

# Measuring tuberculosis burden, trends and the impact of control programmes

## Supporting online material

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### 1. Extended summary

The targets for TB control, framed with reference to the Millennium Development Goals (MDGs), are to ensure that the incidence rate is falling, and that the 1990 prevalence and mortality rates are halved, all by 2015. The targets apply globally but they present a major challenge to individual countries, not just to achieve the targets but to demonstrate that they have been achieved. In monitoring progress in TB control, the ultimate aim for all countries is to count, accurately and comprehensively, TB cases (incidence) and deaths (mortality) through routine surveillance and vital registration. To satisfy that aim, national TB control programmes (NTPs) should carry out systematic assessments of surveillance systems and data to determine how accurately case and death reports measure TB burden, nationally and sub-nationally (districts, provinces etc). These evaluations should give a direct measure of the "case detection rate", which is more accurate than the present, indirectly-derived approximations. Disease prevalence surveys, carried out at intervals of 5 or more years, give additional, direct measures of TB burden and trend. Prevalence surveys are relatively costly and laborious, but justified in high-burden countries where many cases and deaths are missed by routine reporting. All countries should develop reliable death registration systems; where they are not available, verbal autopsy provides an alternative method of assessing TB deaths, but has not yet been fully validated. The tuberculin skin-test (TST) for measuring *Mycobacterium tuberculosis* infection is comparatively cheap but has low specificity in many settings, and cannot reliably predict TB incidence, prevalence or mortality. For epidemiological monitoring, TST is therefore generally more useful as a comparative measure of infection risk, to assess time trend and geographical variation. The specificity of TST can be increased by various methods of calibration, including tuberculin tests on TB patients and with newly-developed, interferon- $\gamma$  release assays. By 2015, every country should be able to respond to MDG targets by evaluating the time trend in national incidence, and the magnitude of reductions in either TB prevalence or deaths.

### 2. Epidemiological background and targets for TB control

In 2005, WHO calculated that there were 8.8 million (95%CL 7.6–10.0) new cases of TB, of which 3.9 million (95%CL 3.4–4.4) were sputum smear-positive.<sup>1</sup> The national TB control programmes (NTPs) of 199 countries reported that 2.3 million new smear-positive cases were diagnosed under the WHO's DOTS strategy, giving a global smear-positive case detection rate of 60% (95%CL 52–69%), as compared with the 70% target

for 2005.<sup>2</sup> The average number of people with active TB (point prevalence) during 2005 was calculated to be 14.1 million, and an estimated 1.6 million TB patients died during that year.

The implementation targets of 70% case detection and 85% cure, set in 1991,<sup>3</sup> were based partly on the logic of expected impact,<sup>4-7</sup> and they have been a powerful stimulus to NTPs. The MDG framework has taken the next logical step, going beyond impact in theory to its measurement in practice. The agreed impact targets for TB are to ensure that the incidence rate is falling by 2015, and to halve prevalence and death rates by 2015 (as compared with levels estimated for 1990).<sup>8</sup> Prompt diagnosis and effective chemotherapy remain the principal mechanisms for achieving these gains, administered via DOTS and the Stop TB Strategy.<sup>9</sup>

Against this background, the hierarchy of problems to be addressed in the main text is: what is the burden of TB now, what are the time trends, and to what extent can these trends be attributed to TB control? Our methodological review leads to a set of recommendations about measurement that are directed at NTPs, and their technical advisers and financial donors. It should be clear at the outset that nothing can be measured with perfect precision, and that every statistic is an "estimate". The overriding question is whether the estimates, and the conclusions drawn from them, are accurate enough to make key decisions about TB control.

### **3. Direct measurement of incidence in prospective cohort studies**

Longitudinal cohort studies are rarely undertaken because incidence rates are low (usually much less than 1%/year), even in areas where TB is considered to be highly-endemic, and it is hard to rule out active TB with available clinical and diagnostic methods. The interval to follow-up must be neither too short (costly, logistically demanding) nor too long (cases may be missed), and the study population must be sufficiently large to guarantee precision. To estimate incidence to a precision (95% confidence interval) of  $a = 0.1$  (10%) requires approximately  $\left(\frac{a}{2}\right)^{-2} = 400$  cases. If the incidence rate is thought to be 100 per 100 000 population (i.e. near the global average), 400 000 people without TB must be enrolled and followed for one year. Enrolment procedures must allow for the fact that some people will refuse to participate (noting both the number and their characteristics), and for losses to follow-up, including those due to death and default. The direct measurement of incidence is more feasible in cohorts of individuals at high risk of developing active TB, such as those infected with HIV.

Incidence has been measured prospectively in the Republic of Korea<sup>10</sup> and in an area of south India.<sup>11</sup> However, the costs of high-precision, longitudinal studies will be prohibitive in most countries. Even where incidence is relatively high, for example as a result of HIV infection, a primary survey plus one follow-up survey is likely to cost in excess of US\$1 million. Added to this is the difficulty of follow-up, especially where patients seek treatment in the unmonitored private sector. Prospective cohort studies have

been<sup>12-15</sup> and will be important in vaccine and other clinical trials, but they are not a viable method for the long-term assessment of incidence in many countries.

#### **4. Four steps to evaluate the accuracy and completeness of surveillance data**

Step (1) is to make an inventory of, and cross-check, data from all possible sources, removing duplications.<sup>16-25</sup> This is conceptually straightforward, but requires exhaustive research into records held in different places – health facilities, laboratories, insurance companies, pharmacies, the national TB control programme, and so on. Cases and deaths will be missing from databases, even where reporting is mandatory, not only for physicians but also for laboratories.<sup>26, 27</sup> Reporting is likely to be deficient in countries where people do not have access to public health services and where the private sector is unregulated.

To complement and extend step (1), capture-recapture techniques (step 2) can be used to estimate case detection from lists of patients that have been "captured" in different ways.<sup>21, 23, 28, 29</sup> In the simplest example with two lists, if  $N_1$  patients appear in list A,  $N_2$  in list B and  $N_{12}$  in both lists, then the number of missing cases is estimated from  $N_1N_2/N_{12}$ .<sup>30</sup> An advantage of capture-recapture over inventory-making or simple list-merging is that it provides an estimate of true incidence without assuming that all patients will appear in at least one list. However, the claim that it is possible to enumerate patients that are never actually seen depends on assumptions that may not be satisfied, and which are not always testable.<sup>30-33</sup> With reference to the above example, three key assumptions are that sources A and B are independent (i.e. the chance that an individual is in list A is identical for those who are and are not in list B), that all individuals have the same chance of being captured by each source, and that the population is closed (e.g. no deaths or migrants).<sup>30</sup> These assumptions need to be examined carefully before concluding that the results of capture-recapture analysis are unbiased.

Step (3) is to explore the spatial and temporal variation of case reports, to check for inconsistencies. Because TB cases arise from a large and widely-distributed reservoir of latent or recent infection, the true incidence does not usually vary greatly over small spaces or short time periods (<5 years). Therefore large variation among case reports, spatially (Figure 1A) or temporally (Figure 1B), may reflect a failure of surveillance. Further investigation is usually needed to find out why the variation exists, making use of additional indicators which quantify, for example, the distribution and use of TB drugs.<sup>34</sup>

Step (4) is to check the consistency of case reports against the norms of TB epidemiology and natural history. For example, there are usually more cases among men than women (Figure 1C) and, notwithstanding variable proportions of extrapulmonary cases, sputum smear-positive cases usually make up at least 65% of all new pulmonary cases in populations with negligible HIV infection, and usually less than half of all new cases (Figure 1D).<sup>1, 35</sup>

Steps (3) and (4) require national surveillance data to be disaggregated by clinic, district, province, case type, age, sex, and so on, and their analysis will be aided by the

development of computer software for managing data on patients individually and in aggregated form.<sup>36</sup> Ideally, all four steps will be carried out together so as to produce an overall estimate of the proportion of cases detected. If that proportion is estimated to be close to 1, then reported cases can be taken to equal incidence. Otherwise, incidence is estimated from equation 1 (Box 1).

## **5. Measures of tuberculosis case detection**

To estimate TB incidence, equation 1 requires a direct measure of the proportion of cases arising in any one year that is detected (denominator). This is not exactly the same as the WHO "case detection rate" (CDR), which is defined as the number of new cases *reported* in any one year (some of which could have arisen in previous years) divided by the estimated incidence of new cases in that year (and refers principally to new sputum smear-positive cases).<sup>1</sup> Although the WHO index is called a rate and expressed as a percentage (implying that it is a proportion), it is actually a dimensionless ratio (no time units). The number of cases reported in any one year can be greater than annual incidence if, for example, case-finding is intense in an area with a backlog of (prevalent) cases that arose in previous years. The case detection rate might also exceed 100% if there has been over-reporting (e.g. double-counting) or over-diagnosis, or if estimates of incidence are too low. Even if the estimate of the average incidence rate over several years is correct, countries that have small numbers of cases might exceed that average in any one year. In reality, the number of cases notified is usually smaller than the estimated incidence because of incomplete coverage by health services, under-diagnosis, or deficient recording and reporting. A review of progress in case detection placed CDR in the range 52–69% globally in 2005, which may underestimate uncertainty around the point estimate of 60%.<sup>2</sup>

In view of the difficulties in estimating incidence, and in using incidence as the denominator of the WHO case detection rate (CDR), the "patient detection rate" (PDR, cases reported in one year divided by point prevalence) has been proposed as an alternative measure of detection.<sup>37</sup> PDR has the virtue that both numerator and denominator can be measured directly. However, use of the PDR requires further guidance on interpretation (e.g. international targets, and the expected impact of meeting them, are expressed in terms of CDR), and the data in Table 2 show that this index cannot easily be measured with a precision greater than  $\pm 25\%$ . The four-step approach to evaluating the completeness of surveillance (main text) must aim to do better than both CDR and PDR.

## **6. Further aspects of the design and conduct of prevalence surveys**

There are various ways to improve the efficiency and lower the cost of surveys (though not necessarily to improve accuracy). An estimate of TB prevalence in India was obtained by calibrating the relation between ARI and prevalence where both have been measured at one site in south India. Four regional estimates of ARI were used to estimate TB prevalence for each region, and then nationally as the sum of the four parts.<sup>38</sup> The 2004 Indonesian TB prevalence survey took advantage of a sampling frame that had been

established for the National Household Health Survey.<sup>39</sup> Other existing, population-based health survey platforms (e.g. Demographic and Health Surveys, DHS) have not been used to measure prevalence because the definitive diagnosis of TB requires bacteriology (sputum smear microscopy and culture). Survey platforms such as DHS typically monitor small populations. Among eight surveys under way in 2007 the median sample size was 16,000 (IQR 9,000–22,000) and all were restricted to individuals aged 10–54 years.<sup>40</sup> Surveys on this scale are useful for monitoring TB suspects and their interactions with health services. With greater sample sizes and wider population coverage, general survey platforms like DHS could also be used to monitor TB, especially if there were a sensitive and specific diagnostic test for active disease based on biomarkers in saliva, urine or blood. Despite the possibilities for antigen and antibody testing, such diagnostic tools do not yet exist.<sup>41-43</sup>

Prevalence surveys can also be used to evaluate the quality of routine surveillance by assessing which patients with active disease, identified in the survey, have already made contact with the routine reporting system. Questionnaires can also be used to explore the importance of various risk factors associated with TB (nutritional status, tobacco, diabetes, and others), with the analysis carried out, for example, as a case-control study.<sup>44</sup>

## 7. References

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