Breaking a law: tuberculosis disobeys Styblo's rule

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In 1985, Karel Styblo derived one of the guiding rules of tuberculosis (TB) epidemiology. Bringing together data from 16 countries, he proposed that an annual incidence of 50 sputum-smear-positive TB cases in a population of 100 000 generates an annual risk of infection of 1%.[1] This rule of thumb quickly became an established and cherished part of the epidemiological canon because it provided a way to estimate, albeit indirectly, an important but elusive quantity (disease incidence) from a comparatively simple measurement procedure (risk of infection via tuberculin surveys). Though the rule has never formally been viewed as anything better than approximate, its theoretical and practical underpinnings have been steadily eroded by the last two decades of epidemiological change. In this issue of the *Bulletin*, van Leth et al. present yet another analysis suggesting that TB disobeys Styblo's rule.[2] The rule can no longer be trusted as a method for estimating TB incidence.

To understand why the rule has become inapplicable, we need to go back to first principles. Working with the limited data available at the time, Styblo deduced that deaths per year, incidence per year and prevalence of smear-positive TB were held in the ratio 1:2:4. That is, in the pre-drug era, a smear-positive TB case remained infectious for an average of 2 years and the case fatality rate was 50%. These observations allowed him to estimate smear-positive incidence from prevalence and mortality data, and compare these incidence estimates with the measured risk of infection. The canonical ratio of smear-positive incidence per 100 000 (I) to per cent risk of infection per year (λ) then comes from $I/\lambda = (I \times 10^5)/(2 \times 10 \times I \times 10^2) = 50$, assuming that each smear-positive case generates an average of 10 new tuberculin-detectable infections each year.

Conventional wisdom also holds that the lifetime risk of progressing from infection to active TB is about 10% on average (5% within 5 years, 5% thereafter). In fact, the chance of progressing to disease depends on various personal characteristics, such as age, sex, genes, physiology, behaviour, and whether or not the exposure is a new infection or reinfection.[3] But if this risk of 10% is roughly correct and noting, with the postulates above, that around half of all new cases will be smear-positive, then each new smear-positive case will generate $10 \times 2 \times 0.1 \times 0.5 = 1$ new smear-positive case over one transmission cycle. Under these conditions, TB is stably endemic in its host population. Styblo's rule is therefore not simply a method for estimating incidence; it is part of the foundations of TB epidemiology.

The rule is vulnerable on its key premises: the two-year duration of infectiousness and the transmission of 10 infections each year. First, drugs are now widely available and are expected to shorten the duration of infectivity, though poor treatment practices can generate chronic illness. Second, improved living conditions with better aeration and a lower density of inhabitants are expected to reduce the number of infective contacts per unit time. Third, when TB is not in a steady-state, incidence will change more slowly than the risk of infection. So as incidence begins to fall, there will appear to be, at any point in time, more cases per infective contact. All three processes would generate ratios of incidence to risk of infection that are greater than 50:1.

In their paper, van Leth et al. have tested just one of the two premises – that each smear-positive TB case transmits about 10 infections per year. Using the ratio of smear-positive prevalence to risk of infection measured in China, the Republic of Korea and the Philippines, they found that the actual number of infections per year lay between 2 and 6. Formally, this result does not disprove Styblo's rule because it examines the relation between risk of infection and prevalence, not incidence. The 50:1 ratio could be preserved if, for example, the duration of illness has increased to offset the reduction in transmission rate. This seems unlikely, however, because drug treatment is expected to reduce the average duration of infectivity, not to increase it.

Adding this new evidence to the similar results of an earlier study,[4] we clearly cannot assume that Styblo's rule still holds. How then should we evaluate TB burden and trends? If measures of the risk of infection cannot reliably estimate incidence, they can at least measure geographical variation and trends in transmission. Disease prevalence surveys will also make an important contribution;[2] despite being costly and logistically demanding, surveys will be carried out in several high-burden countries over the next 5 years. But the ultimate method of assessment is routine surveillance: comprehensively counting cases and deaths in all countries.[5]

The legacy of Karel Styblo is immense and undiminished by these new findings. His bold attempt to distil simplicity out of apparent complexity remains an object lesson. It is a matter of regret, therefore, that his name may appear less frequently in conversation, now that the eponymous rule is defunct. ■

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