
The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection

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SUMMARY

Many aspects of the natural history of tuberculosis are poorly understood. Though it is recognized that clinical tuberculosis may follow shortly after initial infection ('primary' disease), or many years thereafter through either endogenous reactivation or after reinfection, the relative importance of these mechanisms is often disputed. The issue is complicated by the fact that the risks of developing disease are age-dependent, and reflect infection risks which may change over time.

This paper estimates the age-dependent risks of developing tuberculosis using an age-structured deterministic model of the dynamics of tuberculous infection and disease in England and Wales since 1900. The work extends the classical studies of Sutherland and colleagues. The best estimates of the risks of developing 'primary' disease (within 5 years of initial infection) were approximately 4%, 9% and 14% for individuals infected at ages 0–10, 15 years and over 20 years respectively, and a previous infection appeared to impart little protection against (further) reinfection, but 16–41% protection against disease subsequent to reinfection for adolescents and adults. We also provide evidence that reinfection made an important contribution to tuberculous morbidity in the past, as (i) exclusion of exogenous disease from the model considerably worsened the fit to observed notification rates, and (ii) the dramatic decline in the risk of tuberculous infection from 1950 in England and Wales accelerated the decline in morbidity among *all* individuals, even among the older age groups with a high prevalence of tuberculous infection. We conclude that the risk of infection is the single most important factor affecting the magnitude of the tuberculous morbidity in a population, as it determines both the age pattern of initial infection (and hence the risk of developing disease) and the risk of reinfection.

INTRODUCTION

After declining for over a century in developed countries, tuberculosis notifications have recently increased in most countries [1], and the disease has been declared a global emergency by the World Health Organization. The implications of these increases are difficult to assess, as many important

aspects of the pathogenesis of tuberculosis remain poorly understood. It is recognized that clinical disease may follow soon after initial infection with *Mycobacterium tuberculosis* ('primary' disease) or many years thereafter ('post-primary' disease), either through 'endogenous' reactivation or after 'exogenous' reinfection; but the relative importance of these different mechanisms is often disputed. The contribution of exogenous disease is especially con-

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tentious, though there is much evidence (e.g. from autopsy studies [2] and drug-sensitivity and DNA fingerprint analyses [3, 4]) to support its occurrence [5]. Further complications arise because the risks of developing disease are higher for adolescents and adults than among children [6–9]. However, there are no direct estimates of the *age-specific* risks of developing endogenous and exogenous disease, and direct estimates of the risk of developing ‘primary’ disease vary greatly between studies, in part because of difficulties in determining tuberculous infection.

A better understanding of the relative importance of these different mechanisms, and indirect estimates of the age-specific risks of developing disease, can be obtained using modelling techniques to link current knowledge of the pathogenesis of tuberculosis to past morbidity and mortality data. England and Wales are unique in having detailed tuberculosis statistics since the 1850s, which are ideal for such investigations.

Hitherto, only the model of Sutherland and colleagues [10] has explored the relative contribution of exogenous and endogenous disease in a developed country. Their work focused on the incidence of tuberculosis among Dutch adult males (aged 15–69 years), and considered a relatively short time-period (1951–69). Most other models in the tuberculosis literature have been devoted to exploring the effects of different interventions (e.g. BCG vaccination [11, 12], chemoprophylaxis [13–15] and chemotherapy [16]) or, more recently, of HIV infection [17–19] in given settings. Another recent model [20] explored the dynamics of tuberculosis in a hypothetical population spanning centuries and concluded that the decline in developed countries may reflect the natural decline in a long epidemic. None of these models (excepting that of Sutherland and colleagues [10]) considered the contribution of reinfection to the overall disease incidence and few (e.g. [21, 22]) have included age-structure. As age and reinfection are two of the most important factors underlying tuberculosis morbidity in a population, models which fail to consider their effects may be misleading as interpreters or predictors of disease trends.

This paper estimates the age-specific risks of developing ‘primary’, ‘endogenous’ and ‘exogenous’ disease and assesses the relative contribution of these different disease mechanisms to the decline in tuberculosis in England and Wales since 1900 using a model which elaborates and extends the approach of Sutherland and colleagues [10]. This is achieved by fitting model predictions of disease incidence, based on

estimates of past trends in the annual risk of infection (Vynnycky and Fine, in press*) to notifications collected since 1953 in England and Wales.

METHODS

Description of the model

Scope of the model

We restrict these analyses to respiratory (‘pulmonary’) forms of tuberculosis, since these are far more likely to lead to transmission of tubercle bacilli than are other (‘extrapulmonary’) forms. As the contribution of HIV to tuberculosis morbidity in England and Wales has been very small to date [23], HIV is not incorporated in the model.

The analyses presented here are restricted to the indigenous (white ethnic) male population until 1990, to avoid the complications of gender differences (e.g. females experience greater morbidity during adolescence and young adult life than do males, reflecting differences in the risks of infection and/or disease) and immigration from high tuberculosis prevalence countries (immigrants are likely to have faced different infection – and possibly disease – risks compared to the indigenous population in England and Wales, and their notification rates far exceed those in the white ethnic population [24–28]). We first present the general structure of the model and then describe the data and methods used to derive estimates of the risks of developing ‘primary’, ‘endogenous’ and ‘exogenous’ disease.

Structure of the model

Figure 1 shows the model’s structure. Individuals are born into the uninfected class (U), and become infected at a time-specific rate $i(t)$. Infected individuals comprise: (1) those infected for less than 5 years who have not yet experienced (primary) disease (I), and (2) those in the ‘latent’ class (L), defined to be at risk of endogenous reactivation or of reinfection. Diseased individuals are stratified by type of disease (described as either first primary, endogenous or exogenous – see definitions below), and by sputum status (not shown in Fig. 1), which determines their infectiousness. BCG vaccination is also included. The sum of individuals in each of the categories in Figure 1 gives the total population at time t .

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Table 2. *Definitions of transition variables used in the model*

Variable	Definition	Assumption
$i(t)$	Infection and reinfection rates at time t	20% until 1880, declining by 2% pa until 1901, by 4% pa until 1949 and 13% pa thereafter. Derived using childhood tuberculosis meningitis statistics and tuberculin survey data (Vynnycky and Fine, in press), though the estimates before 1901 are unreliable.
$v(a, t)$	Proportion of uninfected individuals of age a immunized at time t .	Determined by vaccine efficacy (77%) and vaccine coverage (assumed 80% since 1960 – see text). Vaccination introduced in 1954 and restricted to 13 year olds. Published numbers of vaccinees used until 1960 [39], assuming that males comprised 50%.
$d_p(a, s)$	Rate of onset of the first primary episode at time s after infection at age a .	Rate immediately after infection follows pattern in Figure 2 <i>a</i> . Rate at time s since infection is a factor ('relative rate') of that immediately after first infection (see Fig. 2 <i>b</i>).
$d_x(a, s)$	Rate of onset of exogenous disease at time s after reinfection at age a .	Relationship between age at and time since reinfection identical to that between $d_p(a, s)$ and age at time since first infection.
$d_n(a)$	Rate of onset of endogenous disease at age a .	Depends on current age of individual (see Fig. 2 <i>a</i>).
$d_+(a)$	Proportion of total disease incidence among cases aged a assumed to be sputum-positive.	Based on data from Norway (see Fig. 2 <i>c</i>).
$k_L(s)$	Rate at which individuals who have been infected or reinfected for time s without developing disease move into the 'latent' class.	Transition occurs exactly 5 years after infection/reinfection, i.e. $k_L(s) = 0$ if $0 < s < 5$ and ∞ for $s = 5$ years. The 5 year cut-off follows Holm's criterion [29].
$r(a, t, \delta)$	Recovery rate for cases of age a at time t at time δ after disease onset.	Individuals are considered diseased for 2 years unless they die in the meantime (see below).
$m_+(t, \delta)$	Case-fatality of sputum-positive cases at time t and time δ since disease onset.	Case fatality in second year is 65% of that in first year i.e. similar to that between the first and second periods of follow-up during the longitudinal study in Bangalore [36]. Overall case-fatality: 50% until 1950, declining to 30% and 25% by 1953 and 1956 respectively, and constant until 1976. Identical to mortality in general population thereafter. See text for references.
$m_g(a, t)$	Mortality rate of sputum-negative and non-diseased individuals in the general population of age a at time t .	Identical to all-cause mortality (after subtracting deaths among sputum-positive cases, estimated in the model). Annual age-specific all-cause mortality rates obtained from Government Actuary's Department since 1841. Data until 1841 obtained by back-extrapolation.

in a tuberculin test. This sensitivity may wane over time [30], though the implications of such waning for 'susceptibility' to further infection and for the risks of developing disease are not understood. We begin by making the conventional assumption that, once infected, individuals remain infected for life. The infection rate, $i(t)$, is here assumed to depend only on calendar year, t (Table 2), declining from about 13% in 1900 to about 2% by 1949 (Vynnycky and Fine, in press). The rate of decline in the infection rate after 1949 is assumed to be the same as that found in other developed countries ($\approx 13\%$ p.a.) [31]. In reality, the infection rate may also be age-dependent [32], though the extent of this trend is unknown and probably varies between populations [32].

There are no empirical data comparing the risks of

initial infection and of reinfection. It might be presumed that reinfection would be more difficult to establish than an initial infection, once an individual has developed some immune response to *M. tuberculosis* antigens. Animal studies have shown that inoculation of tubercle bacilli into guinea-pigs consistently leads to one or more local lesions [2], but that a history of previous infection reduces the risk of haematogenous dissemination (and by inference, the risk of subsequent disease) [33]. For simplicity, we assume that the infection and reinfection rates are identical, but that reinfection cannot occur among individuals with active disease or among those already at (high) risk of developing the first primary episode or exogenous disease (i.e. within 5 years of initial infection or reinfection).

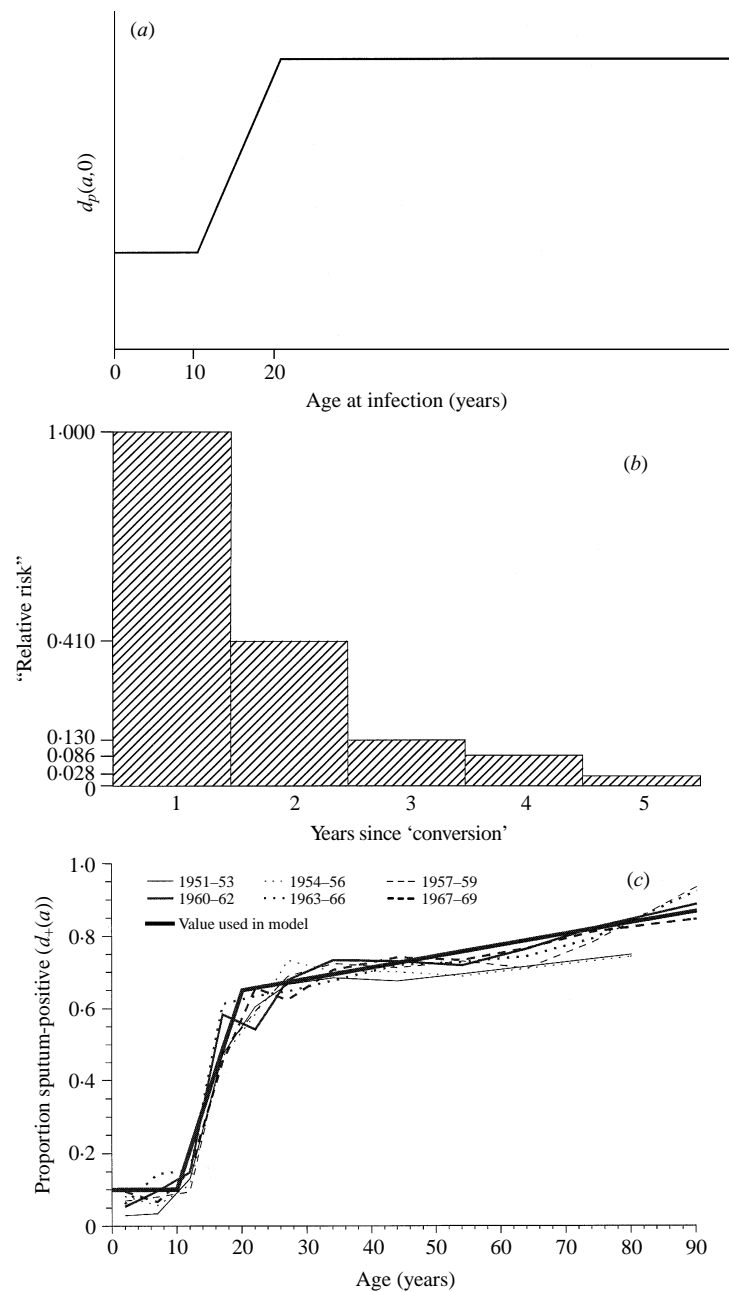


Fig. 2. (a) Relationship between the risk of developing the first primary disease episode and the age at infection assumed in the model. The relationship (i) between the risk of developing exogenous disease and the *age at reinfection*, and (ii) between the risk of developing endogenous disease and the *current age* of an individual are assumed to follow this basic pattern. Note that the rates of disease onset for 10–20 year olds can be expressed in terms of those for individuals aged 0–10 years, and those aged over 20 years. (b) Observed and assumed relationship between the rate at which individuals experience their first primary episode/exogenous disease in each year following infection/reinfection relative to that during the first year after infection/reinfection. These were estimated from the distribution of the time interval between ‘tuberculin conversion’ and disease onset of those who were tuberculin-negative at the start of the UK MRC BCG trial [34]. The ‘relative risk’ for a given year after ‘conversion’ is taken to be the ratio between: (i) the proportion of the total disease incidence among initially tuberculin-negative individuals which occurred in that year following ‘conversion’, and (ii) the corresponding proportion which occurred during the first year after ‘conversion’. (c) Observed and assumed proportion of total respiratory disease incidence among cases of age a attributable to sputum-positive forms, $d_+(a)$. All lines (excluding the heavy solid line) show the relative contribution of sputum-positive disease to age-specific notifications of pulmonary tuberculosis in males in Norway (1951–69). Source: Dr K. Styblo (TSRU) and Dr K. Bjartveit (Norwegian National Health Screening Service).

The model described here implicitly assumes that individuals mix randomly in the population. This was probably more realistic, as far as tuberculosis is concerned, during the early 20th century, when tuberculosis was ubiquitous, than in recent years.

The rates of disease onset, $d_p(a, s)$, $d_n(a)$ and $d_x(a, s)$

We assume that the rates of disease onset differ according to whether individuals are at risk of developing their first primary episode, endogenous or exogenous disease, and that they depend on age as shown in Fig. 2*a*. This is based on findings from many follow-up studies, which have demonstrated convincingly that the risks of developing disease change during adolescence [6–9]. The rates are here assumed to be identical for all individuals aged over 20 years (they may in fact increase in old age, though the magnitude and pattern of the increase is unknown).

The relationship between the rates of onset of the first primary episode or of exogenous disease, and the time since initial infection/reinfection (Table 2, Fig. 2*b*) is derived using data from the UK MRC BCG trial during the 1950s [34]. These data provide the most reliable available evidence that the risks of developing (primary) disease decline with time since ‘infection’. There are no empirical estimates of the relationship between the rate of onset of *exogenous* disease and time since *reinfection*, but we consider the one assumed here to be the most reasonable.

Relative contribution of sputum-positive (i.e. ‘infectious’) forms, $d_+(a)$

Cases with sputum containing bacilli detectable by microscopy (smear) and/or culture are said to be ‘sputum-positive’. ‘Smear-positive’ cases are more infectious than are those who are only culture-positive [5]. For simplicity, we distinguish only between sputum-positive (i.e. infectious) and sputum-negative individuals. The age-specific proportion of disease attributable to sputum-positive forms, $d_+(a)$, is not assumed to depend on the mechanism of disease onset, and is derived using data from Norway (Fig. 2*c*), as this is the most extensive and reliable data set available.

Case-fatality rates

Tuberculosis chemotherapy was introduced during the 1950s. The case-fatality assumed for sputum-positive cases prior to 1950 (50%, see Table 2), is

based on studies from this period (see reviews in [5, 35]) and on the major longitudinal study of the natural history of untreated tuberculosis in Bangalore, South India (1961–6) [36]. The case-fatality assumed after 1950 is based on published estimates. Among all sputum-positive patients notified in Birmingham (England) in 1953, 1956 and 1959 respectively, for example, 29%, 25% and 27% respectively died within 10 years of follow-up [37]. Short-course regimens recommended for use in England and Wales since 1976 have higher success (cure) rates [38]: in a controlled study carried out during the 1970s, none of the deaths among 655 patients traced for up to 54 months was attributable to tuberculosis [38].

The case-fatality rate of *sputum-negative* pulmonary disease is not well-defined. As it is probably lower than that for sputum-positive disease, we assume that it equals the background mortality rate of non-diseased individuals, and with the same age and time-dependent trends.

BCG vaccination

Routine BCG vaccination was introduced for tuberculin negative 13 year olds in England and Wales in 1954, and small numbers of other individuals (e.g. contacts of cases) have also been vaccinated. Vaccination is restricted to 13 year olds in the model. According to official estimates [39], 60% and 70% of each cohort of 13 year olds was vaccinated by 1962 and 1970 respectively, and the proportion has remained constant at 75% since then. As these published estimates refer to all 13 year olds, irrespective of tuberculin status, our assumption of 80% coverage among uninfected individuals since 1960 (Table 2) appears reasonable.

Vaccination is assumed to protect 77% of vaccinees completely against disease. This agrees with estimates of the overall vaccine efficacy from the UK MRC BCG trial during the 1950s, though the apparent efficacy may in fact have declined with time [40].

Estimating the age-specific risks of developing disease and validating the model

Morbidity and mortality data

Notifications of respiratory tuberculosis among white ethnic males for the period 1953–88. Breakdowns of respiratory tuberculosis notifications in England and Wales are not available by ethnic group before 1988; those for 1988 were obtained from the Public Health

Laboratory Service (PHLS) Communicable Disease Surveillance Centre (courtesy of Dr J. Watson). We first estimated the age-specific notifications of respiratory tuberculosis for the period 1953–87 using data on *all forms* of tuberculosis, which are available for 1965, 1971, 1978/9 and 1983, when national surveys of clinical tuberculosis were carried out [24–28].

The notification rates for 0–4, 5–14, 15–24, 25–34, 35–44 and 45–54 year olds for the period 1953–83 were derived by assuming that they declined from their level in 1953 (see below) at the same rates as those of all forms of tuberculosis (provided in [41] for the periods 1953–65, 1965–71, 1971–8/9 and 1978/9–83). The notification rates for the same age groups from 1983 were derived assuming that they declined at a constant rate from the level *estimated* for 1983 to that *observed* in 1988. The notification rates of respiratory tuberculosis for white ethnic males were assumed to equal those in the general population in 1953, when they were probably unaffected by immigration [41]. Notifications of respiratory tuberculosis for 45–54 year olds are not available in statistical breakdowns for 1953 and were assumed to comprise 95% of those of all forms of tuberculosis (i.e. identical to the corresponding proportion for 45–64 year olds in 1953).

As notifications among 55–74 year olds have been relatively unaffected by contributions from the immigrant population [24–28], we assume that the notification rates for 55–64 and 65–74 year old white ethnic males equal those in the general population for the period 1953–87.

Mortality rates. Age and time-specific mortality rates in England and Wales by 10-year-period for the years 1881–1910 were extracted from the Annual Report of the Registrar General for England and Wales. The corresponding rates were provided in [42] by 5 year time-period since 1910.

Methods

The system of partial differential equations in Appendix A was reduced to a system of ordinary differential equations describing the infection and disease dynamics within individual birth cohorts. These were solved using time-steps of one year and the Euler method, so that annual transition risks now replaced continuous-time transition rates, and *annual* data were used in their original format.

For suitable input data, only the six parameters $d_p(10, 0)$, $d_p(20, 0)$, $d_n(10)$, $d_n(20)$, $d_x(10, 0)$ and $d_x(20, 0)$, which correspond to the risks of developing each disease form among 0–10 year olds and among those aged over 20 years, are required to describe the age and time-specific disease incidence. We obtained best-fit estimates of these parameters by minimizing the sum of squares of the differences between the predicted disease incidence and age and time-specific notification rates (see below) using the Levenburg–Marquardt method [43]. Only notifications for individuals born since 1901 were used, as the annual risk of infection can be estimated reliably only since then (Vynnycky and Fine, in press).

Sensitivity analyses and further validation of the model

We repeated the fitting procedure on 50 *simulated* notification data sets in order to explore the reliability of the parameter estimates and their sensitivity to the level of the notification rates. The simulated data sets were derived by assuming that the *variability* in the notifications of *all forms* of tuberculosis during the survey years followed a Poisson distribution (generally used to model random variability in rare diseases and count data [44]) with a mean given by the number of notified cases – see Appendix B for further details. Figure 5 (Appendix B) presents the range in which 95% of the simulated notifications for the survey years occurred.

In the analyses presented here, the notification rates are not adjusted explicitly for under-notification. Published studies suggest that 20–40% of cases are not reported in England and Wales [45, 46], though this has probably varied with age and over time. For most age-groups and years, the expected notification rates after adjusting for, e.g. 40% under-notification lie within the range covered by the simulated notification rates. Thus the notification rates in these data sets represent the range in which the ‘true’ notification rates of respiratory tuberculosis, after adjusting for both random variability and undernotification, probably lie. The parameter estimates derived in these sensitivity analyses describe the range in which the risks of developing disease would have to lie, given the assumptions incorporated into the model, in order to attain these notification rates.

Separate disease risk estimates were also derived (applying the model to the original, rather than the randomly-generated, data set) assuming either that:

1. BCG vaccination conferred no protection against disease. This analysis tested the sensitivity of parameter estimates to the assumption that BCG confers lifelong protection against disease, or

2. each reinfection event imparted (an estimated) protection p_r against further reinfection (i.e. an individual who had been reinfected n times faced a risk $(1-p_r)^n i(t)$ of experiencing further reinfection at time t). In this model, the disease incidence is a function of seven parameters to be estimated ($p_r, d_p(10, 0), d_p(20, 0), d_n(10), d_n(20), d_x(10, 0)$ and $d_x(20, 0)$), or

3. disease could not arise following reinfection.

The validity of the model's assumptions was assessed further by comparing observed mortality rates during the prechemotherapy era against model predictions of the disease incidence within birth cohorts and different age groups.

RESULTS

The estimated risks of developing disease

The best-fitting estimates for the age-specific risks of developing the first primary episode, endogenous and exogenous disease are summarized in Table 3. About 4% of 0–10 year olds are estimated to develop disease within 5 years of initial infection; the risks among individuals aged over 20 years are about threefold greater. Of all the parameter estimates, the risks of

developing endogenous and exogenous disease among 0–10 year olds are the least reliable, as reflected in the broad 95% range derived using the simulated notifications. For adolescents and individuals aged over 20 years, the estimated risk of developing the first primary episode exceeds that of developing exogenous disease and the annual risk of endogenous reactivation. These results imply that initial infection at age 15 and over 20 years imparts about 16% and 41% protection respectively against subsequent reinfection and/or (exogenous) disease (defined as 1-RR, where RR is the relative risk of developing exogenous disease following reinfection, compared to that of developing the first primary episode following initial infection).

The age-specific disease incidence predicted using these parameter estimates compares well against the (observed) notification rates (Fig. 3*a*). Almost all the morbidity among 0–14 year olds and over half of that among adolescents and young adults since 1950 is attributed to first primary episodes. About 60% and 80% of the disease incidence for 40 and 60 year olds respectively during the 1950s is attributed to exogenous reinfection. The relative contribution of exogenous disease to the overall disease incidence for all age groups is estimated to have declined over time, and by 1980, virtually all the morbidity among adolescents and the elderly is attributed to first primary episodes and endogenous reactivation respectively.

Table 3. *Best-estimates of the risks of developing disease (to three significant figures), as derived by fitting model predictions to notifications in white ethnic males in England and Wales. Values for the first primary and exogenous disease episodes refer to the risks during the first year after infection and reinfection respectively and the cumulative risks experienced during the first 5 years after infection/reinfection*

	Age (yrs)	Risks (% pa)		
		1st year	95% range*	Cumulative (5 yrs)
First primary episode	0–10	2.48	2.26–2.63	4.06
	15	5.57	5.22–5.77	8.98
	> 20	8.66	8.17–9.05	13.8
Endogenous	0–10	9.82×10^{-8}	9.03×10^{-9} – 1.52×10^{-3}	N.A.
	15	0.0150	0.0144–0.0159	N.A.
	> 20	0.0299	0.0288–0.0307	N.A.
Exogenous	0–10	4.25	2.98–7.98	6.89
	15	4.68	4.04–6.64	7.57
	> 20	5.11	4.93–5.38	8.25

* These represent the range in which 95% of the parameter estimates occurred when we fitted the model to the randomly generated notification data sets (see Methods).

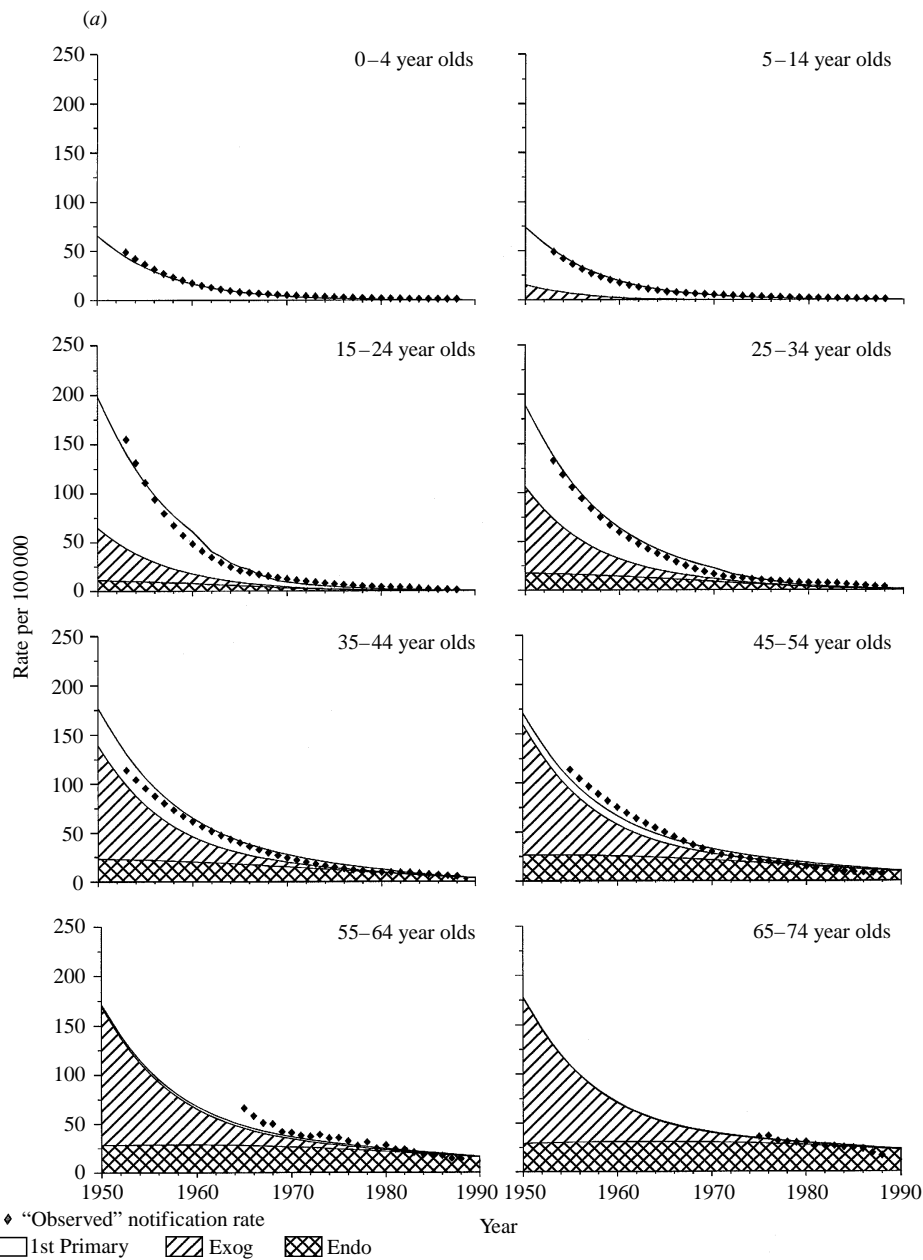


Fig. 3. (a) Comparison between the best-fitting incidence of respiratory tuberculosis in 0–74 year old males derived using the full model, and the notifications used in the fitting process (constructed from notifications of all forms of tuberculosis occurring during the national tuberculosis surveys. See Methods for details). Shaded areas denote the proportion of the disease incidence attributed by the model to first primary episodes, endogenous and exogenous forms.

Most of the disease risk estimates were quite insensitive to assumptions concerning vaccine efficacy (Table 4). The assumption that vaccination imparted no protection against disease led to a slightly lower estimate for the risk of developing the first primary episode among individuals aged over 20 years, as compared with that derived using the original model. Paradoxically, the risk of developing exogenous disease among 0–10 year olds derived assuming that vaccination imparted no protection against disease

was about double that obtained using the original model (9.36% vs. 4.25% respectively during the first year after reinfection). This is explained in the Discussion.

Each (re)infection event was found to impart negligible protection (0.0034%) against (further) reinfection (Table 4). The best-fitting parameter values were virtually identical to those derived using the original model, and only slightly worsened the fit to the notification rates.

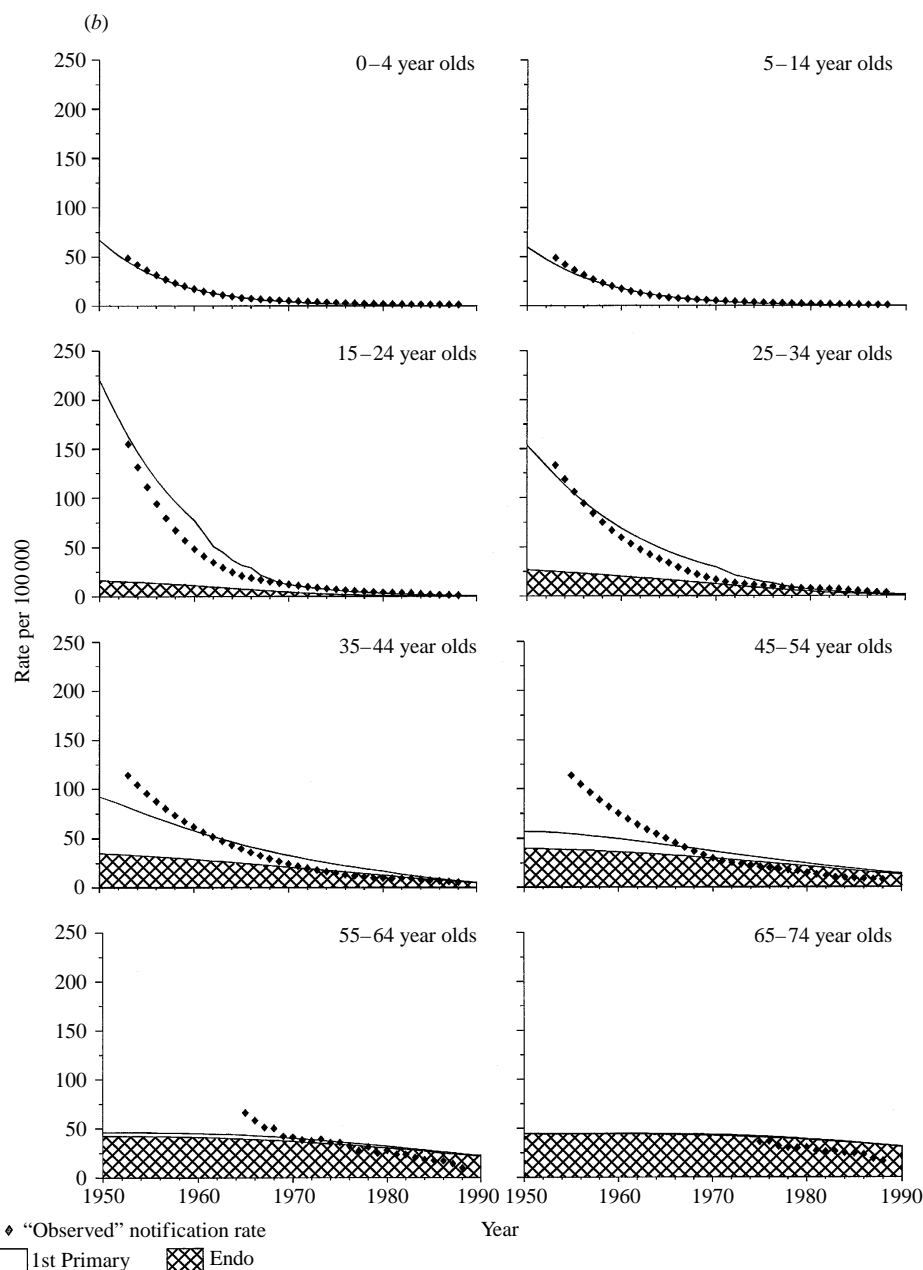


Fig. 3. (b) Comparison between the incidence of respiratory tuberculosis in 0–74 year old males, derived assuming individuals could not experience exogenous disease (see parameters in Table 4), and the notifications used in the fitting process (see Methods for details).

Exclusion of exogenous disease from the model led to high estimates for the risks of developing the first primary episode for individuals aged over 20 years (Table 4) and worsened the overall fit to the notification rates (Fig. 3*b*). The fit is especially poor for the middle-aged and elderly, with model predictions failing to match the rapid decline in notification rates between 1955 and 1970. Exclusion of exogenous disease from the model worsened the fit only slightly for younger individuals.

The relative importance of exogenous disease

The implications of the risk estimates derived using the full model for the predicted morbidity before 1950 are illustrated in Figures 4*a, b*. The fit between the predicted and observed mortality rates within birth cohorts (Fig. 4*a*) is remarkably good, and for all birth cohorts, the predicted disease incidence follows a realistic age-specific pattern i.e. it is high for infants (e.g. 600 per 100 000 for the cohort of 1881–90), low

Table 4. *Best-estimates of the risks of developing disease (to three significant figures) derived for alternative assumptions*

Assumption	Age (years)	Risks (% p.a.)				
		First primary		Endogenous	Exogenous	
		1st year*	Cum†		1st year*	Cum†
0% vaccine efficacy SSq‡ = 6,003	0–10	2.25	3.69	4.82×10^{-8}	9.36	14.8
	15	5.00	8.08	0.0146	7.33	11.7
	> 20	7.75	12.4	0.0293	5.30	8.55
Reduced reinfection risk§ SSq = 5,392	0–10	2.48	4.06	1.72×10^{-7}	4.40	7.14
	15	5.56	8.97	0.0151	4.77	7.71
	> 20	8.65	13.7	0.0301	5.14	8.29
No exogenous disease SSq = 23,591	0–10	2.53	4.13	4.72×10^{-4}	—	—
	15	8.04	12.8	0.0210	—	—
	> 20	13.6	21.0	0.0416	—	—

* Risk during the first year after infection/reinfection.

† Cumulative risks during the first 5 years after infection/reinfection.

‡ Sum of squares of the differences between the observed notifications and predicted disease incidence. Note that SSq for the full model was 5,389.

§ Best-fitting level of protection imparted by previous (re)infection against (further) reinfection: 0.0034%.

for children, peaking during adolescence (e.g. at 700 per 100 000 for the cohort of 1881–90) and declining thereafter.

Figure 4*b* shows the implications of the relative importance of different mechanisms of disease onset for the morbidity within different age groups since 1900. The disease incidence is estimated to have declined over time for all ages (e.g. from about 450 per 100 000 for 10 year olds in 1900 to about 100 per 100 000 by 1950, and from 750–800 per 100 000 in 1900 to 200 per 100 000 by 1950 for adults). For all individuals aged over 10 years, virtually all the morbidity during the early 1900s is attributed to exogenous disease and only a small proportion is attributed to first primary episodes and to endogenous reactivation. For 20–40 year olds, the incidence of first primary episodes is estimated to have increased between 1900 and 1950 at the same time as the incidence of exogenous disease decreased dramatically. For 10 year olds, the incidence of first primary episodes changed little between 1900 and 1950. For all age groups the decline in the disease incidence is estimated to have accelerated from 1950.

DISCUSSION

These analyses provide strong evidence for the importance of age and reinfection in determining the transmission dynamics of *M. tuberculosis* in the past

in developed countries. In so doing, they represent a logical extension of the work of Sutherland and colleagues [10].

It is important to recognize that, as with all modelling exercises, the results depend on the underlying assumptions. Though the model captures the most important elements of the natural history of tuberculosis (e.g. there are three mechanisms of disease onset, which are age-dependent), we have, by necessity, made several simplifications. For example, we have assumed that the risks of infection and of reinfection are independent of age, and that individuals mix randomly in the population. We have also assumed that the individual disease risks among infected individuals remained constant over time, though they too may in fact have changed as living standards improved. Despite these simplifications, our analyses provide important insights into the natural history of tuberculosis and into the dynamics of its decline in developed countries during this century.

Estimated risks of developing disease – the full model

These analyses provide the first *age-specific* estimates of the risks of developing the first primary episode, endogenous and exogenous disease. For most age groups, the risk of developing the first primary episode after initial infection exceeded that of developing endogenous and exogenous disease. Previous infection

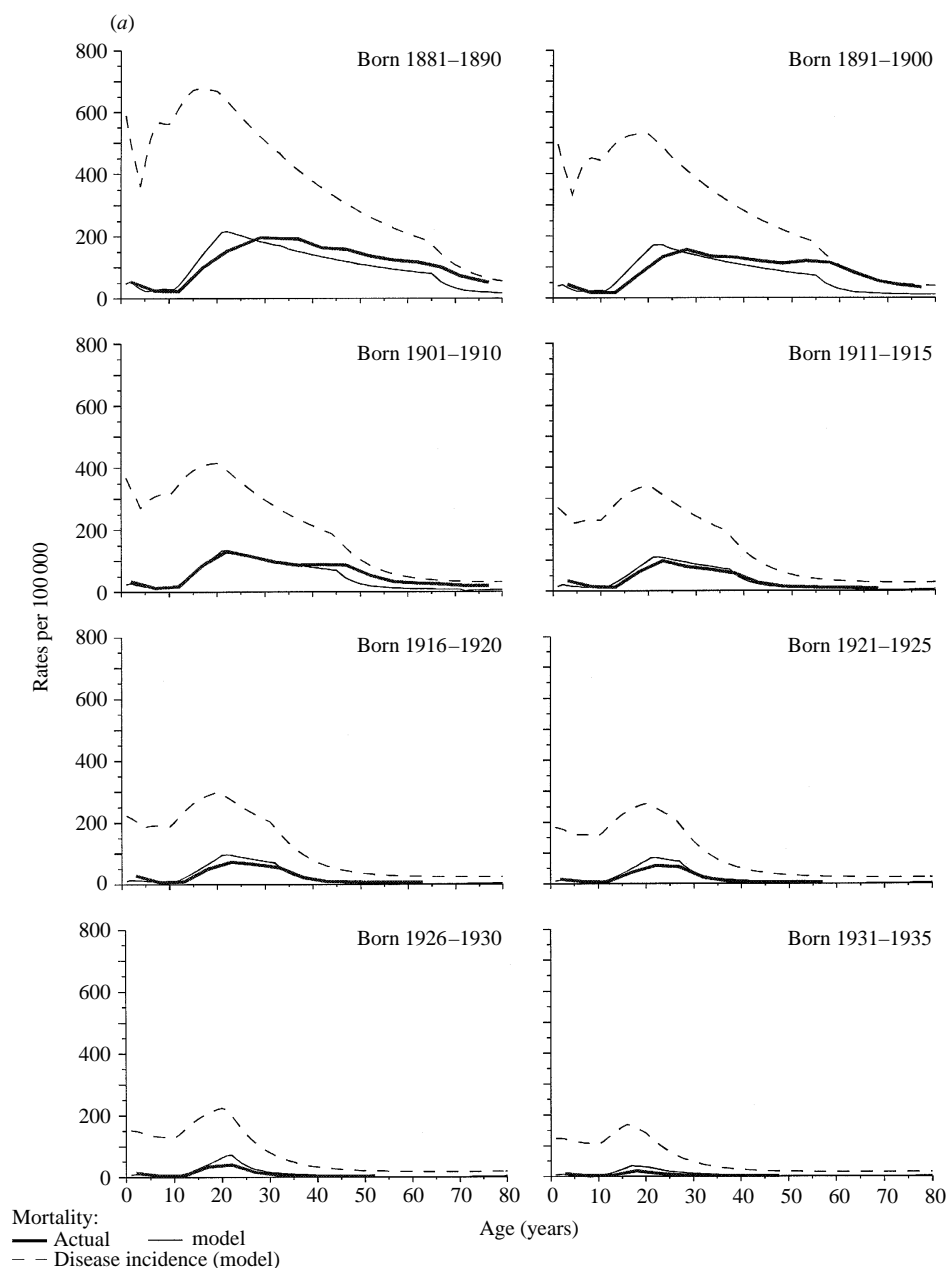


Fig. 4. (a) Comparison between the observed mortality rates from respiratory tuberculosis within birth cohorts and the predicted incidence and mortality rates derived using the model.

was found to impart 16% and 41% protection against disease subsequent to reinfection among adolescents and adults respectively, but little protection against reinfection.

Overall, the estimated risks of developing disease appear realistic in magnitude and their age-specific pattern is consistent with results from studies from both before [6, 7] and during the chemotherapy era [8, 9]. The estimated risk of developing the first primary episode among infected adolescents, for example, is very similar to direct estimates from the

UK MRC BCG trial (8% within 10 years of tuberculin 'conversion', which was defined as a change in induration from 0–5 mm to 100 TU to one of ≥ 8 mm to 3TU). The only other analyses of the risks of developing 'primary', 'endogenous' and 'exogenous' disease (i.e. those of Sutherland and colleagues [10]) found extremely high risks of developing primary disease for 15–69 year olds in the Netherlands (i.e. 22% as compared with 9% and 14% derived for 15 year olds and individuals aged over 20 years in England and Wales). We doubt that tu-

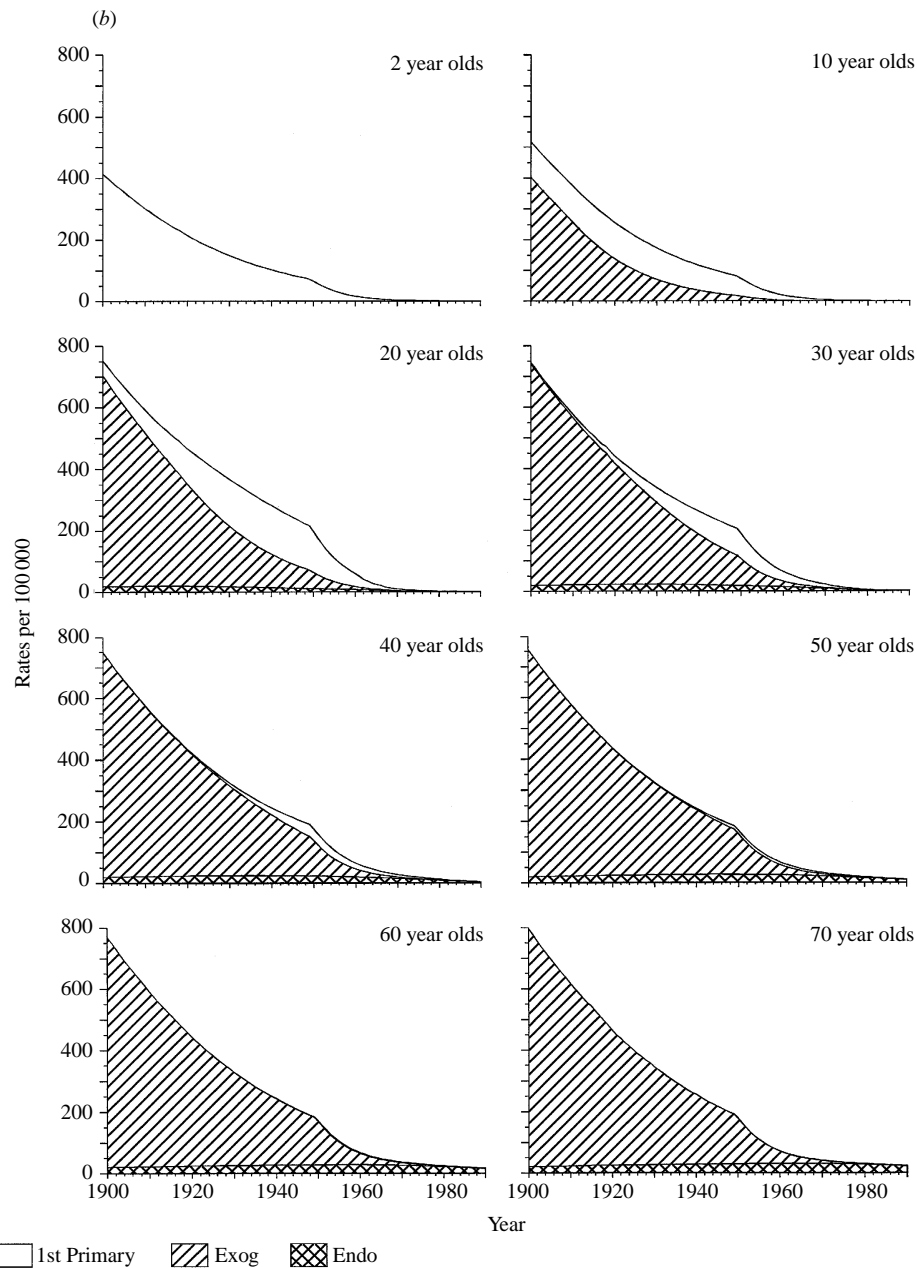


Fig. 4. (b) Estimated age-specific incidence of respiratory tuberculosis since 1900 in England and Wales as predicted using the full model.

berculosis differed substantially between these two populations, and suspect that this difference is in part attributable to the fact that their analyses were based on fewer data points, and covered a shorter time period than those presented here (e.g. the period 1951–70, as compared with 1953–88). The assumptions incorporated in the model of Sutherland and colleagues [10] differed only slightly from those in our analyses, and are unlikely to account entirely for the difference between the results.

The pathogenesis of post-primary disease is still

poorly understood, and there has been much debate as to whether an infection is still ‘active’ (i.e. able to cause disease) 5 years after it has been acquired. Our lower estimated annual risk of developing endogenous disease, as compared with that of developing the first primary episode, is consistent with the results from several studies, which have found that even those most likely to be or to have been infected (i.e. individuals with a strong positive tuberculin response) were less likely to develop disease many years after the start of follow-up, in the absence of apparent

reinfection, than shortly thereafter [9, 47]. This could occur either because the bacilli are no longer viable many years after infection, as suggested by some autopsy studies [2] or because the immune response is able to prevent foci containing living bacilli from reactivating and leading to disease.

There are few hard data on the pathogenesis of exogenous disease among humans. Our results suggest that infection confers 16% and 41% protection against (exogenous) *disease* for 15 and 20 year olds respectively, but that it confers little protection against (further) *reinfection*. This is interesting, given that for many infections, prior infection is thought to impart some protection against the establishment of subsequent infection. This raises the issue of how best to define a 'reinfection' event for tuberculosis. Studies have found that guinea-pigs already infected with *M. tuberculosis* consistently developed one or more local lesions after they were inoculated with even small quantities of bacilli [2], but that the (re)infections were then less likely than primary infections to spread and lead to disease. On this basis, the risk of reinfection for tuberculosis derived in our analyses is best interpreted as the combined likelihood of bacilli being implanted in the lung and subsequently forming a local lesion in someone who has been infected at least once. It may be noted that this definition is appropriate irrespective of whether infections are life-long, or time-limited.

Our finding that the risk of developing exogenous disease is lower than that of developing the first primary episode for most age groups is consistent with results from studies which found that (i) lesions developing as a consequence of reinfection are generally smaller (and thus less likely to lead to disease) than those developing after initial infection [48] and (ii) haematogenous dissemination of bacilli to the spleen (and, by inference, disease) is less likely following reinfection than after initial infection [33]. It is also consistent with the hypothesis that bacillaemia and/or disease following reinfection can only result from a reinfection event if bacilli are implanted in particular regions of the lung (e.g. the sub-apical regions), and that there are no such restrictions for disease to result from an initial infection [50]. In this context we note that the protection associated with BCG vaccination ($\approx 77\%$ against disease among adolescents in England and Wales [40]) has also been attributed not to the prevention of infection, but to the prevention of haematogenous dissemination [49] and subsequent disease; in other words, a first

infection in a BCG vaccinated individual behaves like a reinfection in a non-vaccinated individual.

The estimated level of protection imparted by an initial infection against disease following reinfection (e.g. $\approx 41\%$ for adults) may appear surprising for two reasons. First, it is less than that estimated recently in a literature review, which contrasted the morbidity between tuberculin converters and those already tuberculin positive, following intense exposure to an infectious source [51]. Such direct estimates are difficult to interpret as they depend on the reliability of the tuberculin test in discriminating infected individuals. Second, the estimate is less than the average 77% vaccine efficacy found during the UK MRC BCG trial [40]. The latter comparison may be misleading, however, since the vaccine efficacy observed during the trial appeared to decline over time. In fact, the average vaccine efficacy is heavily weighted to infection shortly after vaccination, and does not reflect the protection imparted by vaccination against disease following *reinfection*, given the low risk of (re)infection and thus incidence of exogenous disease among participants several years after the start of the trial. Our estimates of the protection imparted by initial infection among adults were insensitive to the level and thus duration of vaccine-derived protection assumed in the model (Tables 3, 4) as they are based largely on data points pertaining to unvaccinated individuals. It is hoped that appropriate application of modern molecular tools will ultimately resolve this issue, by providing convincing estimates of the extent of disease attributable to exogenous reinfection.

Overall, the evidence suggests that the model's higher estimated risk of developing exogenous disease among 0–10 year olds (7% within 5 years of reinfection) as compared with that of developing the first primary episode (4% within 5 years of initial infection) is unrealistic. The unreliability is reflected in the broad range it took in the sensitivity analyses (Table 3), and in the fact that it increased when we assumed that vaccination imparted no protection against disease. The latter (paradoxical) result arose from correlations between the risks of developing disease inherent in the model's formulation, and the very small contribution of exogenous disease to the overall tuberculosis morbidity in the young age groups (see Fig. 3*a*). We obtained an equally good fit to the notification rates among 0–10 and 5–14 year olds (see Figs 3*a, b*) assuming that individuals do not experience exogenous disease and using only a slightly higher risk of developing the first primary episode

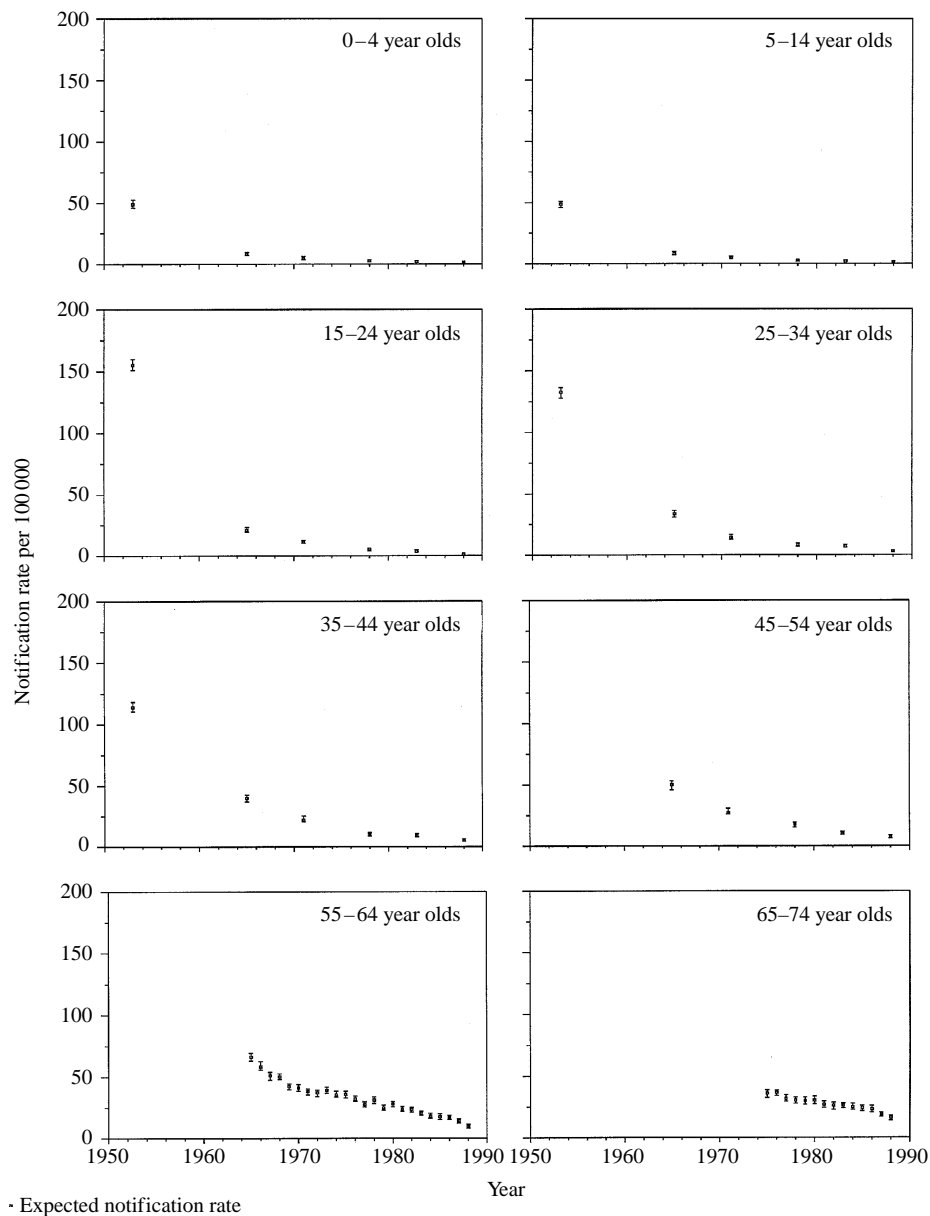


Fig. 5. 95% range of the age-specific notification rates of respiratory tuberculosis during the survey years (for 0–54 year olds) and for all years (for 55–74 years olds) used in the 50 simulated data sets to analyse the sensitivity of the disease risk estimates.

(Table 4) than that estimated using the full model. This suggests that if we were to force the risk of developing exogenous disease to be lower than that of developing the first primary episode among 0–10 year olds, for model predictions to fit the observed notification rates, we would need to incorporate other assumptions (e.g. that the risk of developing the first primary episode increases *before age 10 years*). It is interesting that the Norwegian data shown in Figure 2c hint at such a trend.

The relative importance of exogenous disease

Our analyses provide two lines of evidence for the

importance of reinfection as a major contributor to tuberculosis morbidity in the past.

First, exclusion of exogenous disease from the model leads to unrealistically high estimates for the risk of developing the first primary episode (Table 4) and considerably worsens the fit to notification rates, especially among the middle-aged and elderly for the period 1955–70 (Fig. 3b). If it is assumed that exogenous disease does not occur, then the dramatic decline in the notification rates observed among these individuals could have occurred only if the risk of developing endogenous disease declined dramatically over time (which seems unlikely) or else the incidence

of first primary episodes decreased substantially. The latter is also improbable, as most elderly and middle-aged individuals during the period 1955–70 had been infected early in life, given the high risks of infection estimated for the first half of this century. On this basis, we conclude that a dramatic decline in the incidence of reinfection among the elderly after 1950 was responsible in large part for the reduction in their overall notification rates. Similar declines in the notification rates among the elderly in Alaska during the 1950s have also been attributed to a declining incidence of reinfection and exogenous disease [52].

The second reason relates to the decline in the risk of infection and the associated *increases* in the incidence of initial infection during adolescence/adult life early this century. Styblo noted similar increases in the Netherlands after 1911 [5]. Our analyses demonstrate that these increases would have led to increases in the incidence of first primary episodes among 20–40 year olds (Fig. 4*b*), and thereby slowed down the decline in their overall morbidity. It is interesting that if adolescents and adults did not experience exogenous disease, then given the slow decline in the net incidence of endogenous disease that they experienced during the first half of this century, the increase in the incidence of first primary episodes would have led to an increase in their overall morbidity (see Fig. 4*b*). Therefore the fact that the morbidity among adolescents and adults declined at all during the first half of this century provides further evidence for the importance of reinfection in the past.

This slow decline in morbidity among young adults, as compared with that in other age groups, was observed between the two World Wars in England and Wales, though it has previously been attributed to other factors (e.g. complicated changes in migration patterns) [53]. Such a perverse association of *increases* in morbidity with *decreases* in infection risk has been discussed in relation to other diseases, including polio, mumps and rubella [54]. The decline in the risk of infection with the polio virus, for example is believed to have led to an increase in the average age at infection and an increase in paralytic disease among children, adolescents and young adults in developed countries during the 1940s and 1950s.

There has been much discussion in the literature of the sharp peak during young adult life in the mortality rates in successive birth cohorts during the prechemotherapy era [42, 55–57]. For the birth cohort of 1901–10 in England and Wales, the mortality rates among 20 year olds were almost four times greater than those in childhood. Such differences could not

have been attributable entirely to differences between exposure to tuberculous infection in adolescence and in infancy, as the risk of infection declined during each cohort's lifetime. The striking similarity between these rates and those predicted (Fig. 4*a*) further endorses the validity of the assumptions incorporated into the model and demonstrates that, given the high risks of infection during the prechemotherapy era, the sharp peaks in mortality during young adult life were attributable to the combination of a high incidence of (re)infection and a high risk of developing disease in late adolescence. It is interesting that the model fails to match the peak predicted during adult life for the 1881–90 and 1891–1900 birth cohorts (Fig. 4*a*). This is probably attributable to the fact that these cohorts reached adult life during the First World War, during which they experienced higher case-fatality rates than those assumed in the model, which does not adjust for the effects of war.

Overall, our analyses demonstrate that throughout this century, the risk of infection was the single most important factor affecting the magnitude of the disease incidence in all age groups, as it determined both the age pattern of initial infection (and hence the risk of developing disease) and the risk of reinfection. More recently, the epidemiology of tuberculosis has changed dramatically in developed countries, with recent increases being attributed to the HIV epidemic, to the increasing problem of homelessness and to underfunding of control programmes [58]. The impacts of these factors are difficult to assess without a prior understanding of the basic natural history of tuberculosis. By appreciating the implications of both age and reinfection in the transmission dynamics of *M. tuberculosis* in the past, we become better equipped to assess the epidemiology and control of tuberculosis in the future.

APPENDIX

(A) PDEs describing the model formulation

$$\begin{aligned} \frac{\partial U(a, t)}{\partial a} + \frac{\partial U(a, t)}{\partial t} \\ = -(i(t) + v(a, t) + m_q(a, t)) U(a, t) \end{aligned} \quad (\text{A } 1)$$

$$\begin{aligned} \frac{\partial V(a, t)}{\partial a} + \frac{\partial V(a, t)}{\partial t} \\ = v(a, t) U(a, t) - m_q(a, t) V(a, t) \end{aligned} \quad (\text{A } 2)$$

$$\begin{aligned} \frac{\partial I(a, t, s)}{\partial a} + \frac{\partial I(a, t, s)}{\partial t} + \frac{\partial I(a, t, s)}{\partial s} \\ = -(d_p(a-s, s) + m_q(a, t)) I(a, t, s) \\ - k_L(s) I(a, t, s) \quad (0 < s \leq 5) \end{aligned} \quad (\text{A } 3)$$

$$\begin{aligned} & \frac{\partial P(a, t, \hat{s})}{\partial a} + \frac{\partial P(a, t, \hat{s})}{\partial t} + \frac{\partial P(a, t, \hat{s})}{\partial \hat{s}} \\ &= \int_0^5 d_p(a-s, s) I(a, t, s) ds \\ & \quad - (m_+(t, \hat{s}) d_+(a) + m_g(a, t) d_-(a)) P(a, t, \hat{s}) \\ & \quad - r(a, t, \hat{s}) P(a, t, \hat{s}) \end{aligned} \tag{A 4}$$

$$\begin{aligned} & \frac{\partial L(a, t)}{\partial a} + \frac{\partial L(a, t)}{\partial t} \\ &= (I(a, t, 5) + I_r(a, t, 5)) k_L(5) \\ & \quad + r(a, t, 2) (P(a, t, 2) + E_n(a, t, 2) + E_x(a, t, 2)) \\ & \quad - (i(t) + d_n(a) + m_g(a, t)) L(a, t) \end{aligned} \tag{A 5}$$

$$\begin{aligned} & \frac{\partial I_r(a, t, s)}{\partial a} + \frac{\partial I_r(a, t, s)}{\partial t} + \frac{\partial I_r(a, t, s)}{\partial s} \\ &= -(d_x(a-s, s) + m_g(a, t)) I_r(a, t, s) \\ & \quad - k_L(s) I_r(a, t, s) \quad (0 < s \leq 5) \end{aligned} \tag{A 6}$$

$$\begin{aligned} & \frac{\partial E_x(a, t, \hat{s})}{\partial a} + \frac{\partial E_x(a, t, \hat{s})}{\partial t} + \frac{\partial E_x(a, t, \hat{s})}{\partial \hat{s}} \\ &= \int_0^5 d_x(a-s, s) I_r(a, t, s) ds \\ & \quad - (m_+(t, \hat{s}) d_+(a) + m_g(a, t) d_-(a)) E_x(a, t, \hat{s}) \\ & \quad - r(a, t, \hat{s}) E_x(a, t, \hat{s}) \end{aligned} \tag{A 7}$$

$$\begin{aligned} & \frac{\partial E_n(a, t, \hat{s})}{\partial a} + \frac{\partial E_n(a, t, \hat{s})}{\partial t} + \frac{\partial E_n(a, t, \hat{s})}{\partial \hat{s}} \\ &= d_n(a) L(a, t) - r(a, t, \hat{s}) E_n(a, t, \hat{s}) \\ & \quad - (m_+(t, \hat{s}) d_+(a) + m_g(a, t) d_-(a)) E_n(a, t, \hat{s}). \end{aligned} \tag{A 8}$$

Boundary conditions:

$$\begin{aligned} U(0, t) &= B(t); \\ I(a, t, 0) &= i(t) U(a, t); \\ I_r(a, t, 0) &= i(t) L(a, t). \end{aligned}$$

For notational convenience, we denote $1 - d_+(a)$ by $d_-(a)$.

Note that the assumption that BCG imparts lifelong protection against *disease* is equivalent to assuming that those protected by vaccination *cannot become infected* (thus equations 2 and 3).

(B) Methods used for sensitivity analyses of disease risk estimates

The method used to generate the notification rates for a given age group in the age range 0–54 years in a simulated data set is described by the following algorithm:

1. Randomly generate the number of cases of *all forms* of tuberculosis in 1953 and in each of the survey years (excluding 1988 – see below), assuming that it follows a Poisson distribution with mean given by the ‘actual’ number of cases of *all forms* of tuberculosis in the age group in the survey year (n_a). Calculate the

notification rate of all forms of tuberculosis for this age group and each survey year resulting from these random estimates.

Note that the surveys were carried out for only part of a year, and reports of the surveys published only the *annual notification rates*. The ‘actual’ numbers of cases used in this algorithm refer to the numbers of cases which would have occurred during the entire year. Population estimates for most years were published in the national reports of the surveys [41, 61]; otherwise, we used the original sources described in these publications.

2. Calculate the rate of decline since 1953 and between the survey years for these randomly generated notification rates of *all forms* of tuberculosis.

3. Randomly generate the number of cases of respiratory tuberculosis for 1953 and 1988, assuming that it follows a Poisson distribution with mean given by the ‘actual’ number of cases of respiratory tuberculosis in the age group in these years (n_r). Note that for 45–54 year olds in 1954, n_r was derived assuming that it was 95% of n_a (see main text). Calculate the corresponding notification rate of respiratory tuberculosis in 1953 and 1988 using the randomly generated estimate.

4. Calculate the rate of decline in notifications of respiratory tuberculosis between 1983 and 1988 based on the randomly generated estimates.

5. Derive estimates of the age-specific notifications of respiratory tuberculosis for the period 1954–83 assuming that they declined from the level in 1953 calculated in step 3 at the rates calculated in step 2 above. Similarly calculate the notifications for the period 1984–8 assuming that they declined from the (simulated) level in 1983 at the rate calculated in step 4.

The notification rate for a given year for 55–64 and 65–74 year olds in a simulated data set was generated more simply, i.e. by repeating step 3 for each year (between 1965 and 1988, and 1975 and 1988 respectively) using the published or observed number of cases of respiratory tuberculosis for that year.

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