, the predicted decline in incidence prior to the expansion of ''Directly Observed Treatment Short Course'' (The DOTS strategy) was 3.7% per year (observed = 3.9% per year). After DOTS expansion, the predicted decline was very similar to the observed decline of 5.8% per year. **Conclusions.** We successfully developed and validated a TB model, which uses a proxy for population health to estimate changes in key epidemiology parameters. Population health contributed significantly to improvement in TB outcomes observed in Peru. Changing population health should be incorporated into evaluative models for global TB control. **Key words:** cost-effectiveness analysis; decision analysis; Markov models; priority setting for spending; strengthening health systems; infectious disease. **(Med Decis Making 2011;31:53–68)**

Tuberculosis (TB) continues to account for a substantial burden of death and disability worldwide. The World Health Organization (WHO) estimated in 2006 that there were 8 million new cases with 2 million deaths, ranking in the top 10 most important causes of mortality in developing countries.[1,2] Recent decades have witnessed a TB resurgence; the international community has responded with increased commitment and funding to control the pandemic.[1,3] In response to this increased funding, stakeholders have outlined various strategies to reduce morbidity and mortality. However, there remains considerable debate as to the optimal use of these resources.

The epidemiology of TB is complex, notably the long, unpredictable latency period between acquisition of infection and development of contagious clinical disease. In addition, transmission varies with clinical parameters as well as disease setting. The important contribution of influences such as HIV infection and nutritional status to TB pathogenesis can also be difficult to understand and tease apart. Computer simulation models have proved particularly useful in informing choices between alternative TB control interventions: their strength has been the ability to forecast events over a long

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time horizon and the capacity to model explicitly the influence of key parameters such as changes in HIV coinfection rates and TB drug resistance.[4,5] However, no such simulation model has explicitly captured the impact of background changes in general population health.

Nonetheless, general population health is important to capture in any model used for evaluation and decision making, as its impact on TB-specific outcomes may be substantial. Improved general health accounted for declining TB morbidity in the first half of the 20th century in many Western European countries,[6] before the advent of effective treatment. The important influence of general health in the past makes it highly relevant to understanding current and future TB burden in low- and middle-income countries where general health and living standards are now improving.

A deterministic disease simulation model can incorporate the impact of changing population health. The advantage is the flexibility and the transparency of the model, which lends itself well to decision making, notably via cost-effectiveness evaluation.[7] In order to accurately capture the impact of general health on TB outcomes, it must first be incorporated into a simplified disease model representing the natural history of TB, without other modifiers such as diagnosis and treatment. As in previous modeling efforts,[8] data from the pre–antibiotic era in Western Europe can be used for development and validation. Once the impact of general health on the natural history of TB is suitably modeled, then diagnosis, treatment, HIV infection, and drug resistance can all be integrated and the distinct contribution of each addressed. The model can then predict and compare the impact of new TB control interventions in modern settings where general health conditions are evolving substantially.

Our first objective was therefore to develop and validate a deterministic model that accurately captures the influence of general population health on TB outcomes. To better represent the epidemic, the model also incorporates a novel approach to simulating the transmission of TB infections within a population. As a case study, we examined Peru as a setting where recent changes in general health may have influenced TB epidemiology, at a time of improvement in both the TB control program and general living conditions. Specifically, we compared a treatment scale-up intervention to a minimal treatment strategy, to demonstrate the potential application of our model to a modern setting.

METHODS

Overview

We first developed a deterministic simulation model, using probabilistic methods, with a changing population level risk of TB infection that can be estimated iteratively. The TB transmission model included a number of Markov processes and was developed to predict the natural history and associated outcomes of an untreated TB epidemic over a time period of 40 years. Over the 40 years, the model tracks a hypothetical population through a sequence of yearly transitions between health states. These health states describe the population's current health. At the start of the analysis, the population is divided into the following categories: uninfected, infected with latent TB, prevalent active TB case, and spontaneously cured TB case. From each of these states, TB disease progression is estimated during each Markov cycle. As examples, in each year, progression from latent TB infection to active TB disease will occur for a fixed percentage of the infected population, and a variable percentage of those who were previously uninfected will become infected with TB (depending on infection risk in each specific year). Estimated transitional probabilities, obtained mostly from the literature, are used to determine the path followed through each transitional process and ultimately the health state that the population moves into in the subsequent year. The probability of developing TB disease and cumulative probability of generating infections from active TB cases and dying from TB are tracked for the population over time, from entry into the simulation until death or when the end of the analysis is reached.

The model was developed using published data from the first half of the 20th century in England and Wales. TB pathogenetic estimates were taken from published literature; for those where there was uncertainty, data from 1900 were used for calibration. Background changes in general health were incorporated by assuming relevant changes in specific TB pathogenetic parameters. Models were evaluated by comparing predicted outcomes with reported outcomes. The model was validated using reported data from the corresponding time period in the Netherlands. Finally, pathogenetic parameters were recalibrated and applied to Peru to consider the potential impact of improving general health in a modern setting. To capture key aspects of TB epidemiology in our model, we identified essential aspects of TB pathogenesis, which we will first review.

TB Pathogenesis

Latent TB infection (LTBI) is defined as the presence of latent or dormant infection with *Mycobacterium tuberculosis* with no clinical, radiological, or microbiological evidence of active disease. It is detectable only by testing for the body's immune reaction to *M. tuberculosis* reactivity via the tuberculin skin test and more recently with new blood tests (interferon γ release assays). After acquiring TB infection, some patients (~5%) will progress immediately to active disease. For others, the infection remains latent for an extended period of time, but disease develops later in life (~5%). The development of active disease after a period of latency is known as reactivation. Immunocompetent persons with TB infection are believed to have a cumulative 10% lifetime risk of developing active disease[9]; 90% never develop active TB disease.

Since the early 20th century, active pulmonary TB disease has been diagnosed and characterized by microbiological examination of sputum, meaning direct microscopy and culture. Specifically, patients are described as having sputum smear-positive or smear-negative pulmonary TB. Smear-positive disease implies a burden of bacteria and disease sufficient that TB bacteria are seen on direct microscopic examination of a sputum sample. Smear-negative disease implies a lower bacterial burden, so that bacteria are only identified with culture of the sputum sample. Smear-positive disease is typically symptomatic, progressive, and highly contagious. Smear-negative disease is variably symptomatic, indolent, and less contagious. Only persons with active pulmonary TB can spread the infection to others. Figure 1 summarizes the natural history of TB in general terms.

We adapted the pathogenetic process described above into a probabilistic framework. At the start of the analysis, the simulated cohort was divided into 3 main states: uninfected, latent TB infection, and active TB disease. Figure 2 shows a simplified overview of the distribution of the population. Active TB cases were further divided into smear-positive and smear-negative cases. Both types of cases could transmit TB infection, but smear-positive cases were considered 5 times more contagious than smear-negative cases,[10] and annual mortality of smear-positive cases was 4 times that of smear-negative cases.[11–14] Hence, while the annual number of new infections caused by smear-negative cases was likely much fewer, their much longer survival meant that the total number of transmitted infections would be very similar. Latent TB infection was divided into recently and remotely acquired infection, in view of their different associated risks of reactivation.[15,16] Recent infection was further divided into recent primary TB infection and recent reinfection because of the protective effect of antecedent primary infection. Estimates of the protection conferred by previous infection were obtained from 2 cohort studies in the pre–antibiotic era.[17,18]

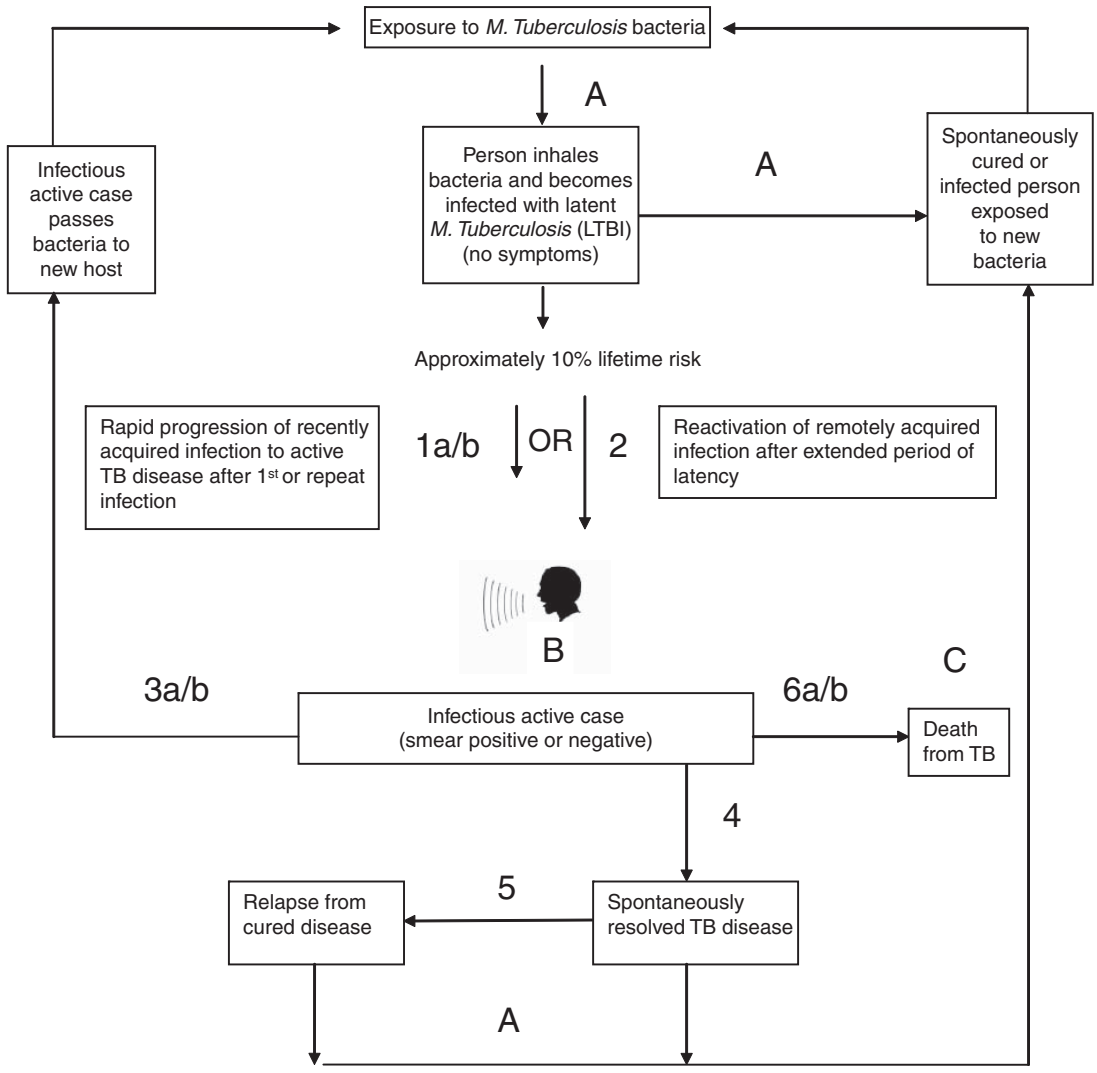
Using the same probabilistic framework, the TB disease process has been placed into a larger framework in Figure 3. This figure demonstrates the points of action of various interventions for disease control, some of which are considered in this study and some of which are not.

Reported TB Outcome Data Used for Model Calibration and Assessment

Reported TB infection or TB mortality rates could both potentially be used for model calibration and assessment as detailed data for both outcomes were available from the appropriate period in England and the Netherlands. We focused on risk of infection as this was believed more reliable than adult TB mortality in the pre–antibiotic era (see Discussion). Community risk of TB infection can be observed either directly from tuberculin skin testing surveys or inferred indirectly by extrapolating from infant meningeal TB mortality rates. This is because 1) newly infected infants have a high risk of this form of disease soon after acquiring TB infection, and 2) case fatality of meningeal disease is close to 100% when treatment is not available. Thus, using methods described by Styblo,[19] reported rates from a population can be used to estimate the risk of TB infection. In England and Wales, tuberculin skin test surveys were not carried out in the pre–antibiotic era, but meningeal TB mortality was collected in detail. Accordingly, for calibration purposes, our gold standard for actual community risk of TB infection in the pre–antibiotic era was annual risk of TB infection that was derived from reported infant mortality from TB meningitis, as calculated by Vynnycky et al.[20]

Incorporating a Population Level Transmission Component

Estimation of the annual risk of TB infection based on the number of smear-positive cases[6] has been criticized as no longer applicable in modern settings.[21] Therefore, in order to develop a model that could iteratively predict the population risk of TB infection, and that could ultimately be used to accurately estimate the impact of interventions on transmission, we developed a novel method to estimate the TB



LEGEND:

TB related outcomes estimated by model:

A = annual risk of acquiring TB infection (dynamic)
B = number of new active TB cases
C = number of TB-related deaths

Key Model inputs:

1a/b. Probability of progressing to active TB disease after new 1st /repeat infection
2. Probability of reactivation from latent infection to active TB disease
3a/b. Number of infections generated from a smear positive/negative active TB case
4. Probability of spontaneous resolution of a smear positive or negative active TB case
5. Probability of relapse from spontaneously cured active TB case
6a/b. Case fatality rate for smear positive/negative active TB disease

Figure 1 Summary of the natural history of tuberculosis.

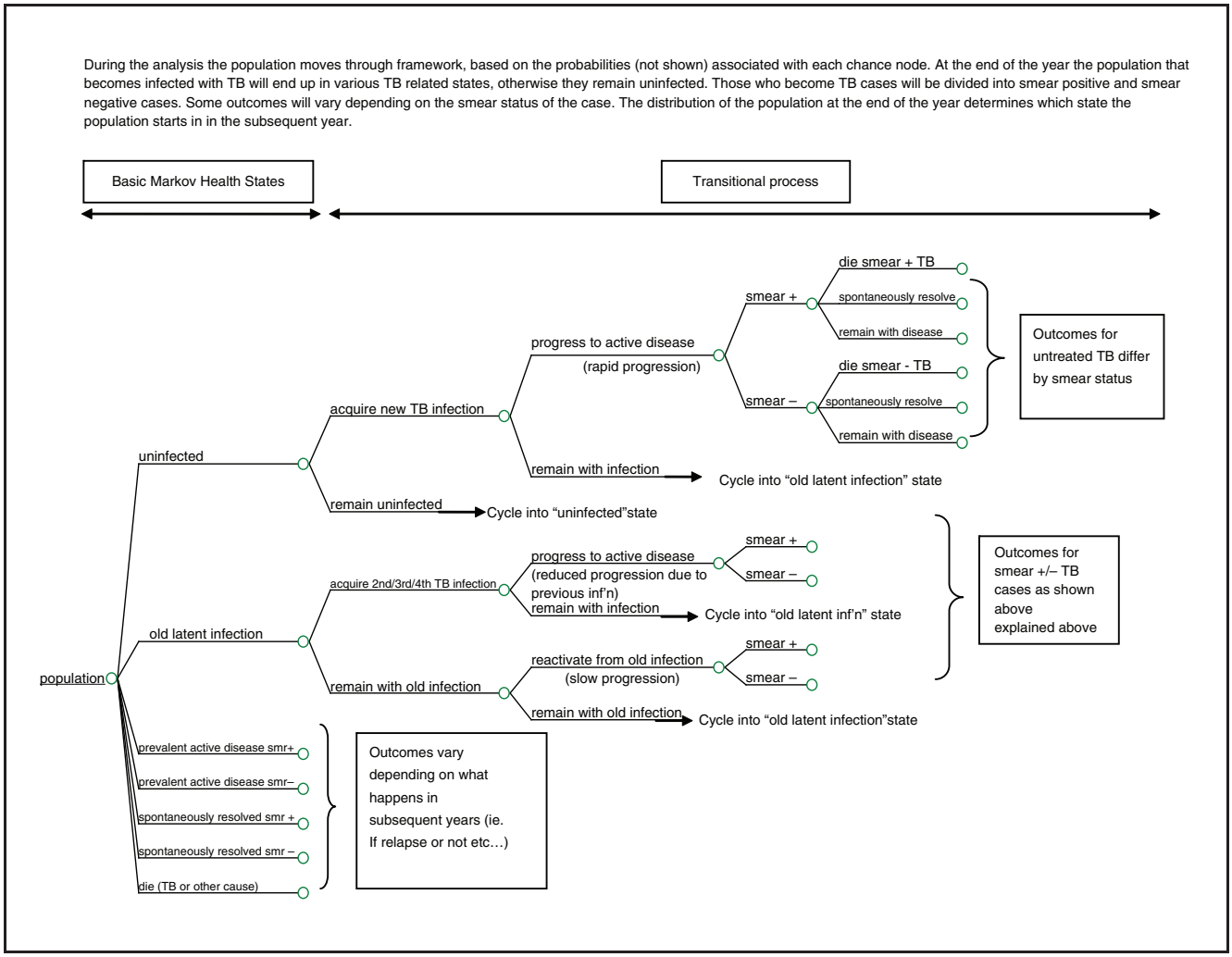


Figure 2 Disease model translated into a probabilistic framework (simplified).

infection risk using our model. In each year, we estimated the number of smear-positive and -negative TB cases, each of whom generated a specific number of new infections that year (Figure 4A). The number of infections generated by each case, termed the ''infectivity,'' depended upon whether the case was smear positive or negative (Figure 4B) and the outcome: death, spontaneous resolution, or persistence to the next year (Figure 4C). The total number of infections generated from all active cases over the year was summed and used to calculate the risk of TB infection that was applied to the population during the following model year (Figure 4D). In summary, the TB infection risk in each year reflected the incidence and outcomes of all active TB in the population in the preceding year.

Developing and Calibrating the Model for England and Wales

We developed a transmission model that included a number of Markov process in order to predict outcomes in a cohort of adults over a 40-year period. Models were built using decision analysis software (Treeage Professional 2007, Williamstown, MA). The population was dynamic as the proportion that died each year was reintroduced into the model in the subsequent year, allowing new susceptibles to enter each year. This new population represented a group of young adults. Within the new group, some had latent infection, some had prevalent smear-positive or -negative TB disease, and some had no infection.

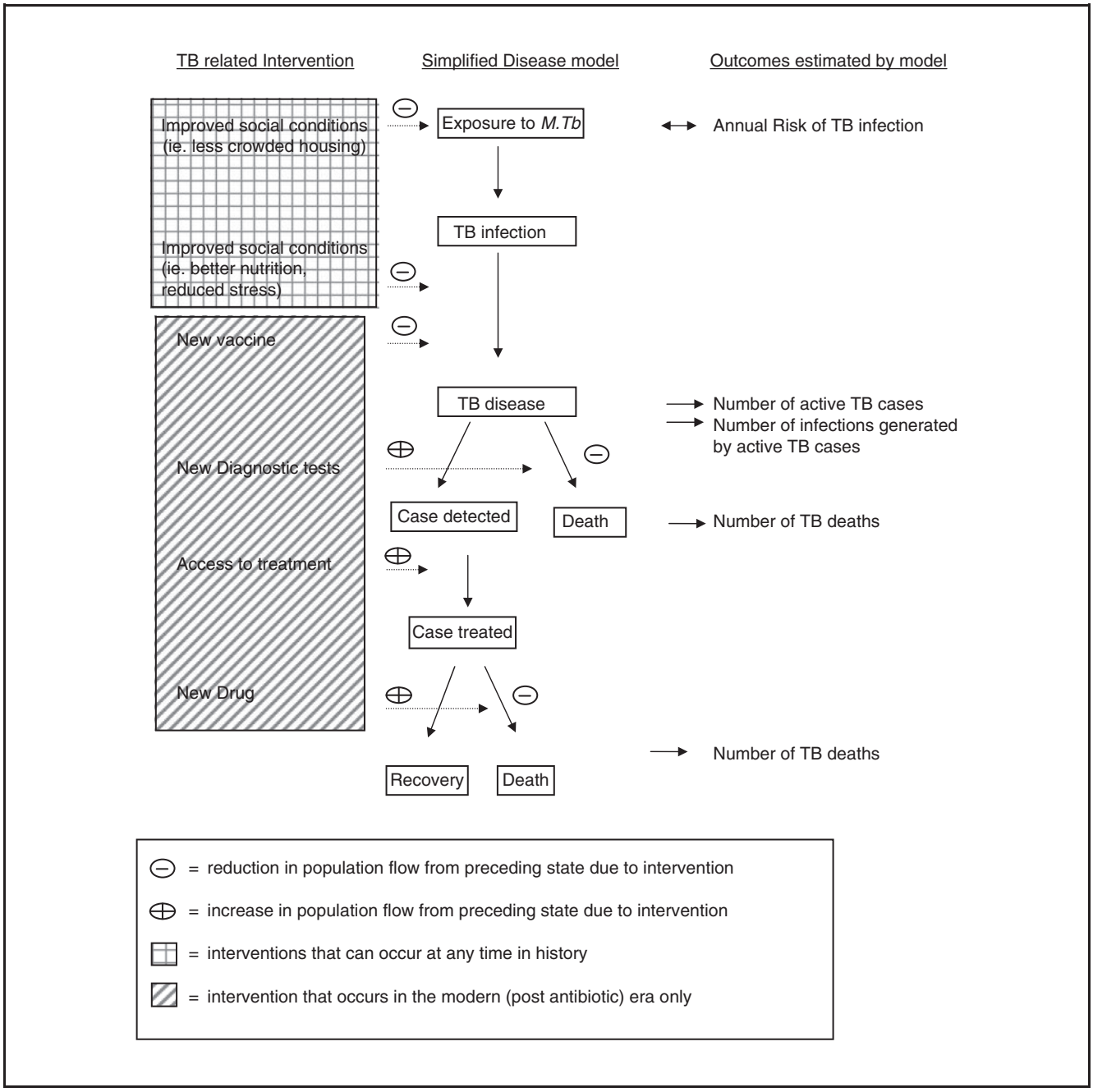
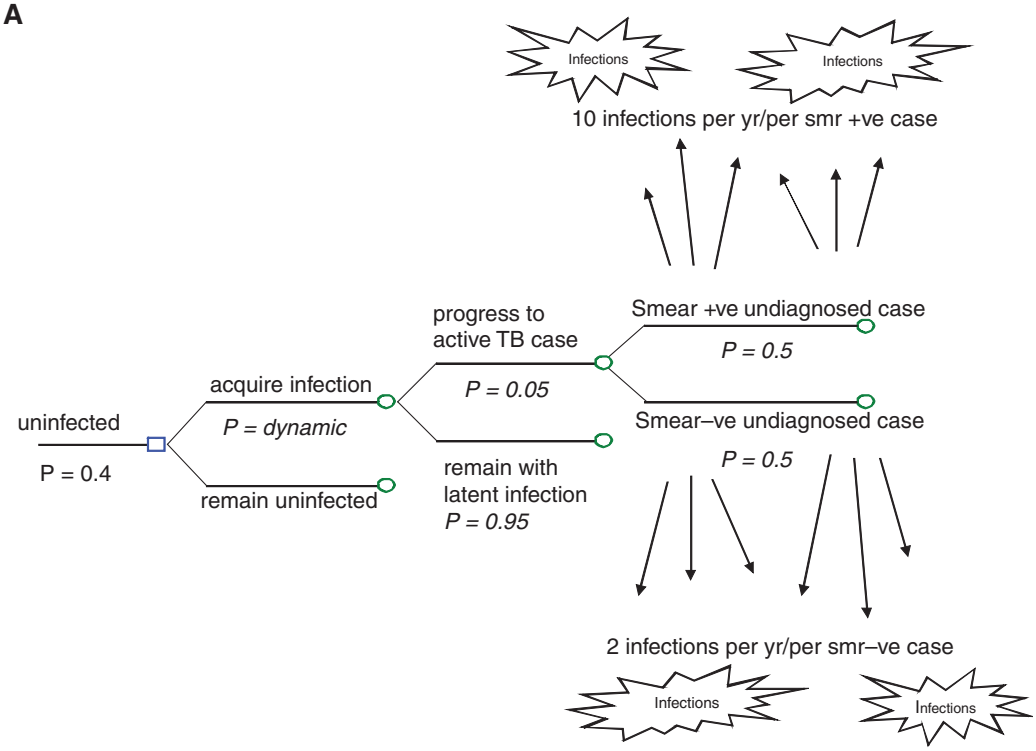


Figure 3 Simplified outline of how a disease model could integrate with interventions and outcomes (not representative of model described in main text).

The proportion with latent infection was determined by the age of the new population, while the number of prevalent cases matched the proportion of prevalent cases in the preceding year of the simulation. The remainder of the new population was uninfected and thus susceptible to acquiring new infection.

Models assumed no effective interventions for TB control. At the end of each year, 3 outputs were generated by the model: number of new TB

A



smr +ve = smear positive active TB case
smr – ve = smear negative active TB case
P = probability of event occurring

B

Risk of TB infection generated from newly infected TB cases[†]:

=(0.4*0.10*0.05*0.5) * 10 infections from undiagnosed active smr positive cases= 0.001*10=0.01= 1%

=(0.4*0.10*0.05*0.5) * 2 infections from undiagnosed active smr negative cases= 0.001*2=0.002= 0.2%

Risk of TB infection generated from newly infected smr +ve and smr –ve cases = 1%+0.2%=1.2%[††]

[†]Assumes risk of TB infection in previous year is 10%. Probabilities for decision nodes obtained from Table 1.
[††]Risk of TB infection increases when infections generated from other types of cases are accounted for

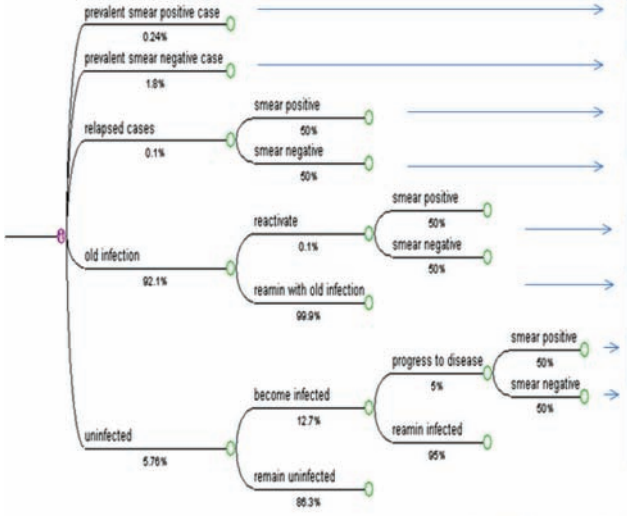
smr +ve= smear positive active TB case
smr -ve= smear negative active TB case

(continued)

C

Type of active TB case	Duration of infectivity	Number of infections generated over period- if **smear positive case**	Number of infections generated over period- if **smear negative case**
Undiagnosed- prevalent active case	Full year	10	2
Spontaneously resolved	Half year	5	1
Relapsed	Half year	5	1
Case that dies (from TB or other cause)	Half year	5	1

D



Infn's generated	Contribution to Risk of TB infection
10	=0.0024*10=0.024=**2.4%**
2	=0.018*2=0.036=**3.6%**
5	=0.001*0.5*5=0.0025 =**0.25%**
1	=0.001*0.5*1=0.0005 =**0.05%**
5	=0.921*0.001*0.5*5 =0.0023=**0.23%**
1	=0.921*0.001*0.5*1 =0.00046=**0.046%**
5	=0.0576*0.127*0.05*5 =0.0018=**0.18%**
1	=0.0576*0.127*0.05*1 =0.00037=**0.037%**

TOTAL RISK OF TB INFN IN YEAR ∑=6.8%*

*Model is simp lified for illustrative purposes. Probabilities and risk of TB infection estimates are not accurate as they are for illustration only.

Infn= Infection

Figure 4 (A) Illustration of the process of generating infections from infectious smear-positive and smear-negative active tuberculosis (TB) cases. (B) Generating a dynamic risk of TB infection using decision nodes and the sum of infections from smear-positive and smear-negative cases in the population each year. (C) Infections generated from all subtypes of TB cases. (D) Illustration of decision nodes, infections generated from subtypes of TB cases, and their contribution to the total risk of TB infection.

infections (used to calculate risk of TB infection), as well as the number of TB cases and TB-related deaths.

In order to deal with uncertainty in the initial prevalence of TB-related epidemiological states, and the values of TB pathogenetic parameters in 1901, the model was calibrated so that it could accurately predict reported risk of TB infection in England and Wales in 1901. More detail about the model calibration process is described in the Supplementary Appendix (Model Calibration) and shown in Supplementary Figures S1A to S1C. Initial prevalence estimates of disease-related states, used only in the first year of the model, are listed in Table 1. Final values for each specific probability of making a transition between disease-related states (i.e., transitional

Table 1 Observed Risk of Tuberculosis (TB) Infection and Estimated Prevalence of Different TB States at Start of Modeling in England and Wales and in the Netherlands

Epidemiological Parameters	England and Wales in 1901[a]	the Netherlands in 1910[a]
Annual risk of TB infection	12.7%[b]	11.3%[b]
Prevalence of TB states		
Latent infection		
First infection	7.0%	7.5%
Second or more	85.1%	84.7%
Active TB disease		
Smear positive	0.24%	0.21%
Smear negative	1.7%	1.6%
Spontaneously resolved active cases		
Smear positive	1.6%	1.5%
Smear negative	2.2%	2.0%
Uninfected	1.93%	2.4%

a. These values above apply to the starting year only. In all subsequent years, all values vary over time.
b. Source: References 6, 20.

Table 2 Ranges and Final Values of Transitional Probabilities for Tuberculosis (TB) Pathogenetic Parameters Used at Start of Modeling for England and Wales in 1901

TB Pathogenetic Parameters	Range	References	Value Used at Start (1901)
Progression parameters			
Progression to disease after new first infection	2%–5% (2-year risk)	(15, 22)	4% (2-year risk)
Protection conferred by earlier TB infection against progressing to TB disease after repeat infection	74%–90%	(23, 24)	77%
Reactivation from latent infection to TB disease	0.02%–0.3% per year	(16, 25, 26)	0.26% per year
Infectivity parameters			
Number of infections generated from an untreated smear-positive case over 12 months	1–22 infections per year	(6, 27)	17.5 infections per year
Number of infections generated from an untreated smear-negative case over 12 months	Smear-positive number of infections per year/5	(10, 28)	3.5 infections per year
Other parameters			
Spontaneous resolution of smear-positive or -negative TB disease	25% (overall)	(29)	25%
Relapse from spontaneously cured disease	1.3%–2.5% per year	(29, 30)	2.5% per year
Mortality from smear-positive TB	81%–90% over 5 years	(11–13)	36.4% per year or 90% over 5 years
Mortality from smear-negative TB	28%–35% over 5 years	(14, 31)	7.5% per year or 32% over 5 years

probabilities) are found in Table 2. In order to assess the accuracy of the model, predicted TB infection and mortality rates over time were compared to those reported for males and females of all ages together.[20,32] The Pearson correlation coefficient and R^2 indices were used to compare the model predicted events to those observed.[33]

Incorporating Changes in General Health

In this study, general population health was defined as the health and well-being of groups of individuals. This parameter is influenced by multiple determinants of health including the implementation of medical interventions, changes to health

services and policy, as well as aspects of environmental (both physical and social) and individual behavior. Several specific changes that occurred in Western Europe in the pre–antibiotic era that may have acted to improve population health include the following: better access to a more varied food supply leading to improvements in nutrition, improved sanitation and water supply with the implementation of sewer systems, improved housing with better ventilation, a reduction in family size, and the isolation of sick persons in segregated accommodation (poor houses). In Peru in the 1990s, improvements in general population health may have been attributed to better nutrition and programs focusing on children's health.

To address the main objective of developing a model that accounted for changes in general population health, we had to select a demographic indicator that best captured changes in general health and select the TB epidemiological or pathogenetic parameters that would be affected by these changes. Life expectancy, which was adjusted for TB mortality, was chosen as the indicator of general health for several reasons: 1) detailed year-by-year data were available for more than 40 years in the relevant period in both the United Kingdom and the Netherlands; 2) life expectancy data are available from all countries nowadays, allowing application of the findings to modern settings; and 3) life expectancy is considered a valid indicator of general health; for example, the World Bank states ''changes in life expectancy reflect changes in the overall health of a country's population, in people's living conditions (environmental, economic, social) and in the quality of health care.''[34] Details on how the life expectancy indicator was adjusted for TB mortality can be found in the Supplementary Appendix (Adjusting Life Expectancy Estimates for TB Mortality).

Changes in life expectancy were assumed to affect 2 categories of TB pathogenetic parameters: 1) risk of reactivation or progression from latent to active TB (''progression''), and 2) the number of new TB infections generated per year by each case of active TB (''infectivity''). Three model parameters addressed the risk of progression: risk of reactivation of disease within 2 years after primary TB infection, risk of reactivation of disease within 2 years after reinfection, and risk of reactivation from latent infection present for more than 2 years. These parameters were selected as they have been shown to be affected by immune suppression[35] and malnutrition.[36,37] The decline in ''infectivity'' of both smear-positive and -negative active TB cases was felt plausible given the improvements in environmental factors, such as crowding and housing in England and Wales in those years.[27] Changes in other TB pathogenetic parameters shown in Table 2 may have been responsible for the decline; thus, their role was investigated in sensitivity analysis, as described in the Supplementary Appendix (Sensitivity Analysis on Additional TB Pathogenetic Parameters).

The relationship between change in adjusted life expectancy and change in TB outcomes between 1900 and 1939 was calculated as follows (see equation below and also Supplementary Tables S1A, S1B, and S2 in the Supplementary Appendix for detailed calculations in each country). First, we calculated the ratio between the average annual change in observed TB infection risk and the average annual change in adjusted life expectancy in each country.[20,38] Next, we multiplied this ratio by the percentage change in adjusted life expectancy in each country, in each year. Finally, to estimate the magnitude of change in the TB pathogenetic parameters, we multiplied this number by our selected epidemiological parameter: 1) risk of reactivation of disease within 2 years after primary TB infection, 2) risk of reactivation of disease within 2 years after reinfection, 3) risk of reactivation from latent infection present for more than 2 years, 4) the number of infections generated by each active smear-positive TB case each year, and 5) the number of infections generated annually by each smear-negative TB case.

$x/y * z$ = multiplier used to determine the percentage decline in selected epidemiological parameters (value changes in each year).

x = average annual change in observed TB infection risk (%).

y = average annual change in reported adjusted life expectancy (%).

z = change in adjusted life expectancy in that year (%).

The same methods were used to estimate the magnitude of change by year for the additional parameters considered in sensitivity analysis. Detailed calculations for each parameter varied in sensitivity analysis are shown in Supplementary Table S3 in the Supplementary Appendix.

Validating the Model: the Netherlands, 1910–1949

The model was validated using adjusted life expectancy and TB infection data from the

Netherlands from 1910 to 1949.[6,38] The risk of TB infection in the Netherlands in these years could be estimated from tuberculin surveys or by using data on infant mortality from TB meningitis,[19] as was done in England and Wales. The estimates of risk using these 2 approaches were very similar ($r = 0.97$), as shown in Supplementary Figure S2. Because the tuberculin survey data were available for a longer time period, these were used for the observed TB infection risk. Using methods previously described, the initial prevalence of all TB-related states and transitional probabilities were recalibrated using the reported risk of TB infection in the Netherlands in 1910 (as in Supplementary Figures S1A–C in the Supplementary Appendix, but in the setting of the Netherlands).

Life expectancy estimates from the Netherlands were adjusted to remove the effect of TB mortality, as was done for England and Wales. The same 5 TB pathogenetic parameters were programmed to decline, based on the rate of increase of adjusted life expectancy in the Netherlands, and using the ratio of the relationship between changes in adjusted life expectancy and TB infection rates calculated for England and Wales. Supplementary Table S4 shows annual change in adjusted life expectancy and the specific values for each pathogenetic parameter by year. Again, a measure of goodness-of-fit was used to assess how well this model, derived from England and Wales data, was able to predict reported TB infection and mortality rates in the Netherlands.

Applying the Model to Peru, 1980–1999

Because reliable TB outcome and general health data are available for 10 years before and 10 years after the nationwide implementation of the WHO-supported TB control strategy known as ''Directly Observed Treatment Short Course'' (The DOTS strategy) in 1990, Peru offers the opportunity to assess the independent impact of changes in general health and modern TB treatment. Using methods detailed above, and in the Supplementary Appendix (Model Calibration), key TB pathogenetic parameters were recalibrated using the estimated number of TB cases in Peru in 1980.[39] Final transitional probabilities used prior to DOTS expansion, in 1980, are summarized in Supplementary Table S5. In the model, TB treatment was minimal between 1980 and 1989 (Supplementary Table S6); then, capacity for diagnosis and treatment increased after 1990 to represent countrywide DOTS implementation[39] (Supplementary Table S7). Changes in life expectancy reported over the entire period (1980–1999) were incorporated into the simulation in order to account for changes in population health[40] (see Supplementary Tables S8A–C for more detail). Predicted annual declines in estimated cases and risk of TB infection over time were compared to reported data.[6,39] The contribution of general health to the decline in TB during the period of DOTS expansion was quantified by comparing rates predicted by the model that included improvements in general health but minimal treatment to one that included the same background changes in general health plus scaled-up treatment. More details related to the modeling and specific parameters used are available in the Supplementary Appendix (Applying the Model to Peru).

RESULTS

Developing the Model and Incorporating the Relationship between Adjusted Life Expectancy and TB Infection in England and Wales, 1901–1940

When the average annual increase in life expectancy (recalculated to exclude TB mortality) was calculated between 1901 and 1940, it increased by 0.52% per year. During the same period, the risk of TB infection, based on TB meningitis data from infants, declined 3.8% each year. Thus, the ratio used in all subsequent analyses (calculated by dividing the average annual decline risk of TB infection [3.8%] by the average annual increase in adjusted life expectancy [0.52%]) was 7.3 (i.e., a 1% improvement in adjusted life expectancy was associated with a 7.3% decline in TB infection).

When this ratio was used to estimate the concomitant change in 5 TB pathogenetic parameters (reactivation from long-standing infection, rapid progression after initial infection or reinfection, plus infectivity of smear-positive and -negative active cases), the model accurately predicted TB infection and TB mortality between 1901 and 1940. The R^2 value for correlation between observed and predicted data was 0.91 for TB infection and 0.99 for TB mortality. Figures 5A and 5B show the predicted and observed decline in TB infection and mortality in those years. The mechanisms behind the rapid increase in TB mortality during World Wars I and II were not explored in this study so these years (dotted lines in Figure 5B) were excluded from the R^2 calculations. TB mortality was consistently overestimated by the model, but the trend in mortality was very accurately predicted, as reflected by the high R^2 values

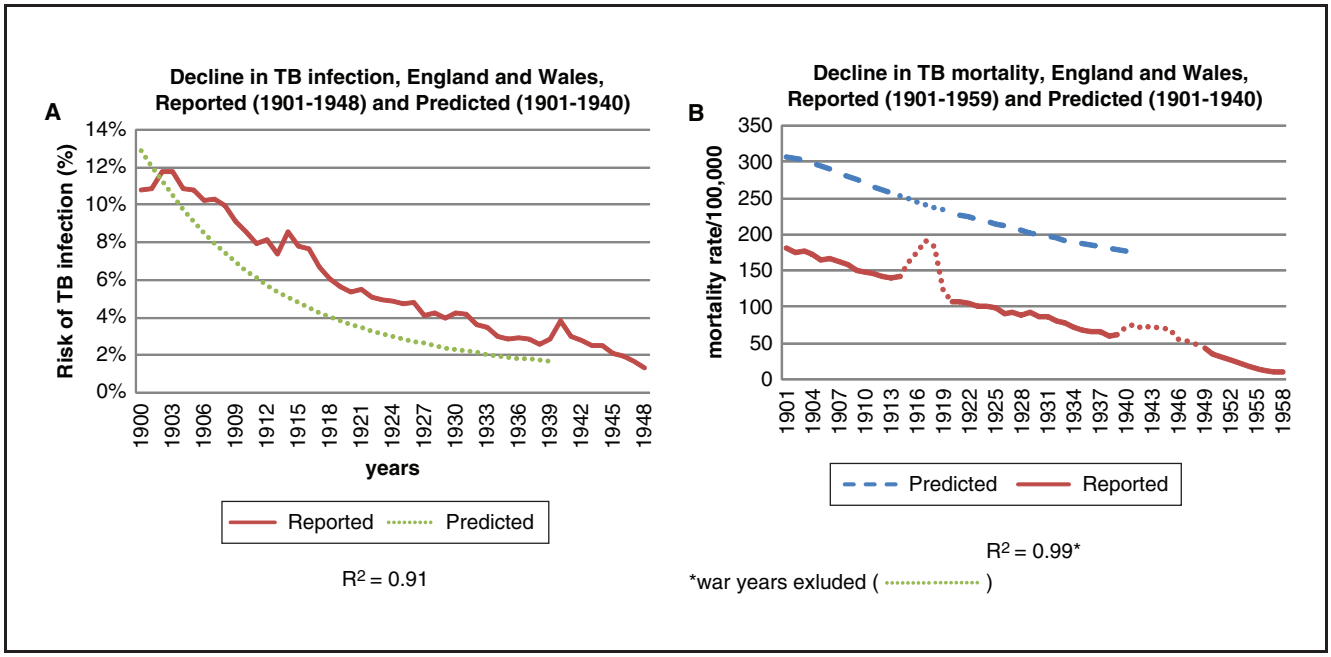


Figure 5 (A) Comparison of the annual risk of tuberculosis (TB) infection predicted by the model between 1901 to 1940 to that reported between 1901 and 1948. (B) Comparison of TB mortality predicted by the model between 1901 to 1940 to that reported between 1901 and 1959.

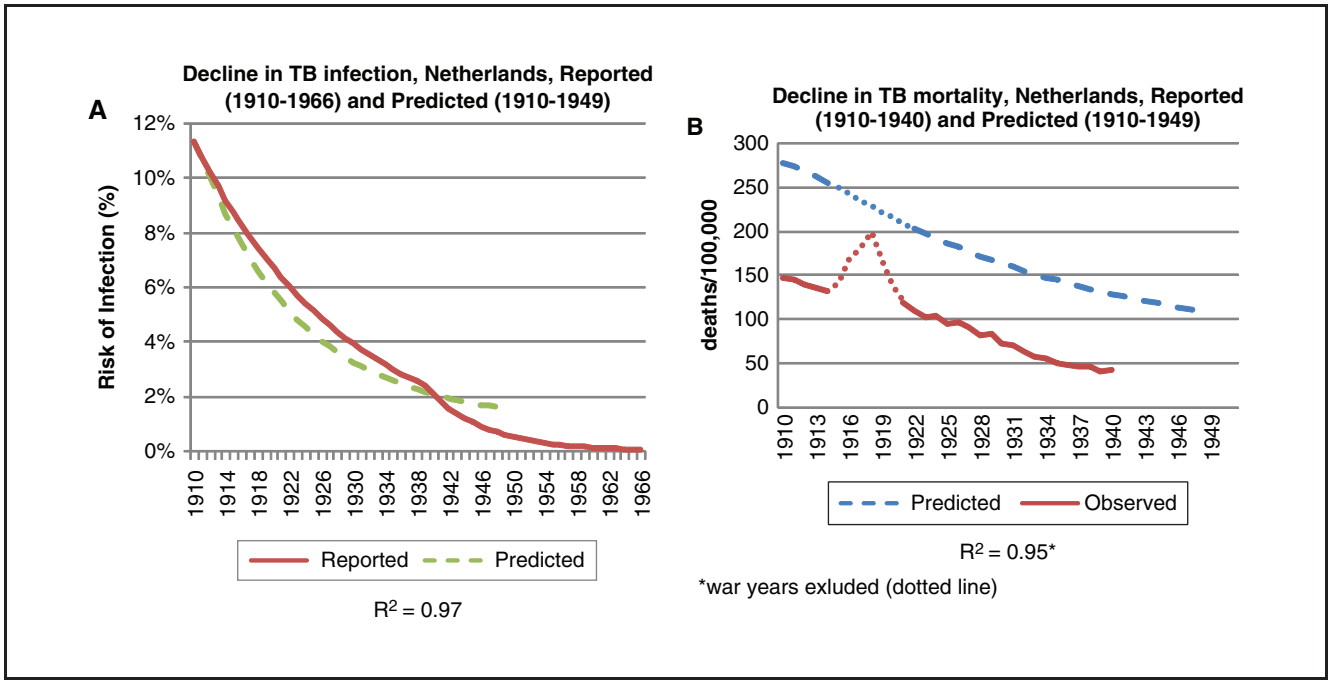


Figure 6 Using the England and Wales model to predict outcomes in the Netherlands. (A) Comparison of the annual risk of tuberculosis (TB) infection predicted by the model between 1910 to 1949 to that reported between 1910 and 1966. (B) Comparison of TB mortality predicted by the model between 1910 to 1949 to that reported between 1910 and 1940.

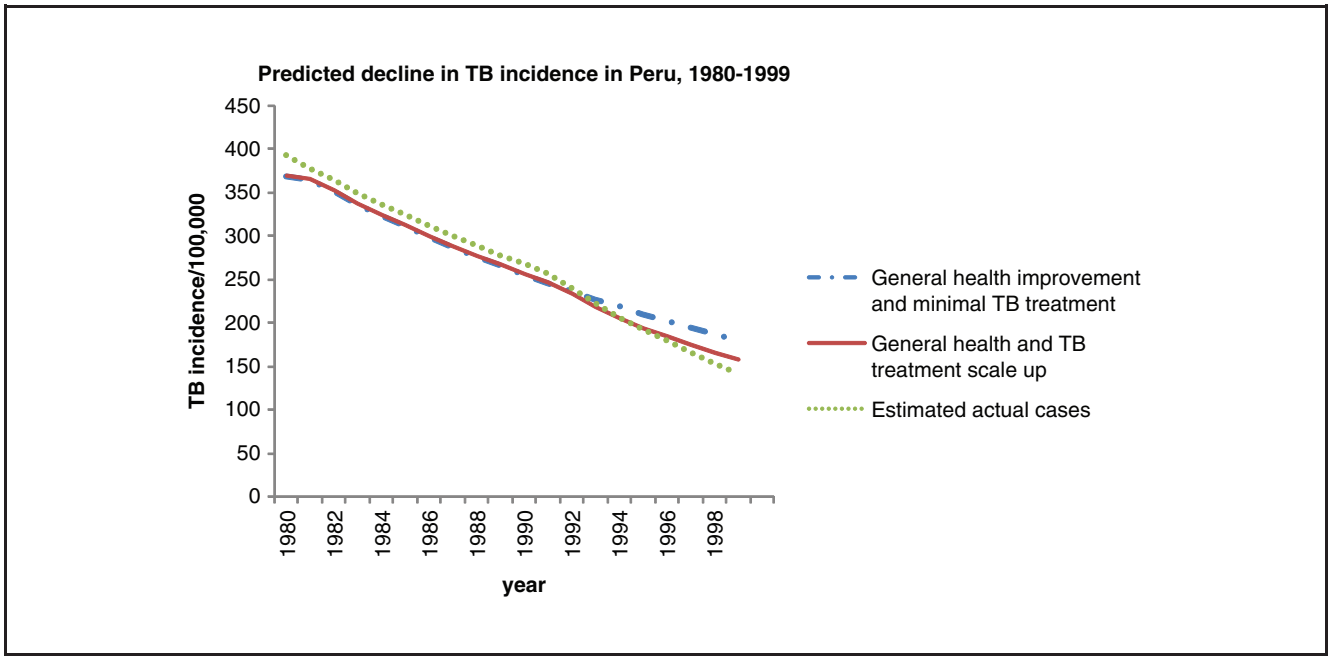


Figure 7 Predicted decline in tuberculosis (TB) cases, with observed improvements in general health and no change in treatment or with the same improvements in general health plus observed improved treatment outcomes after introduction of DOTS in 1990.

that measure trends rather than absolute values. Results of the sensitivity analysis are described in the Supplementary Appendix (Sensitivity Analysis).

Validating the Model in the Netherlands, 1910–1949

When the model was validated in the setting of the Netherlands, a good fit with the trend of the reported data was achieved; however, like in England and Wales, the model overestimated TB mortality. Possible reasons for the discrepancy between reported and predicted data are provided in the discussion section. The R^2 was 0.97 for infection and 0.95 for mortality, as illustrated in Figures 6A and 6B. As in England and Wales, an upsurge in TB mortality was seen during World War I in the Netherlands, although there is no reported data available during World War II.[6] Again, these war years were excluded from R^2 calculations.

Applying the Model to Peru, 1980–1999

When minimal (1980–1989) and then scaled-up treatment (1990–1999) were modeled in Peru, together with background changes in population health, rates of decline in case rates and risk of TB infection were accurately predicted in both periods. Between 1980 and 1990, when there was minimal TB treatment and improving population health, the average annual decline in TB cases was predicted to be 3.7% per year compared to the observed decline of 3.9% per year[39] (Supplementary Table S9). In a second model when TB treatment was scaled up after 1990, the annual decline in TB cases was predicted to increase to 5.7%. This corresponds very well with the observed decline of 5.8% per year reported for smear-positive cases in Peru.[39] The decline predicted in the absence of treatment scale-up in the later period was 4.0% per year, suggesting that improvements in general health were responsible for approximately 70% of the total decline in TB morbidity between 1990 to 1999 (Figure 7).

Annual risk of TB infection was predicted to decline annually by an average of 5.5% in 1980 to 1989 (in a setting of minimal treatment) and 12.3% annually in 1990 to 1999 after treatment scale-up. The latter decline corresponds very well to the 12% to 13% annual decline in TB infection rates following the introduction of effective treatment in Western Europe.[6] In the absence of TB infection data from Peru itself, more specific comparisons are not possible.

DISCUSSION

Using reported TB outcomes, and adjusted life expectancy as a proxy for general health, a deterministic TB transmission model that captures changes in population health was developed. It was calibrated using data from England and Wales, validated in the Netherlands, and applied to the modern setting of Peru. A good fit was achieved when the model was validated in the Netherlands, and very accurate rates of decline in cases and risk of TB infection were predicted in Peru. Importantly, improvements in general health accounted for more than half of the observed decline in TB morbidity in Peru during the period of treatment scale-up in 1990 to 1999.

Our model is the first to explicitly incorporate the impact of population health on the TB epidemic in several different settings. This study illustrates that the impact of population health can be substantial in countries that are undergoing rapid transition. In addition, it highlights that the typical medical picture of TB control that is often captured in modeling studies may not be sufficient for accurate evaluation of interventions, as the impact of poverty may confound results. Based on these findings, future models that assess the impact of modern interventions (such as vaccines, drugs, and new diagnostics) on key transitional probabilities should also consider the impact of indirect influences (such as population health).

The work outlined in this paper is unique because not only does it address background population health, but it also uses new methods to combine Markov modeling and decision analysis with a dynamic transmission process. This has been done by few others in the past as many of those who have used Markov modeling and decision analysis have made assumptions about transmission from active cases[41,42] rather than incorporating a feedback mechanism that is sensitive to changes to the number of infectious cases as we have done. Others who have included a transmission component in their work have done so using SIR (Suceptible-Infected-Recovered) models that rely on differential equations to control the population flow between different states of health and disease.[43–47] Many current models that use this approach have focused on drug resistance.[48–50] Some of the advantages of using the modeling approach outlined in our study are that complex models with many substrata can easily be constructed and visually inspected. Detailed sensitivity analysis can also easily be performed. Finally, models based on these methods can be readily modified for future cost-effectiveness analyses. The novel method used to dynamically calculate the number of infections generated from active cases, at different points in time, and the corresponding estimate of population risk of infection will be especially useful when used to evaluate interventions in which the population level impact is unknown. The estimates that we calculated for the number of TB infections generated annually by each untreated smear-positive case at the end of the pre–antibiotic period are comparable to modern published estimates. For example, a recent study estimated that in the 1970s and 1980s, only 4 new TB infections were generated per untreated smear-positive case.[21] We estimated that after 40 years of decline in this parameter (from a starting point of 17.5 new infections generated per untreated smear-positive case per year), the infectivity of an untreated smear-positive case would be 3.8 new infections per year. However, there are several limitations to our modeling study. One limitation relates to available data, from different sources and over a lengthy period of time. Accuracy of diagnoses and reporting may have varied over time and between countries. For example, the mortality predicted by the model was consistently higher than that observed. This may in part be due to inaccuracies of reporting in the pre–antibiotic era through missed diagnoses, changes in diagnostic criteria, or underreporting of TB-related deaths. In historical and contemporary settings, inaccuracies of routinely collected mortality data have been noted,[51–54] particularly if autopsy was not performed on all cases.[54–56] These potential limitations of reported data increase the inherent uncertainty surrounding point estimates for TB outcomes. However, assuming that such error remained constant over the time period considered, trends should be useful, and the results generated by the model can be used to estimate relative changes in epidemiological parameters rather than the absolute number of cases or deaths.

Life expectancy data from each country were adjusted to remove any known contribution from TB to this parameter. The adjustment relied on data from Northern Ireland because data from England and Wales and the Netherlands were not available for each year covered in our analysis. However, although absolute mortality rates differed by country, the trends in TB mortality and all-cause mortality in Northern Ireland were very similar to those in England and Wales in the early 20th century[57] (see Supplementary Figures S4A and S4B[57]). In addition, the proportion of background mortality attributed to TB in Northern Ireland is comparable to estimates

from other European countries, such as Denmark and Scotland where TB was responsible for 17%[25] and 15%[58] of all deaths in 1900, respectively.

There are many potential determinants of TB pathogenesis and epidemiology, and different combinations of assumed values could have produced the predicted outcomes we generated. However, each determinant used in the model was investigated carefully in sensitivity analysis, and the plausible ranges identified for each determinant were relatively narrow. This reduced the likelihood that multiple different combinations of values for these determinants could have yielded the same findings.

This study outlines the development and validation of a TB transmission model using data from England and Wales and the Netherlands that predated TB-specific interventions such as antibiotics and the Bacillus Calmette-Guerin (BCG) vaccine.[32] The wealth of epidemiological data from those countries in that era provides a unique opportunity to understand the impact of general health on TB outcomes because the reductions in TB infection, disease, and mortality could reflect only the indirect effects of general improvements to health.

Health indicators are now changing in many low- and middle-income countries, some improving and some worsening.[40] Teasing apart the influence of medical and non medical interventions on key pathogenetic and epidemiological parameters will be essential in future evaluations of interventions. This will become even more important when more complex scenarios are considered and cost and cost-effectiveness analyses are conducted. Based on the important relationship between general health and TB, and the observation that many countries are currently undergoing rapid health transition, changes in general population health should be explicitly accounted for when modeling the impact of modern interventions for TB control.

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