

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. To complement the theme of this month's *Bulletin*, Martien W. Borgdorff reviews the 1988 document by George M. Cauthen, Antonio Pio & H. Gerard ten Dam on the annual risk of tuberculous infection that constituted the basis for many statistics on tuberculosis. The original, unpublished except as a WHO document, is reproduced below.

Annual risk of tuberculous infection — time for an update?

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The document by Cauthen et al. (1) is an unusual public health classic because it has never been formally published. However, it has been quoted widely, despite its limited distribution, in particular for making estimates of the global tuberculosis (TB) burden.

In 1977, before Cauthen et al.'s document, WHO identified high-burden areas for TB, separately for prevalence of infection, notification rates, and mortality (2). Since tuberculin surveys had been conducted in different age groups, a direct comparison of infection prevalences between areas was not possible. TB incidence and mortality were estimated from notification rates of countries reporting these and were extrapolated to other countries. The global numbers of new TB cases and deaths were estimated at 4 million (111/100 000) and 0.4 million (12/100 000) respectively.

The document of Cauthen et al. made two important contributions. It applied the concept of the annual risk of infection to data from a broad range of countries and it included an assessment of trend, rather than of current status only. The concept of annual risk of infection had been developed and applied to Dutch data by Styblo et al. (3). The attraction of this measure is that, contrary to notification data, it is independent of the quality and comprehensiveness of the notification system.

Estimates of TB incidence in developing countries by Murray et al. (4) used the prevalence of infection data summarized by Cauthen et al. (1). However, results were extrapolated from countries covered by tuberculin surveys to countries not covered, and TB incidence was estimated using Styblo's rule (5). Styblo had found that in the absence of control, an annual risk of infection of 1% corresponded to an incidence of new, smear-positive TB of approximately 50/100 000. In other words, the ratio of the annual risk of infection to the incidence of new, smear-positive TB was approximately 20:1, suggesting that each case infected on average 20 people. Based on this correlation, the incidence of new, smear-positive TB in developing countries in 1990 was estimated at 3.2 million cases (77/100 000) and the incidence of all TB at 7.3 million (175/100 000).

The next global estimates produced by WHO adopted the same approach. They also made adjustments to account for

the effect of the human immunodeficiency virus (HIV), resulting in a global TB incidence estimate in 1990 of 8 million cases (152/100 000), 300 000 of whom were attributed to HIV infection (6). TB mortality was estimated at 2.6–2.9 million deaths, assuming a 50% case-fatality rate among undetected cases. Later estimates reverted to using notification rates where these were available, resulting in a somewhat lower global estimate of the incidence of all TB (7.5 million cases) and TB-related mortality (2.5 million cases) in 1990 (7, 8). The mortality estimate was lowered further by Murray & Lopez, who required internal consistency, i.e. the sum of all cause-specific deaths was required to equal the total number of deaths (9). They estimated 2 million deaths due to TB for 1990, excluding deaths attributable to HIV.

Finally, Dye et al. (10) integrated different information sources. Relationships were postulated between various parameters such as annual risk of infection, incidence rate, proportion of cases detected, notification rate, disease duration, prevalence, and case-fatality rates depending on treatment received. Based on available information (including the tuberculin survey results summarized by Cauthen et al. (1)), estimates of disease incidence and mortality were produced and discussed in expert panels. Total TB incidence in 1997 was estimated at 8 million cases per year, and total TB-related mortality at 1.9 million. An important outcome of that exercise has been the identification of 22 high-burden countries in which 80% of all cases occur. These estimates are updated annually.

Although the results of Cauthen et al. on infection prevalence (1) have been helpful to estimate global TB incidence, this application is controversial. First, Cauthen et al. themselves warned against the extrapolation of their results to countries which were not surveyed. Second, estimating disease incidence from the annual risk of infection using Styblo's rule has been criticized (11). This criticism concerns in part the relatively small database on which the relationship was established, but also fundamentally questions the relationship itself because the condition of absence of control is no longer met. If TB programmes identify many cases at an early stage of their disease and cure them, the average number of infections per case may be expected to go down (and a 1% annual risk of infection is expected to correspond to a higher incidence rate).

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Moreover, the number of infections probably depends on socioeconomic development through changes of housing conditions, crowding, and social mixing patterns.

Third, in countries with a high prevalence of HIV infection, the relationship between risk of TB infection and the incidence of TB may be altered, depending on the infectiousness of HIV-infected TB cases. Although the number of infections generated before diagnosis of new, smear-positive cases does not depend strongly on HIV infection (12), mortality is much higher in HIV-infected patients, probably leading to fewer infections per case, in particular in countries with a low TB case detection rate. It is important to note here that the ratio of the risk of infection and disease incidence depends on the number of infections generated per case and not on the probability of disease after infection.

If variation of the ratio of TB infection and disease were random, country-to-country variation might be partly cancelled out in global estimates. However, some causes of variation, such as epidemiological changes due to TB control or HIV infection, are systematic and may be a source of bias of global estimates. For individual countries, TB incidence estimates based on Styblo's rule are extremely uncertain.

Finally, the methodology of estimating infection prevalence and the annual risk of infection itself is controversial (11) and problematic (11, 13). To reduce such problems, the training and supervision of survey teams is vital. In addition, better tests for the diagnosis of TB infection would be extremely helpful and these are indeed being developed (14).

However, even with the currently available tuberculin, tuberculin surveys provide important information, in particular on the trend of the TB problem. Trend estimates based on tuberculin surveys are fairly robust, and do not depend strongly on the proportion of children with BCG scars, or on the cut-off point used for defining a "positive" skin test (15, 16). Because of measurement imprecision, changes of infection prevalence should be interpreted as correlates rather than exact measures of actual changes of infection risk (13). Moreover, rather large differences are needed to demonstrate clearly a decline or increase of the annual risk of infection, suggesting that tuberculin surveys should take place only once every 5–10 years. The tool is thus not useful for monitoring short-term trends, but very important for the assessment of long-term trends in high-burden countries. In recent years, for instance, tuberculin surveys have been very helpful to estimate the impact of the HIV epidemic on TB transmission in Africa (15, 16).

In conclusion, the classic document of Cauthen et al. has been an important contribution to knowledge on the size and trend of the TB problem. The time has come to produce an update of this public health classic to include results from tuberculin surveys since 1985. In view of the limitations of notification data, in particular for the assessment of long-term trends, and in view of the relatively high cost of TB disease prevalence surveys (in the order of 10 times that of tuberculin surveys), the tuberculin survey remains an important epidemiological tool to assess TB trends. ■

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