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Interpreting the decline in tuberculosis: the role of secular trends in effective contact

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Background	The dramatic decline in tuberculosis (TB) in developed countries during the past century has been attributed to many factors, including improvements in living and social conditions and, more recently, effective treatment. Each of these changes should have reduced the average number of individuals 'effectively contacted' (i.e. sufficiently to transmit infection) by each infectious TB case.
Method	Estimates of the average number of individuals effectively contacted by each infectious TB case, for each year since 1900 in England and Wales, are derived as the ratio between published estimates of the annual risk of infection and estimates of the prevalence of infectious cases, as derived using a published model of the epidemiology of TB.
Results	The results suggest that each infectious case contacted, on average, about 22 individuals in 1900 sufficiently to transmit *Mycobacterium tuberculosis* infection, and that this number declined to about 10 by 1950 and to approximately one by 1990.
Conclusions	Although several factors contributed to the decline in TB in developed countries during this century, a major contributor has been the decline in the number of effective contacts by each case over time. Similar declines have doubtless occurred over the past century for many infections in developed countries.

Keywords	Tuberculosis, epidemiology, model, decline, contact
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The dramatic decline in tuberculosis (TB) in developed countries during the past century, even prior to the introduction of effective anti-TB drugs, has been attributed to many factors, including improvements in social conditions and nutrition,[1] reduced crowding[2] and segregation of infectious cases either to workhouses or sanatoria.[3] Whilst the risk of tuberculous infection has declined in many developed countries, at least since the early years of this century,[4,5] the extent to which the reduced morbidity was attributable to a reduction in infection transmission per case, as opposed to a reduced risk of developing disease among infected individuals, is unknown. Reductions in transmission could have occurred either through changes in the degree of exposure to infectious cases, for example as a result of changing behaviour, reduced crowding or increasing segregation of infectious cases to sanatoria, or else because of declines in the susceptibility to infection of those exposed, perhaps through improved hygiene or nutrition.

The effects of these changes should be reflected in trends in the average number of individuals 'effectively' contacted by each infectious TB case. To date, the trend in this statistic in any single population throughout this century has not yet been measured, though several studies have explored related questions. For example, one study correlated the annual risk of infection to the estimated incidence of smear-positive cases in many different populations and concluded that an incidence of 50 per 100 000 reflects an annual risk of infection of 1%.[6,7] Assuming an average duration of infectiousness of 2 years, this implies that on average each smear-positive case contacts 10 individuals per year.[8] This particular study did not determine whether this statistic had changed over time. Another study derived a related statistic for the Netherlands, namely the ratio between the annual risk of infection and mortality rates from all forms of TB and found that it hardly declined at all during the time period considered (1921–1938).[7] A more recent study, also carried out in the Netherlands, found that yet another measure, the number of individuals contacted by each (all forms) TB case, declined from about three individuals contacted in 1950 to about 1.8 individuals contacted in 1980.[9]

In the analyses presented here, we extend these estimates using an age-structured model of the transmission dynamics of *Mycobacterium tuberculosis* in England and Wales. We first estimate the prevalence of infectious cases since 1900, and relate these figures to estimates of the annual risk of infection,[5] in order to assess the extent to which the decline in TB morbidity in developed countries reflects changes in the number of individuals infected by each infectious case.

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Methods

General structure and assumptions in the model

Figure 1 shows the general structure of the model, which extends the work of Sutherland *et al.*[10] and describes the dynamics of all forms of pulmonary TB in England and Wales over the past century. The derivation and validation of the model are described in detail elsewhere.[11] The input parameters and their values are summarized in Table 1. Analyses presented here relate to white ethnic males in the absence of HIV infection,[11] and thus avoid the complications of gender differences, immigration and the HIV epidemic in the recent epidemiology of TB in England and Wales.

Individuals are born uninfected, and face an annual risk of infection ($i(t)$), dependent on calendar year (see below). Infected individuals are divided into those infected for <5 years who have not experienced (primary) disease ($I(a,t,s)$), and those in the 'latent' class ($L(a,t)$), who are at risk of endogenous disease or of reinfection, followed by exogenous disease. The 'latent' class comprises individuals who have been infected for >5 years, and also those who have been (re)infected for <5 years but have already experienced disease in the meantime.

The risks of initial infection and of reinfection are assumed to be identical, though reinfection is less likely to lead to disease than is an initial infection due to the (partial) immunity induced by previous infection.[11] These assumptions stem from the results from our previous analyses,[11] which found that the best fit to the observed data (see below) occurred if we assumed that infection confers no protection against reinfection *per se*, though it did reduce the probability that the reinfection event led to disease. In reality, it is likely that the risks of infection

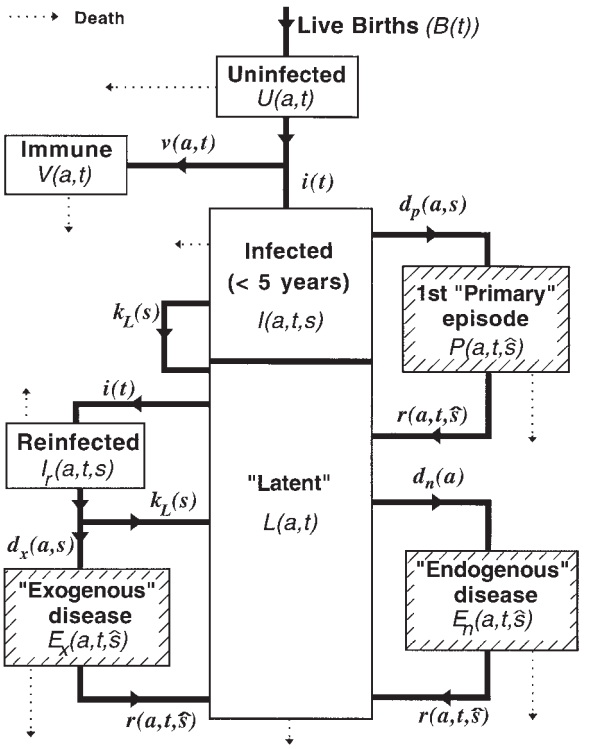

Figure 1 Schematic diagram of the model. Primary disease is defined as disease within 5 years of initial infection;[34] exogenous disease is here defined as the first disease episode within 5 years of the most recent reinfection. Endogenous disease includes disease occurring >5 years after the most recent (re)infection event, and *second or subsequent disease episodes* occurring <5 years after the most recent (re)infection event

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Table 1 Summary of parameter values used in 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 1950 and 13% pa thereafter.[5]
$v(a,t)$	Proportion of uninfected individuals of age a immunized at time t.	Vaccination introduced in 1954 and restricted to 13 year olds. Vaccine efficacy assumed to be 77% and vaccine coverage increasing to approximately 80% since 1960.[11]
$d_p(a,s)$	Risk of developing the first primary episode at time s after infection at age a.	Declines with time since initial infection (Figure 2B). Cumulative risks within 5 years of initial infection: 4.06%, 8.98% and 13.8% for 0–10 year olds, 15 year olds and individuals aged >20 years respectively.[11]
$d_x(a,s)$	Risk of developing exogenous disease at time s after reinfection at age a.	Declines with time since reinfection (Figure 2B). Risks within 5 years of reinfection: 6.89%, 7.57% and 8.25% for 0–10 year olds, 15 year olds and individuals aged >20 years respectively.[11]
$d_n(a)$	Annual risk of developing endogenous disease at age a.	9.82×10^{-8}%, 0.0150%, and 0.0299% for 0–10 year olds, 15 year olds and individuals aged >20 years respectively.[11]
$d_+(a)$	Proportion of total disease incidence among cases	10% for 0–10 year olds, increasing linearly to 65% for 20 year olds and aged a assumed to be infectious. increasing linearly to 85% for 90 year olds (Figure 2C).
$k_L(s)$	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.
$r(a,t,\hat{s})$	Recovery rate for cases of age a at time t and time $\hat{s}$ after disease onset.	Individuals are diseased for 2 years unless they die in the meantime (see below).
$m_+(t,\hat{s})$	Case-fatality of infectious pulmonary cases at time t and time $\hat{s}$ since disease onset.	Case fatality in second year after disease onset is 65% of that in first year. 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.[11]
$m_g(a,t)$	Mortality rate of non-infectious and non-diseased individuals in the general population of age a at time t.	Identical to all-cause mortality (after subtracting deaths among infectious cases, estimated in the model). Annual age-specific all-cause mortality rates obtained from Government's Actuary's Department since 1841. Data until 1841 obtained by back-extrapolation.

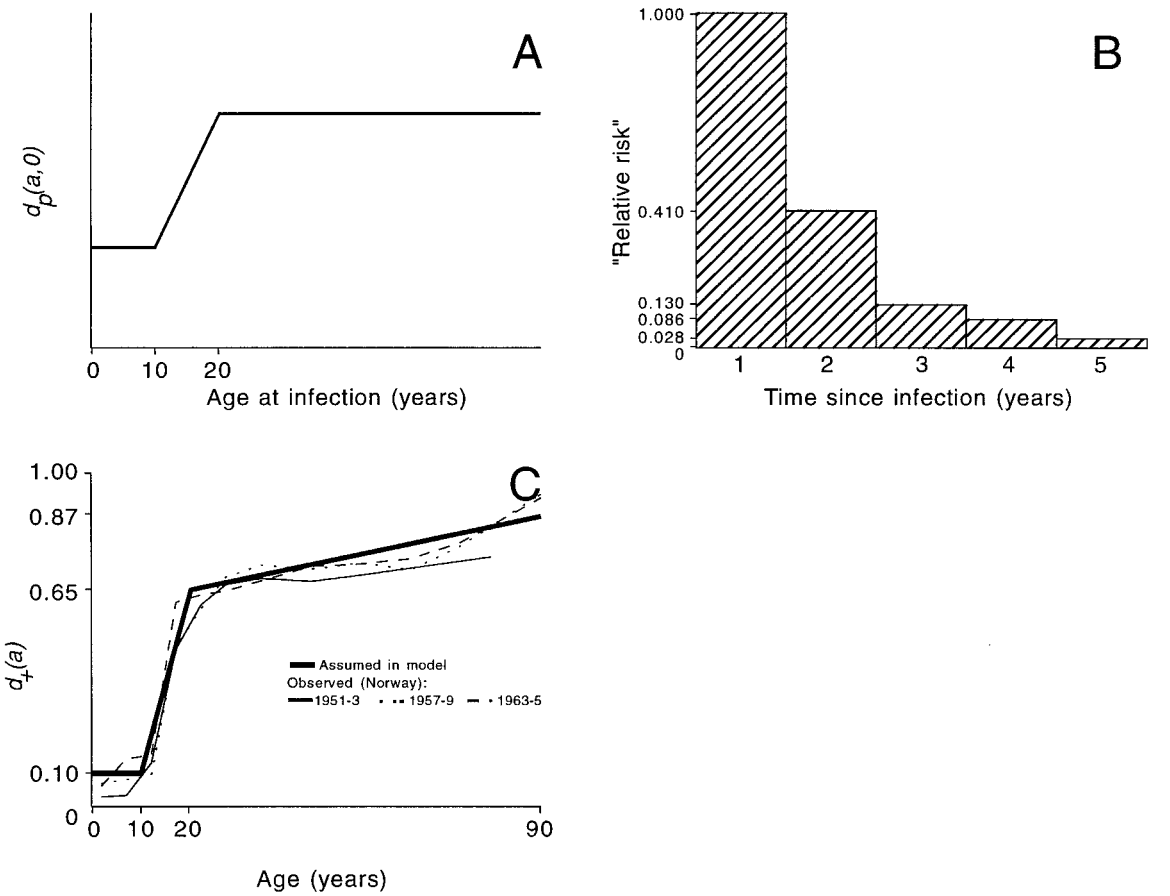

Figure 2 Summary of main assumptions in the model relating to the risks of developing disease

A General relationship between the risk of developing the first primary episode (during the first year after infection) and age at infection. An identical relationship is assumed to hold between the risk of exogenous disease and the age at reinfection and between the risk of endogenous disease and the current age of individuals. See Table 1 for the magnitude of the disease risks.

B Risk of developing the first primary episode (or exogenous disease) in each year following initial infection (or reinfection), relative to that experienced in the first year after infection. The relationship was derived using data from the UK MRC BCG trial during the 1950s.[35]

C Proportion of respiratory disease incidence manifested as sputum-positive (i.e. infectious forms), *based on Norwegian data provided by the late Dr K Styblo (TSRU) and Dr K Bjartveit (Norwegian National Health Screening Service).*

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and of reinfection differ, either because the immune response resulting from a previous infection makes reinfection difficult to establish, or because individuals who are already infected live in situations which predispose them to further (re)infection. For simplicity, the reinfection risk is assumed to be negligible for recently (re)infected individuals who are already at risk of developing their first primary episode or exogenous disease.[11]

The risks of developing disease are age-dependent; those of developing the first primary episode ($d_p(a,s)$) and of exogenous disease ($d_x(a,s)$) depend also on time since infection and reinfection respectively (Figures 2A and B). Neither of these risks is assumed to depend on calendar year—we discuss the implications of this assumption below. Estimates of the risks of developing disease have been derived by fitting model predictions to notifications of pulmonary TB in England and Wales from the period 1953–1988, assuming that individuals either could or could not develop disease following reinfection.[11] The sensitivity of the model to various assumptions has been explored in an earlier publication.[11] In particular, the exclusion of the reinfection disease pathway considerably worsened the fit to notification rates, especially among the elderly.[11]

An age-specific proportion of disease is assumed to be 'sputum-positive', i.e. infectious ($d_+(a)$). This is independent of the mechanism of disease onset and of whether it is a first or subsequent disease episode (Figure 2C). It is assumed that individuals are diseased for 2 years unless they die in the meantime. The case-fatality rate is assumed to be 50% during the prechemotherapy era, which is similar to that found in several observational studies[12] (see also reviews in[6,8]) and in a major longitudinal study of the natural history of TB in the absence of treatment.[13] Disease-attributable deaths are distributed over 2 years following disease onset (Table 1). Treatment first became generally available from about 1950, and lasted 6 months to over 2 years during the 1950s,[14] with short-course regimens (e.g. 9 months) having been introduced in 1976 in England

and Wales.[15] To incorporate the contribution of treatment to the transmission dynamics of *M. tuberculosis* in the model, the duration of infectiousness is assumed to decrease gradually from 2 years in 1950 to one year in 1976. The BCG vaccination of 13 year olds since 1954, assuming a vaccine efficacy of 77%[11] has also been incorporated (Table 1).

Estimation of infection risk trends

The estimation of the annual risk of infection since 1900 in England and Wales has been described elsewhere.[5] Briefly, the annual risk of infection between 1900 and 1949 was derived using tuberculous meningitis mortality rates among 0–4 year olds, assuming (as found elsewhere[4]) that 1% of new infections in this age group led to fatal tuberculous meningitis. The infection risks thus derived led to a good fit between the expected prevalence of tuberculous infection and the observed prevalence of tuberculin sensitivity among individuals tested during the 1949–1950 national tuberculin survey in England and Wales.[16] Given the absence of appropriate data for England and Wales after 1950, it is assumed that the annual risk of infection declined from 1950 at 13% per annum, as was found in the Netherlands (which has the most reliable estimates of trends in infection risks over time).[4]

Evaluation of the reliability of model predictions prior to 1950

Here we examine the reliability of model predictions for the prechemotherapy era. Given the absence of appropriate routine TB morbidity data prior to 1950, we compared model predictions of the *mortality rates* (among males) from respiratory TB as an age-standardized population statistic, and in different age groups, against those observed. The annual mortality rates from 1901 until 1957 were calculated using the numbers of deaths from respiratory TB (using the appropriate classification), extracted from Revisions I–V of the historic data files (available in electronic form from the Office for Population and Census Surveys (OPCS), now known as the Office for National Statistics) and population estimates calculated by OPCS in 1991.

In previous analyses of TB trends from 1950, the exclusion of the reinfection disease pathway from the model led to a poor fit to notification rates especially among the elderly.[11] Given that the contribution of reinfection to the transmission dynamics of *M. tuberculosis* is disputed,[17] we also compared predictions of the mortality rates against those observed, assuming that disease could not result from reinfection and using the best-fitting disease risks which resulted from this assumption.[11]

Estimates of the 'effective contact number'

An effective contact between an infectious pulmonary case and another individual is here defined, as by Frost,[18] as that sort of contact which is sufficient to lead to infection if the contacted individual has never been infected in the past. The number of individuals effectively contacted by each infectious case (the 'effective contact number') was derived for each year during the period 1900–1990 as the ratio between the annual risk of infection and the prevalence of infectious cases. Given the absence of reliable notifications until the 1950s in England and Wales, the latter were generated using the model which best matched the observed magnitude and trend in the age-specific mortality rates until 1950.

Results

Figure 3 demonstrates that predicted trends in mortality of TB depend greatly on whether we assume that disease did or did not arise following reinfection in the past. For individuals aged <65 years, predictions derived using the full model (i.e. assuming that disease could occur as a consequence of reinfection) provide a good fit to the mortality rates, which is considerably better than that derived assuming that reinfection did not lead to disease in the past. For 15–24 and 25–34 year olds, the estimates derived using the full model slightly overestimate the observed mortality rates, especially for the early 1900s, and the fit is best for individuals aged 35–44 and 45–54 years. The fit to the mortality rates during the period 1914–1918 and the early 1940s is poor, coinciding with the two World Wars (no attempt was made to incorporate the effects of war on TB trends in the model). Model predictions suggest that if it is assumed that reinfection did *not* lead to disease, then the TB-specific mortality rates would have been considerably lower than those observed for all age groups, and for the younger age groups (those aged <65 years) they would have *increased* until 1950 (this is explained below). For individuals aged >65 years, the fit to the observed data is poor irrespective of the reinfection assumption, and that derived using the full model is especially poor for individuals aged >75 years.

Figure 4 shows that predictions of the age-standardized TB-specific mortality rates derived using the full model closely match the decline in the observed rates, though they slightly overestimate the overall magnitude of these rates. In contrast, predictions derived assuming that disease did not arise through reinfection *underestimate* the observed mortality rates, and predict that the overall mortality rates should have *increased* during this century.

Figure 5 summarizes estimates of the annual risk of infection (Figure 5A) as derived elsewhere,[5] and estimates of the overall prevalence of infectious pulmonary cases in England and Wales since 1900 (Figure 5B), as derived using the full model, which provided the best fit to the observed mortality rates (see above). The prevalence of infectious cases is estimated to have declined dramatically during this century, from approximately 600 per 100 000 in 1900 to about 200 per 100 000 by 1950, with the decline accelerating after 1950.

The implications for the effective contact number are shown in Figure 5C. This suggests that the number of effective contacts per case declined during this century—on average, each infectious pulmonary case effectively contacted about 22 individuals in 1900; this declined to about 10 by 1950 and to about one by 1990.

Discussion and Conclusions

These analyses present evidence that the decline in TB morbidity during the past century in developed countries was associated with a decline in the degree of effective contact between individuals.

The conclusions are based in part on a model which simplifies the epidemiology of TB, while attempting to preserve the essential characteristics of the disease. Among the model's major assumptions is that of random mixing, which is likely to have been more realistic for the first half of this century than for more recent years. This assumption means that our estimates of the effective contact number may be particularly unreliable for

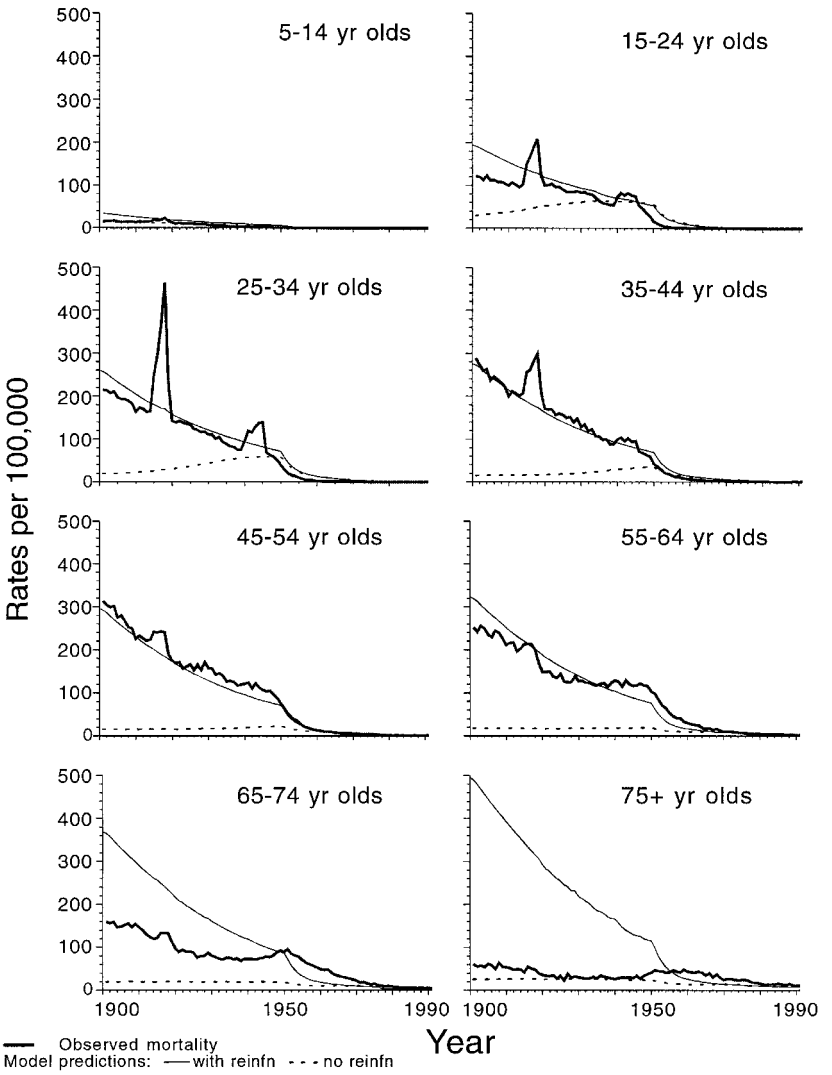

Figure 3 Comparison between observed age-specific mortality rates attributable to respiratory tuberculosis in England and Wales in males since 1901, against those predicted by the model, assuming that reinfection did and did not occur, using best-fitting disease risks for the corresponding assumption. (Risks of disease based on the assumption that reinfection did not affect disease risks: 2.53% and 13.6% for individuals during the first year after infection at age 0–10 years and >20 years respectively; annual risk of developing endogenous disease: 4.72×10^{-4}% and 0.0416% for 0–10 year olds and those aged >20 years respectively[11].)

recent years. Another important assumption is that the disease risks among infected individuals depend only upon age and time since (re)infection, but not otherwise on calendar time. We discuss the implications of this assumption below.

The reliability of prevalence estimates prior to 1950

The full model (which assumes that disease could result from reinfection) appears to provide a credible description of TB trends in England and Wales during the prechemotherapy era, with model predictions matching the magnitude and trend observed in both the age-standardized and age-specific mortality rates (Figures 3 and 4). The alternative assumption, that reinfection could not lead to disease, predicted trends which were very different from those observed, with low mortality rates during the early years of this century, followed by an increase in mortality rates until about 1950.

The finding that reinfection needs to be incorporated in the model for predictions to match observed trends is consistent with the results from previous analyses of the transmission dynamics of *M. tuberculosis* in England and Wales since the 1950s.[5] Those analyses found that if it was assumed that disease could not result from reinfection, then the model predicted a slower decline and lower levels in the morbidity among older individuals than those actually observed. In the analyses presented here, the importance of reinfection in the model stems from the very high annual infection risks estimated for the start of this century (e.g. 12% in England and Wales in 1900[5]), which implies a very high prevalence of infection among adults alive

during this time. This suggests that, if it is assumed that individuals could *not* experience disease following reinfection in the past, then, given these high infection risks early this century, model predictions can only match observed trends if it is assumed that the risks of developing endogenous disease were much higher than those assumed and that they declined dramatically over time.

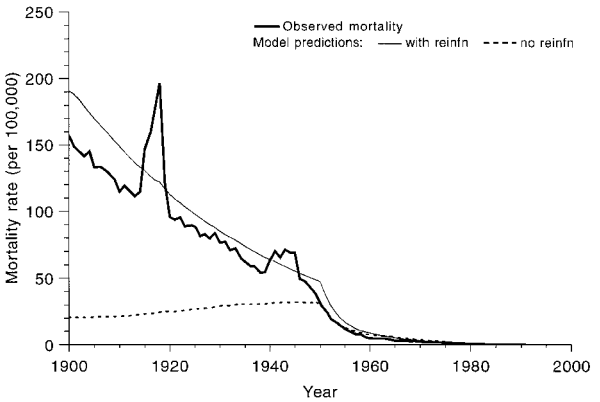

Figure 4 Comparison between the observed average age-standardized mortality rates attributable to respiratory tuberculosis in England and Wales in males since 1901, against those predicted by the model, assuming that reinfection did and did not occur, using the best-fitting disease risks for the corresponding assumption. (See caption to Figure 3 for values of the disease risks)

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Although not assumed in the model, some decline in disease risks among infected individuals is not unreasonable, and thus a reduction in the contribution of reinfection-attributable disease was probably not the sole factor determining tuberculosis trends in England and Wales in the past. Disease risks could have declined for two reasons: through a decline in intensity (dose) of exposure, or through an improvement in the general health status of infected individuals, associated perhaps with nutrition. There is some evidence suggesting that the risk of developing primary disease given infection is higher among individuals who are exposed to a high dose of tubercle bacilli, as compared with those less intensely exposed.[19] It is likely that the risk of developing disease following reinfection is also dose-dependent. Although there is no evidence that dose of initial exposure affects the risk of endogenous reactivation many years thereafter, such a relationship is plausible, as initial dose could determine the number and magnitude of lesions, and hence the probability that reactivation disease occurs. Insofar as this is true, in populations where the overall annual risk of infection early this century was lower than in countries such as England and Wales, a reduction in infecting dose might have been as important as a reduction in reinfection-attributable disease in determining tuberculosis trends.

Despite the excellent fit for younger and middle-aged individuals, we note that predictions derived using the full model greatly overestimate the observed mortality rates for older individuals during the prechemotherapy era, especially for those

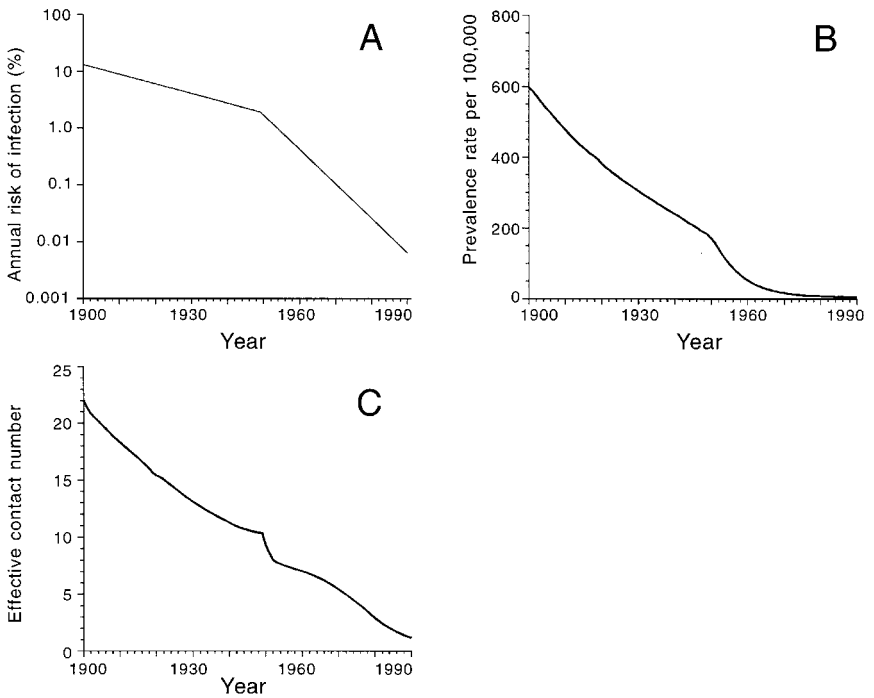

Figure 5 Estimating the effective contact number in England and Wales since 1900

A The annual risk of infection (derived using tuberculous meningitis statistics and tuberculin sensitivity data[5]).

B Prevalence of infectious pulmonary cases since 1900, as derived using the full model.

C The estimated effective contact number, derived as the ratio between the annual risk of infection and the prevalence of infectious cases

aged ⩾75 years (Figure 3). There are several possible explanations for this discrepancy. First, it could be true that reinfection was not important in determining the morbidity among the elderly, either because older individuals had more immunity to reinfection due to previous infection, or were less *exposed* to new infections than were younger individuals. Second, the low mortality rates among the elderly could be a residue of high mortality rates experienced by susceptible members of these cohorts when they passed through young adult life—there has been much discussion of this issue in the literature.[20–23] A third explanation is that some of the TB-attributable mortality at older ages was not recognized. This is supported by an autopsy study carried out during the period 1935–1944, which found that open tuberculous lesions were present in about 50% of individuals aged >50 years who were recorded as having died of causes other than TB.[24]

Estimates of the effective contact number for tuberculosis

There is a large literature on the decline in TB and other infectious diseases during the past century in developed countries. Our analyses suggest that this decline was associated with a decline in the average number of individuals 'effectively contacted' by each infectious case.

Such a decline in the effective contact number is not unreasonable, and can be attributed to many factors. Among the obvious influences is a decline in the degree of domestic crowding. During the latter part of the 19th century, about 8% of the population in England and Wales lived in accommodation with more than two individuals per room, as compared with 5.5% and about 1% by 1901 and 1951 respectively.[25] By 1991, only 0.25% of the population lived in accommodation with more than 1.5 individuals per room.[25] The average size of each household has also decreased over time, from about 5 individuals in 1901 to about 2.5 by 1990.[26] The importance of general living conditions in determining transmission was demonstrated by a study in 1931, which compared the prevalence of tuberculin sensitivity among individuals living in accommodation rated as 'poor', 'fair' and 'good' (determined on the basis of income, locality and general hygiene) and in which there was a source of infection.[27] The prevalence of tuberculin sensitivity among contacts was inversely proportional to the standards of housing, and a similar comparison in households without a source of infection showed little association between the prevalence of tuberculin sensitivity and housing standards. It is also likely that ventilation in homes and workplaces has improved appreciably during this century, which should have reduced the risk of aerosol transfer of infection.

Other changes must also have reduced the opportunity for exposure to infectious cases in the domestic setting. The proportion of elderly individuals (important as sources of tuberculous infection[24]) living either alone or in institutions has increased over time, thereby reducing exposure opportunities to younger individuals in the population.[26] Improvements in the nutritional status in the population[28] may have contributed to reductions in the effective contact number, by reducing the probability of a contact becoming infected with *M. tuberculosis* given a certain exposure. Improvements have occurred in the general hygiene in the population (and in behaviour associated with sneezing, coughing and spitting). The effective contact number should also have declined as a result of increasing proportions of infectious individuals being removed from the population to sanatoria during the prechemotherapy era. During the early 1900s, there were only three TB sanatoria in England and Wales, and one TB dispensary; by the 1930s there were more than 300 sanatoria and hospitals and about 500 TB dispensaries.[29] It has also been pointed out that infectious cases were effectively segregated even before the 1900s, as a consequence of the removal of the poor to workhouses.[3]

Most of these factors should have influenced the effective contact number for other infectious diseases in addition to TB, many of which have declined during this century. A study of childhood bronchitis and pneumonia has suggested that the decline in childhood infections was related to declines in fertility rates, which, by reducing the size of the average household, increased the average age at infection.[30] It is possible that these concurrent declines in acute infections may have themselves contributed to reductions in TB morbidity, as some studies have suggested that individuals may be more susceptible to tuberculous infection and/or disease after experiencing acute viral infections.[31] Ironically, the effective contact number for some infections may have increased over this century, as a consequence of increasing proportions of children attending crêches or pre-school day-care nurseries. This increased mixing among young children is likely to be much less important for the transmission dynamics of *M. tuberculosis* than for acute respiratory and enteric infections, however, as very few children develop infectious pulmonary forms of TB.

The decline in the effective contact number from 1950 estimated here (Figure 5) is particularly interesting. Much of the decline during the 1950s is attributable to the availability of effective antibiotics for TB after 1950, which must have had a marked effect on reducing exposure by shortening the duration and the infectiousness of each case. It also plausible that the effective contact number after 1950 was affected by changes in the age distribution of infectious cases over time, as an increasing proportion of infectious cases from the 1950s were middle-aged or elderly —it is likely that these individuals contact fewer individuals than do younger individuals who comprised most of the infectious sources earlier this century. It has been suggested that this particular factor contributed to the similar decline which was observed in the number of individuals contacted by each (all forms) TB case in the Netherlands between 1950 and 1980.[9]

The effective contact number for a given infection influences another important epidemiological statistic, the basic reproduction number, defined as the number of secondary infectious cases resulting from a typical infectious case in a 'totally susceptible' population. For simple infections such as measles, for which all infected individuals develop infectious forms of the disease, the total number of individuals effectively contacted by a case during his/her infectious period in a 'totally susceptible' population will be identical to the basic reproduction number. For TB, the relationship between the effective contact number and the basic reproduction number is complicated by the fact that not all of those infected go on to develop infectious disease, by the age-dependence in disease risks, and by the fact that reinfection can occur. The implications of the factors for the basic reproduction number for TB are discussed in detail elsewhere.[32]

These analyses indicate that many factors have influenced the transmission dynamics of *M. tuberculosis* in the past, and provide evidence that a declining effective contact number was important in determining the decline in tuberculosis morbidity through most of this century. It is interesting that the decline in TB incidence was halted in several countries during the 1980s, a change which has been attributed to several influences, in particular the HIV epidemic, changes in immigration patterns, the increasing problem of homelessness and underfunding of control programmes.[33] Though recent data for the US indicate that the recent increase was only a brief setback, comparable perhaps to the increases observed during the two World Wars earlier this century, the full implications in different countries is yet to be seen. Whatever unfolds, an appreciation of the factors underlying past trends should help us to interpret the future epidemiology of TB.

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