The rise and fall and rise of tuberculosis

A mathematical approach to the transmission dynamics of tuberculosis offers a new understanding of past epidemics and suggests future interventions (pages 815–821).

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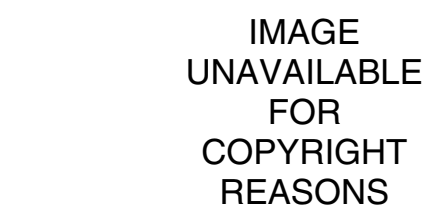
In Victorian times, death from infectious diseases was much more common in developed countries than it is today. Tuberculosis was a major killer, whose aetiology gave rise to a curious literature of romantic melancholy (for example, *The Magic Mountain*, *Death in Venice* and *Lady of the Camellias*). In the developed world, however, the lethal incidence of tuberculosis declined throughout the nineteenth century, long before antibiotic cures became available in the 1940s.

Why this decline? Various explanations have been offered. Perhaps there has been selection for strains of *Mycobacterium tuberculosis* of lower virulence (an argument sometimes buttressed with shallow notions about "successful parasites becoming harmless"), or perhaps natural selection has increased host resistance. Perhaps better health measures have helped, such as segregating infectious people in sanatoria and forbidding the once-common practice of spitting in public. Or perhaps transmission has been reduced simply by higher standards of hygiene, both public (cleaner cities) and private (more use of soap). Others have argued that "washing hands is no more effective than wringing them" and have attributed the decline of tuberculosis and other infectious diseases in developed countries to better nutrition and higher living standards[1].

On page 815 of this issue of *Nature Medicine*, Sally Blower and her colleagues[2] argue for a new and different explanation. Extending a basic mathematical framework that has been successfully applied to other infectious diseases of humans[3], they ask what kind of time course would we expect for a tuberculosis epidemic, given the transmission dynamics of the bacterium. Specifically, they construct mathematical models that reflect the observed facts that infectious individuals can develop tuberculosis either by direct progression, with disease developing soon after infection, or by 'endogenous reactivation', with disease developing many years after infection. There are correspondingly two kinds of tuberculosis; 'fast' or primary progressive tuberculosis, and 'slow' or reactivation tuberculosis (as in *Lady of the Camellias*). The majority of infected individuals, however, never develop tuberculosis.

Blower and her collaborators elucidate the nonlinear dynamics of their models, using extensive simulations combined with analytic insights. They find that the typical tuberculosis epidemic operates on a very long time scale, 100 years or more. These very slow dynamics are associated with the large pool of latently infected individuals who do not become infectious until later in life ('slow' tuberculosis), thus setting a basic time unit of many decades. In more detail, the early stages of such an epidemic are characterized by 'fast' cases. As the epidemic develops, this early phase gives way to a much slower phase, with the age distribution of cases shifting to older people (cases are predominantly due to endogenous reactivation rather than direct progression). Various realistic refinements to the model leave the essential conclusions intact.



Estimated cumulative worldwide tuberculosis cases from 1990–1999 (total cases = 88 million). (Reproduced from the World Health Organization bulletin, Global Tuberculosis Incidence and Mortality, 1990–2000 (1994)).

On this basis, Blower *et al.* suggest that the major epidemics of tuberculosis in Europe, beginning around the year 1600 and peaking towards the end of the 18th century, and in North America somewhat later, were caused by population densities exceeding transmission threshold levels. Before this, tuberculosis could not maintain itself in human populations, even though it could continually appear by cross-infection from other species. These European and North American epidemics built, and then slowly relaxed toward endemic equilibrium levels throughout the nineteenth century, on the century-long time scales suggested by Blower *et al.*

The researchers acknowledge that other factors — hygiene, nutrition and the rest — must also have played a part in the pre-1940s decline of tuberculosis. But they emphasize that these other factors were — and are — "constrained to operate within the slow response time dictated by the intrinsic dynamics".

All this affords a new perspective on historic events. It would, however, be a big mistake to think of tuberculosis as an affliction of the past. On the contrary, tuberculosis remains the world's leading killer among infectious diseases. An estimated 8 million new cases and 2.9 million deaths occur each year. In the developing world, tuberculosis is responsible for roughly 7 per cent of all deaths, and 19 per cent of deaths among adults between 19 and 59 years of age[4]. And, partly as an epiphenomenon of the AIDS pandemic, this horseman is again abroad in the developed world. Blower and colleagues' analysis of the dynamics of tuberculosis epidemics, and especially the results on their multiphase nature, suggest that optimal control strategies are likely to change as an epidemic develops. In offering a new view of the past, their paper may shed light on the best action for the future.

1. McKeown, T. *The Role of Modern Medicine: Dream, Mirage, or Nemesis?* (Princeton Univ. Press, Princeton, 1979).
2. Blower, S. *et al.* The intrinsic transmission dynamics of tuberculosis epidemics. *Nature Med.* 1, 815–821 (1995).
3. Anderson, R. M. & May, R. M. *Infectious Diseases of Human: Dynamics and Control* (Oxford Univ. Press, Oxford, 1991).
4. May, R.M. in *Health and the Environment* (ed. Cartledge, B.) 150–171 (Oxford Univ. Press, Oxford, 1994).

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