Supporting Online Material for

The Population Dynamics and Control of Tuberculosis

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The Population Dynamics and Control of Tuberculosis

Supporting Online Material

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1. TB natural history and epidemiology

This section gives further information on TB natural history, to expand on the brief description in the main text. The flow chart in Fig. 1 shows the standard compartmental model of tuberculosis transmission, infection and disease. The response to infection is usually represented as two dichotomies. At the first, a proportion of infected people progress rapidly to active TB (by convention, within 5 years), while the rest enter a latent state from which *M. tuberculosis* can reactivate for years or decades thereafter, but at a comparatively low rate annually. Latently infected individuals may develop TB following reinfection, but their primary infections confer partial immunity. At the second dichotomy, individuals who develop active TB, whether sooner or later, are classified as either infectious (moderate to severe pulmonary disease) or non-infectious (mild pulmonary or extrapulmonary disease).

Latent infection is traditionally identified by a positive tuberculin skin test, and more recently by interferon-γ release assays, though these tests do not measure the response to infection in the same way (1). Chest X-rays are sensitive but not specific for active pulmonary TB; a definitive diagnosis of TB requires the identification of *M. tuberculosis* in sputum or another tissue sample. As a convenient approximation, infectiousness is equated with having a sputum smear in which acid fast bacilli are visible microscopically. Smear positive patients typically have more severe pulmonary disease than smear negatives, and are the principal, but not exclusive, sources of infection.
Extrapulmonary TB can occur in any organ of the body, but lymphadenitis is the most common presentation outside the lung. It is relatively frequent among women and people infected with HIV. Tuberculous meningitis and disseminated miliary disease are among the most severe forms of extrapulmonary disease, to which children under 5 years are especially vulnerable.

Before TB drugs became available in the 1940s, a minority of patients spontaneously resolved their illness. The majority died. For the past 40 years, four-drug combinations including isoniazid and rifampicin have been able to cure permanently almost all patients carrying drug-sensitive strains, provided they seek diagnosis and treatment, and then comply fully with the 6-month course of therapy. Late diagnosis of active TB and inadequate treatment are causes of persistent transmission.

To calculate the expected rate of spread of TB through populations and the response to control measures, we can quantify the transitions among states in Fig. 1. The case reproduction number, $R$, is the number of secondary cases that arise in the next $M. tuberculosis$ generation from each primary case in the present generation. $R$ is the product of the infectiousness period ($d$), the number of infections transmitted by each infectious case each year through contact with others ($b$), and the proportion of infections that lead to active infectious TB ($p$).

The traditional, quantitative rules of thumb are as follows (2). Each infectious case survives an average of 2 years without treatment, infecting about 10 others each year. This means that, before drugs became available, the mortality rate, incidence rate and prevalence of infectious TB were found in the ratio 1:2:4. Among those infected, 10% develop active TB, 5% within 5 years and 5% during the rest of their lives. The implication is that 90% of infected people are innately immune to active disease. Among patients with active pulmonary TB, about half will be infectious and half non-infectious. So $R = dbp = 2 \times 10 \times 0.1 \times 0.5 = 1$. This, therefore, is stably endemic TB, where each case leads to one further case in the next generation. In the simplest mathematical models, this stable equilibrium is assumed to exist in a closed population, with no immigration or emigration and a constant number of people at each age.

As the system is pushed away from equilibrium, especially through efforts to control TB, it is useful to calculate the maximum number of secondary cases that could arise from each
primary case, known as the basic case reproduction number, $R_0$. This quantity measures the potential for re-emergence of TB at the point of elimination. Because *M. tuberculosis* has a comparatively low $R_0$ ($< 5$) among infectious diseases, it should be relatively easy to put TB on a course to elimination ($R_0 < 1$). But the slow dynamics linked to low $R_0$ and the long life expectancy of each infection (years), also mean that the epidemic has a long doubling time when case numbers are increasing, and a long half life when they are in decline.

The following calculation of $R_0$ is approximate. If at equilibrium there are 100 smear-positive TB cases per 100,000 people per year and each episode lasts an average of 2 years, the prevalence would be 200 per 100,000. With 10 contacts per case per year, the annual risk of infection per capita is 2%. Given a life expectancy from birth of 70 years, simple TB models show that about half the population would be infected due to the build up of latent infection. Knowing that $R$ at equilibrium is $R^* = R_0S^* = 1$, where $S^*$ is the equilibrium fraction of people susceptible to developing TB (3), and assuming that latency protects two thirds of those infected ($x = 0.33$) (4) gives, with $R_0 \approx 1/(S^* + x(1-S^*))$, an estimate of $R_0 \approx 1/(0.5 + 0.5/3) = 1.5$.

Such quantitative arguments surrounding the standard model have heuristic value, but are no more than a point of departure for understanding TB epidemiology around the world today. The evidence in the main text suggests that both the structure of the standard model, and the quantitative values of parameters, are likely to change from place to place and from time to time. As just two examples, (1) the 5% lifetime breakdown from latent infection is not a constant, but depends on the intensity of reinfection; (2) the effective contact rate is expected to change through time, and such changes have been measured in at least one population (see section 2).

2. Logic of drug treatment for active TB

Although the formula for $R_0$ gives equal weight to the infectious period, the contact rate and susceptibility (they are multiplied), there are two reasons why control focuses on the drug treatment of active TB cases. First, drugs curtail illness and prevent death as well as shortening the infectious period. The case fatality is reduced immediately, and incidence after a delay governed by the latent period. By contrast, stopping the progression from infection to
disease, by vaccination or preventive therapy, reduces the number of cases and hence transmission, but has no effect on the duration of illness or case fatality.

Second, the options for reducing the contact rate and susceptibility are still limited. Infectious contacts can be reduced by isolating patients, historically in sanatoria. The contact rate declined slowly in England & Wales since (at least) 1900 (5), presumably for a mix of reasons including sanatoria, hygienic behaviours, and improved nutritional and housing conditions. Contemporary estimates of the number of contacts that lead to established infections (positive tuberculin tests) are typically well below the 10 proposed by Styblo (2, 6-7).

Susceptibility to TB, before or after exposure to infection, could also be reduced by immunization, but the current vaccine, BCG, is reliably protective only against non-infectious meningitis and miliary TB in young children (6, 8). Isoniazid preventive therapy (IPT) for latently infected individuals is highly efficacious (up to 90%) for those who can stay the course. IPT has not been effective at population level because the small chance of progressing to active TB is not perceived to be worth the cost and effort of at least 6 months of daily therapy, plus the risk of hepatitis as a side effect. Furthermore, the impact would be small in an area of high transmission where a minority of cases comes from reactivation and the majority from recent infection.

In sum, the principles formulated in the standard model, confronted by the current practicalities of diagnosis, drug treatment and vaccination, explain why drug therapy for active TB is still considered to be the most effective and cost-effective option for reducing disease burden.

3. Epidemiological impact of population ageing

During demographic transition, the average age of a population increases as people live longer and fertility falls. The scheme in Fig. S1 is a simple way to explore the possible consequences for TB epidemiology. Here birth and deaths rates are equal, so the population is of constant size, and the demographic transition can be represented as a fall in the value of μ.
Figure S1. Schematic diagram of TB model. The proportion of people that are uninfected is $S$, that have a latent infection is $L$, and that have active TB is $D$. The contact rate is $\beta$, the proportion of infected cases that progress rapidly (instantly) to disease is $f$, the rate at which latent cases progress to active TB is $\nu$, the fraction of latently infected individuals who are susceptible to reinfection is $x$, the background mortality rate is $\mu$ and the (combined) rate of recovery, treatment or death is $\mu_D$.

Recalling that $R_0 \approx 1/(S^* + x(1 - S^*))$ (section 1), the steady state prevalence of TB is approximately

$$D^* \approx \frac{(R_0 - 1)(\nu + \mu)}{\beta(1 - f)(1 - x)}$$

In this simple model, $D^*$ and $\mu$ decrease together in an aging population. However, the decline would be offset if the values of $f$, $\nu$ or $x$ increase in an aging population, as they might if older people tend to be more susceptible to developing TB after exposure to infection. And even if $D^*$ is falling, the total number of cases will fall more slowly or increase as populations continue to grow. The balance between the demographic and epidemiological forces that push $D^*$ up and down need to be investigated for specific populations, and with a more realistic (age-structured) model than that in Fig. S1.

**Supplementary References**