On the Risk of Being and Becoming Infected with *Mycobacterium tuberculosis*

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(See the article by Middelkoop et al. on pages 349–55)

In the late 1980s, the World Health Organization asked the US Centers for Disease Control’s top tuberculosis epidemiologist to review the accumulated reports regarding tuberculin skin test prevalence surveys and to analyze those that were judged to have high scientific merit. The result was an epidemiologic masterpiece that compared the trends in the annual risk of infection in a multitude of countries in the world (excluding industrialized countries) [1, 2]. It demonstrated that the risk for a child to become infected or reinfected with *Mycobacterium tuberculosis* had decreased virtually everywhere, albeit to a varying degree, over the preceding decades. For the 8 countries in the World Health Organization African region available for analysis (Botswana, Burundi, Cameroon, Ethiopia, Gambia, Lesotho, Nigeria, and Tanzania), the risk appeared to have decreased by 1%–5% annually to ≅2% annually by 1980. No data were available for South Africa at that time. Of the countries considered, at that time, only Tanzania had a national, functional, and comprehensive tuberculosis case surveillance system in place, and it was capable of providing just an inkling of the impact that the growing epidemic of HIV infection would have on the tuberculosis epidemic [3].

In this issue of *Clinical Infectious Diseases*, Middelkoop et al. [4] present the staggering magnitude of transmission of *M. tuberculosis* to children in Cape Town, South Africa. The annual risk of infection was ≈4%. The authors noted that the annual risk of infection was constant across the age groups of the 5–17-year-old participants who were enrolled in the survey.

Ideally, one would like to know the incidence of infection, but technical reasons (e.g., the boosting effect in tuberculin skin testing, test operation characteristics, and cost) prevent its measurement. As an alternative, the mean annual risk that is required to arrive at an observed prevalence at a given age is algebraically derived from the observed prevalence [5]. This indicator is useful, although it is important to recognize that it ignores the effects of cohort and age. If the sources of infection in the community increased annually by >15% over a decade, as the authors report for Cape Town, then one would expect that the resulting increase in transmission would also be reflected in the children’s risk of becoming infected, unless they were totally separated from any contact with the community.

**Figure 1.** Expected prevalence of infection due to *Mycobacterium tuberculosis* among children in Cape Town, assuming a constantly increasing infection risk, compared with the observed prevalence in the study by Middelkoop et al. [4].
This may not be the case in Cape Town, as shown in figure 1. In this simplified model, it is assumed that the risk of becoming infected with *M. tuberculosis* was 1.5% in 1995 and that the risk increased by 10% annually. The oldest children in the survey were born when the risk was still relatively low (in this example, the risk was 1% in 1991) and aged while an increasing risk peaked during the most-recent period of their lives. In contrast, the youngest children were born at a time when the risk of becoming infected had already doubled (the risk was 1.9% in 1998). This oversimplified model (neglecting any effect of age) fits the prevalence of infection observed by Middelkoop et al. [4] remarkably well. It suggests, alternatively, that the epidemic increase in sources of tuberculosis infection in the community did not, in fact, spare the children.

The annual risk of infection is useful if one keeps in mind that it is an approximation of the incidence of infection that existed at some time between the date of birth for the observed cohort and the date that the tuberculin skin test prevalence survey was performed. The precise point at which the calculated risk was identical to the incidence can only be approximated from a single survey, but undoubtedly, it lies further in the past for the older children than for the younger children.

It may well be the case that the sheer magnitude of the epidemic in Cape Town dwarfs any age-specific difference in infection at any given time. However, as children grow up, they come into contact with different population segments that all have a differing incidence of sources of infection.

The resurgence of tuberculosis in the United States in the period 1985–1992 was predominantly urban and disproportionately affected the black community [6]. Nevertheless, during this period, the proportional increase of tuberculosis was larger among white children aged <5 years than among black children aged <5 years [7]. This suggests that the nonlinear relationship between sources of infection among adults and the risk of infection among children postulated by Middelkoop et al. [4] is of great importance when interpreting tuberculin skin test surveys. Nevertheless, in Cape Town, the impact of HIV infection–associated tuberculosis may indeed have reached all strata of society.

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**References**