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

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The targets for tuberculosis control, framed within the United Nations' Millennium Development Goals, are to ensure that the incidence per head of tuberculosis is falling by 2015, and that the 1990 prevalence and mortality per head are halved by 2015. In monitoring progress in tuberculosis control, the ultimate aim for all countries is to count tuberculosis cases (incidence) accurately through routine surveillance. Disease prevalence surveys are costly and laborious, but give unbiased measures of tuberculosis burden and trends, and are justified in high-burden countries where many cases and deaths are missed by surveillance systems. Most countries in which tuberculosis is highly endemic do not yet have reliable death registration systems. Verbal autopsy, used in cause-of-death surveys, is an alternative, interim method of assessing tuberculosis mortality, but needs further validation. Although several new assays for *Mycobacterium tuberculosis* infection have recently been devised, the tuberculin skin test remains the only practical method of measuring infection in populations. However, this test typically has low specificity and is therefore best used comparatively to assess geographical and temporal variation in risk of infection. By 2015, every country should be able to assess progress in tuberculosis control by estimating the time trend in incidence, and the magnitude of reductions in either prevalence or deaths.

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See Online for webappendix

Introduction

Each year, WHO publishes estimates of tuberculosis incidence, prevalence, and deaths, and their trends through time for every country in the world (see webappendix).[1] On the basis of these statistics, tuberculosis is among the top ten causes of death worldwide.[2] These data are used to assess progress towards targets for tuberculosis control (available from the United Nations' Statistics Division website http://mdgs.un.org/unsd/mdg/), which are to be achieved mainly through the diagnosis and treatment of tuberculosis cases.[3] Targets for implementation are to detect 70% of sputum smear-positive cases and to cure 85% of those detected;[4] targets for impact, set with reference to the United Nations' Millennium Development Goals (MDGs), are to ensure that incidence falls by 2015, and to halve prevalence and mortality per head by 2015 (compared with 1990).[5]

The sources of data and methods used to measure tuberculosis burden and trends have previously been summarised.[1,6,7] Commentaries have made reference to the poor quality of data and potential biases behind the estimates,[8–10] but there is no published, critical overview of methods. Now that tuberculosis control programmes are being urged to assess progress towards the MDGs,[1,11] our aim is to review the different approaches to measuring tuberculosis burden, trends, and the epidemiological impact of control, and to discuss their strengths and weaknesses. Whereas many indicators are used to monitor tuberculosis epidemics and to assess control efforts,[12] this Review is limited to those directly relevant to the MDGs: incidence (and by implication case detection), prevalence, and mortality.

Tuberculosis incidence and case detection

The number of new tuberculosis cases arising per head each year (incidence) is the central measure of progress towards elimination (<1 case per million population per year), and the principal, long-term goal of tuberculosis control.[5] Incidence is also the predominant MDG indicator (goal 6, target 8),[5] and incidence estimates (for sputum smear-positive cases) form the denominator of the WHO case detection rate with notified cases as the numerator.[1] The case detection rate, together with treatment success (percentage of patients known to be cured plus those who completed treatment), have been the main measures of progress in implementing the WHO DOTS Strategy (based on directly observed short-course chemotherapy) and the broader Stop TB Strategy.[3]

A comparative disadvantage of incidence as an epidemiological indicator is that it usually changes more slowly than prevalence or deaths in response to control efforts.[13] Chemotherapy programmes are expected to achieve a decline in the incidence per head of only 5–10% per year (in the absence of HIV co-infection),[14] so changes over a period of less than 5 years are difficult to detect statistically (table 1).

If systematic assessment shows that case reports are almost complete, then routine surveillance effectively counts incident cases. In situations in which this is not true, there are broadly two approaches to estimate tuberculosis incidence: (1) direct measurement through longitudinal cohort studies; and (2) indirect estimation from assessment of the completeness of case reports, from measures of the prevalence of infection or active disease, and from estimates or counts of tuberculosis deaths.

Direct measurement of incidence in prospective cohort studies

In principle, individuals without active tuberculosis can be followed to find out how many develop the disease in a given time period. In practice, such longitudinal studies

are rarely undertaken because incidence is low (usually much less than 1% per year), follow-up is demanding, and the study population must number several hundred thousand to obtain adequate precision. This approach to measuring tuberculosis incidence is more feasible in cohorts of individuals at high risk of developing active tuberculosis (eg, those infected with HIV; table 1, webappendix).

Indirect estimation of incidence

All countries have functioning tuberculosis surveillance systems, although the data are highly variable in quality.[1,8] Four steps can be taken to assess the accuracy and completeness of surveillance data, to estimate the proportion of cases detected (equation 1, panel), and to strengthen recording and reporting systems, with long-term benefits. In brief, these steps are as follows (for

	Advantage	Disadvantage
Disease incidence	Measure of denominator of WHO case detection rate; MDG indicator	Falls slowly after reductions in transmission
From prospective cohort studies	Direct measure of incidence; more feasible for cohorts of individuals at high risk of developing tuberculosis (eg, people infected with HIV)	Costly; logistically complex; requires two or more surveys with large cohort and carefully judged survey period and follow-up of individual patients
From case notifications	Absolute incidence can be obtained from routine case reports, most accurately if case detection is estimated to be complete; trends can be judged from series of routine case reports if measured consistently; every country has a surveillance system, reporting annually or sub-annually, which should become the standard method for assessing tuberculosis incidence and its trend	Case detection is low in many high-burden countries (underestimates incidence), and may vary through time (inaccurate trends) because of changes in case identification
Disease prevalence	Component due to duration changes relatively quickly in response to drug treatment; MDG indicator	Component due to incidence falls slowly after reductions in transmission
From population-based surveys	Unbiased measure of bacteriologically confirmed disease; should change quickly in response to drug treatment; surveys useful if routine surveillance data are poor; serve as a platform for related investigations (eg, risk factors for tuberculosis, and interactions between patients and health system)	Costly; large sample size needed; logistically complex (especially with radiography); cannot easily be measured annually or with a precision better than ±25%; surveys usually exclude children and extrapulmonary disease; without bacteriological confirmation, diagnosis is unreliable; does not lead to a precise estimate of tuberculosis incidence (denominator of WHO case detection rate) because duration cannot be measured accurately
Tuberculosis mortality	Direct measure of tuberculosis burden accounting for a high proportion of years of life lost; case fatality falls quickly in a new drug treatment programme; MDG indicator	Component due to incidence falls slowly after reductions in transmission; case fatality may already be low in low-incidence countries and not easily reduced further
From prospective cohort studies	Direct count of deaths in sample cohort	As for measuring incidence, but more costly; not generally feasible
From observations on patient cohorts	Direct count of number of patients dying; approaching total deaths if case notifications complete and all patients monitored throughout treatment	Deaths observed are those in cohort only, not in the population at large, and not beyond the period of cohort follow-up; deaths among defaulters and transfers usually unknown; tuberculosis not always the cause of death for patients on tuberculosis treatment
From product of incidence and case-fatality rate	Simple and widely applicable	Relies on accurate measures of incidence (above) and case-fatality rate; case fatality measurable in observed DOTS cohorts, but not among patients treated elsewhere or untreated
From routine death reports (vital registration)	Direct measure of tuberculosis deaths and trends; can be reported annually or sub-annually; the ultimate method for evaluating tuberculosis deaths nationally	Vital registration does not yet exist in most high-burden countries, notably in Africa and Asia; sensitivity and specificity mostly untested
From verbal autopsy in conjunction with sample vital registration	Review of registered deaths can improve accuracy of cause of death statistics	Sensitivity and specificity of verbal autopsy not fully evaluated; where no vital registration system exists, laborious to compile deaths from a rare disease, and requires large sample sizes
Infection prevalence	Risk of infection changes relatively quickly in response to treatment of active tuberculosis (but prevalence, from which risk is calculated, changes slowly)	Measures infection, not disease burden; not an MDG indicator
From population-based surveys	Tuberculin surveys relatively cheap and logistically straightforward; can be used to assess time trends and geographical variation in risk of infection; IGRAs have high specificity, and might be used to calibrate tuberculin	Recommended procedures must be followed rigorously to avoid pitfalls, including digit preference; low specificity means that results may be hard to interpret if infection rates are low and if BCG coverage or exposure to environmental mycobacteria are high; measures average risk of infection over past 5–10 years; IGRAs not yet fully evaluated, relatively costly and require blood by venepuncture; Styblo's[15] 1:50 rule for indirectly estimating disease incidence no longer generally applicable

IGRAs=interferon-γ release assays. MDG=Millennium Development Goal.

Table 1: **Strengths and weaknesses of various indicators and measures of tuberculosis burden and trends**

further details, see webappendix). First, make an inventory of, and cross-check, data from all possible sources, removing errors and duplications.[16–25] Second, use capture-recapture techniques to estimate case detection from lists of patients that have been captured in different ways.[21,23,26,27] Third, explore the spatial and temporal variation of case reports (figure 1); inconsistencies in the data require further investigations, which may reveal failures of case detection.[28] Fourth, check the consistency of case reports against the norms of tuberculosis epidemiology and natural history (figure 1); departures from these norms might also be explained by incomplete case detection.[28]

Absolute estimates of incidence are typically less accurate than (comparative) measures of the variation in incidence, temporally or geographically. Provided the efficiency of case finding does not vary through time (eg, no new diagnostic procedures, no initiatives to improve case detection), then the annual change in case notifications will be the same as the annual change in incidence. Figure 2 shows examples of trends in case notifications that are assumed to represent trends in incidence. Note that the MDG targets only require incidence to be falling, which, in terms of measurement, is not as demanding as reducing incidence to some absolute level.

Equations 2–4 (panel) show how incidence can also be derived from the prevalence of disease or annual risk of infection, and from counts or estimates of tuberculosis deaths. In fact, measures of prevalence and mortality are most useful as primary indicators of tuberculosis burden and trends, and not as an approach to estimating incidence, as explained below.

Prevalence of active tuberculosis

Like incidence, disease prevalence has the advantage of being a direct measure of illness caused by tuberculosis in a population (and is an MDG indicator; table 1). Unlike incidence, an unbiased measure of prevalence can be made in a single population-based survey. However, prevalence captures another facet of disease burden by accounting for illness duration. The prevalence of infectious cases also determines how much transmission takes place in any population, because the annual risk of infection (ARI or λ) equals the number of infectious contacts made by each case per person per year (β) multiplied by the prevalence of infectious cases (P): $\lambda=\beta P$. In its dependence on the duration of illness, prevalence responds more rapidly than incidence to improved case finding and drug treatment (which shorten the duration). This is part of the reason why repeated prevalence surveys in China, Indonesia, Philippines, South Korea, and parts of south India have been able to track the decline in tuberculosis over years or even decades.[29–33]

However, prevalence surveys have some important limitations. The sample sizes needed to make precise measurements are large (although not as large as required to measure incidence). Whereas there are usually more prevalent tuberculosis cases present at any one time than there are incident cases in any year, health facilities see many more incident cases (tens of thousands in high-burden countries) than are usually found in sample surveys (hundreds). Surveys do not generally look for extrapulmonary disease. Furthermore, children are usually excluded from surveys because tuberculosis is less common in 5–14-year olds than in other age-groups, and because of the difficulties of collecting sputa from children. If the prevalence of sputum smear-positive tuberculosis is 100 per 100 000 population, then a random sample of 100 000 people is expected to yield 100 cases. Allowing for incomplete data and the design effect of a cluster-randomised survey, a good approximation is to double the sample size.[34] If two surveys are done 5 years apart with the aim of detecting a 30% reduction in prevalence (to 70 per 100 000 population) with 90% power and 5% significance (excluding any design effect), approximately 200 000 people would need to be examined at each survey.[35] If the aim is to measure the absolute prevalence at each survey with precision of plus or minus 10% and with 95% confidence, the sample size would need to be about 400 000. Prevalence surveys have rarely been planned to achieve these levels of power and precision: the six national surveys done since 1995 have measured smear-positive prevalence with a precision that varies from 25% (China, Korea) to 60% (Eritrea) of estimated smear-positive prevalence (table 2). The cost of a prevalence survey is US$4–15 per person surveyed, and up to $25 per person with radiographic screening, if new equipment is needed (our data from surveys in Cambodia, Eritrea, India, and Philippines). A survey of 50 000 people, of limited precision, would typically cost $200 000–750 000. The practical implication is that prevalence surveys can only be used to distinguish large spatial and temporal differences.

Surveys to measure prevalence subnationally (eg, in states or provinces) have been done since 1995 using various methods in Bangladesh, Botswana, Ethiopia, India, Uganda, and Vietnam.[38–48] Subnational surveys have typically been underpowered, and thus give less precise estimates than do most national surveys.

***Panel:* Four equations to estimate tuberculosis incidence (in principle), from prevalence, mortality, and the risk of *Mycobacterium tuberculosis* infection**

$$(1)\ \text{Incidence} = \frac{\text{case notifications}}{\text{proportion of cases detected}}$$

$$(2)\ \text{Incidence} = \frac{\text{prevalence}}{\text{duration of condition}}$$

$$(3)\ \text{Incidence} = \frac{\text{deaths}}{\text{proportion of incident cases that die}}$$

(4) Incidence (smear positive)=annual risk of infection×coefficient

The merits of each approach are discussed in the text.

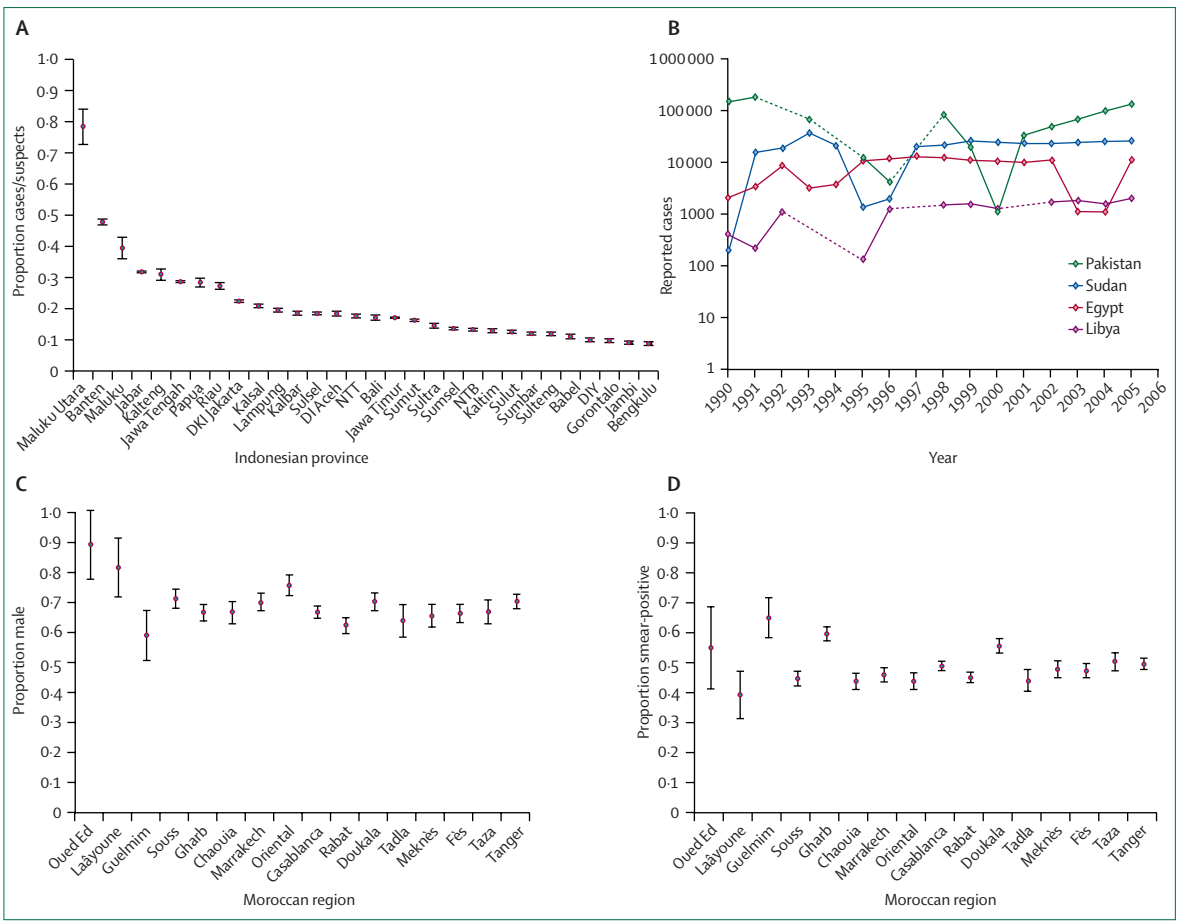

Figure 1: **Consistency and plausibility used to check the reliability of routine surveillance data**
(A) Variation in the proportion of tuberculosis cases among suspects is unexplained, but may reflect variation in case detection. (B) Large annual variations during the 1990s give way to more stable case reports after 2000, reflecting improvements in surveillance.[1] Dotted lines indicate missing annual data. (C) Consistent excess of male over female patients in regions of Morocco.[28] (D) Reported smear-positive cases are 40–50% of the total in most regions of Morocco.[28] (C, D) The patterns are as expected and give additional confidence in the data. Error bars indicate 95% CI.

There are other aspects to the inevitable trade-off between cost and precision. A key factor in the design of a survey is the procedure used to select people from whom sputum specimens (usually two, spot and early morning) are taken for microscopy and culture. Chest radiographs provide a sensitive but non-specific test for active tuberculosis, often with substantial intra-observer and inter-observer variation. Radiography therefore tends to produce false positives in surveys or when used as part of routine surveillance, but is nevertheless a useful screening method. Symptoms of chest illness (eg, cough for ≥2 weeks) are indicative of tuberculosis, but are neither sensitive nor specific. With this in mind, most prevalence surveys have used a combination of chest radiograph and symptoms to identify tuberculosis suspects, although with many procedural variations (table 2). Screening on the basis of symptoms only is less costly, but is almost certain to miss some mildly symptomatic and asymptomatic patients.[49] Another low-cost option, requiring minimum technology, is to abandon all screening methods, and try to obtain sputum from all eligible participants. However, this approach generates large numbers of negative samples, many containing no sputum, that must be accurately processed by microscopy and culture (ie, samples from suspects have low positive predictive value). One risk is that microscopists miss rare positive samples among the many negatives. Additionally, sputum smear microscopy, when used without culture, is an insensitive method of diagnosis, particularly for individuals infected with HIV.[50,51]

Some questionnaire surveys have attempted to assess the duration of an episode of active tuberculosis with a view to estimating incidence from prevalence (equation 2, panel).[36,52] However, the results are of doubtful accuracy because patients typically underestimate how long they have been ill. Prevalence surveys are therefore mainly for measuring prevalence, and not for estimating incidence.

In summary, the rationale for carrying out a prevalence survey is stronger for countries that have the following: (1) a large and uncertain burden of tuberculosis; (2) already carried out a prevalence survey, so that at least one more

survey will measure trend; (3) a weak or poorly informative system for surveillance of cases and deaths; (4) insufficient information about where patients are diagnosed and treated; (5) the staff and funding capacity to carry out a survey; (6) security for field staff and a survey is logistically feasible; and (7) a population that is willing to participate.

Given the cost in time, effort, and money, most countries are unlikely to be able to do two or more prevalence surveys to measure progress between 2007 and the MDG target year of 2015. Nevertheless, more surveys, particularly those that follow standard methods,[34,53] are needed in high-burden countries to show whether tuberculosis control programmes can reduce prevalence, by how much, and under what conditions.

Tuberculosis mortality

Tuberculosis holds a prominent place in public-health statistics, in part because it is listed among the top ten causes of death worldwide.[2] Most of the burden of tuberculosis, as measured in disability-adjusted life-years (the common, if controversial, currency of morbidity and mortality),[54–56] is caused by premature deaths of young adults. Moreover, in chemotherapy programmes, tuberculosis mortality can usually be reduced more quickly than incidence, because treatment cuts both transmission and case fatality rate (equation 3, panel). For these reasons, accurate counts or estimates of tuberculosis deaths are essential.

There are three ways to assess tuberculosis mortality: (1) direct counts through vital registration, or (2) verbal autopsy (a structured set of questions put to caregivers or family members of the deceased) used in cause-of-death surveys, and (3) indirect estimates from the product of incidence and case fatality. In the long term, all countries should be able to report tuberculosis deaths among routine death registrations (coded as in the International Classification of Diseases, 10th revision), in systems that give data of proven completeness and accuracy.

In 2003, a review of the quality of vital registration data found that only a third of the 56 million deaths from all causes that occur every year were reported by vital registration.[57] Only 23 countries had high-quality data (≥90% complete, ill-defined codes <10%) among 115 that reported deaths and their causes. They included none of the 22 countries that have a high burden of tuberculosis. Among 55 countries with data of medium quality (70–90% completeness), three were among high-burden countries: Brazil, Philippines, and Russia. The accuracy of the tuberculosis records, among all other causes of death, has been investigated only in Brazil. Two other high-burden countries, South Africa and Thailand, provided death registrations of low quality. Most countries in the WHO African and southeast Asia regions did not have national systems for death registration. A general problem with death certification is that tuberculosis may be recorded as the immediate, intervening, or underlying cause, but a death is usually attributed to tuberculosis only when it is reported as the underlying cause. If HIV co-infection is the underlying cause, the death of a person with tuberculosis might be recorded as an AIDS death. As a further complication, tuberculosis associated with HIV infection might not be recognised if the clinical presentation is unusual (eg, extrapulmonary disease).

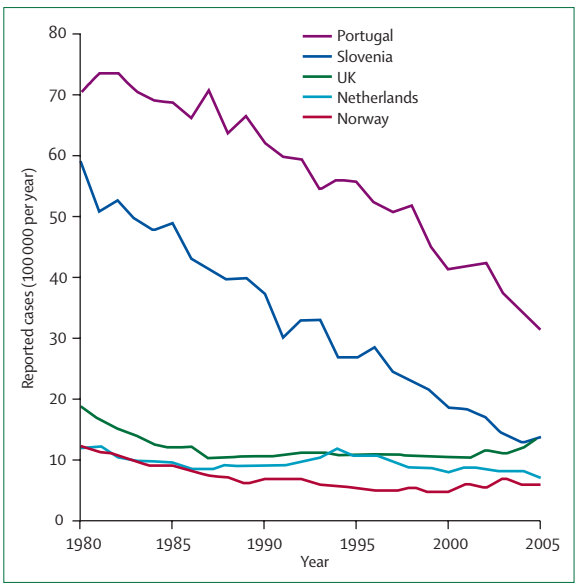

Figure 2: **Case notification series that are assumed by WHO to represent the true underlying trends in incidence[1]**

The establishment of reliable vital registration in most countries will take many years, but there are interim solutions. One is to use verbal autopsy as a component of sample vital registration,[58] or in conjunction with studies of risks such as tobacco smoking.[59,60] Sample vital registration has the advantage that a rare event (tuberculosis death) can be examined among a set of more common events (all deaths), and death from tuberculosis can be assessed by differential diagnosis.[61]

For more information on the **International Classification of Diseases** see http://www.who.int/classifications/icd/en/

In Chennai, India, verbal autopsy has been used to reduce substantially the number of deaths unattributed to specifc causes on death certificates, reclassifying many as tuberculosis deaths, although with unknown accuracy.[62,63] One study in China found that verbal autopsy often misclassified common causes of death among adults, but with about the same numbers of false positives and negatives, yielding approximately the same total number of tuberculosis deaths as in medical records.[64] Further investigations in China and Tanzania found that verbal autopsy for tuberculosis deaths met validation criteria based on sensitivity and the similarity between verbal autopsy and medical records.[65,66] Whereas substantially more work needs to be done on validation, there are so few reliable data on tuberculosis deaths in most high-burden countries that verbal autopsy is almost certain to give useful additional information. Part of the validation process is to check that verbal autopsy is able to capture non-pulmonary and other fatal forms of

	Study design	Age	Screening	Number examined	Number of cases [prevalence per 100 000 (95% CI)]		
					Active pulmonary	Culture positive	Smear positive
South Korea (1995)[29]	Stratified, cluster randomised	≥5 years	Radiographic (miniature)	64 713	668 [1032 (952–1112)]*†	142 [219 (182–256)]‡	60 [93 (69–117)]
Philippines (1997)[32]	Stratified, cluster randomised	≥10 years	Radiographic	21 960	537 [4200 (3500–4800)]	124 [810 (635–981)]	47 [310 (214–510)]
China (2000)[30]	Stratified, cluster randomised	≥3 months	Tuberculin, symptom, fluoroscopy	365 097	1340 [367 (340–397)]	584 [160 (144–177)]	447 [122 (110–137)]
Cambodia (2002)[36]	Stratified, cluster randomised	≥10 years	Radiographic, symptom	22 160	580 [1916 (1639–2239)]	271 [899 (741–1087)]‡	81 [269 (211–343)]
Indonesia (2004)[31]	Stratified, cluster randomised	≥15 years	Symptom	50 154	..	48 [186 (132–240)]§	80 [104 (66–142)]
Eritrea (2004)[37]	Stratified, cluster randomised	≥15 years	None	18 152	..	..	15 [50 (19–80)]

*All prevalence estimates are for the whole population, although children are often excluded from surveys. †Our underestimates of 95% CI for South Korea are calculated as 2√(N), where N is the sample size, which does not account for the design effect. ‡Culture positive and/or smear positive. §Prevalence in a subsample of 11 provinces of Indonesia.

Table 2: **The six national tuberculosis prevalence surveys done since 1995**

tuberculosis (ie, meningeal and miliary tuberculosis) in children and in settings with high HIV prevalence.

In countries in which tuberculosis deaths are not counted directly, they can be calculated as the product of estimated incidence and case fatality rates (equation 3, panel).[7,8,67] The method is simple, but only as reliable as the underlying estimates of incidence and case fatality.

Typically, case fatality is accurately recorded for patients on treatment, especially in DOTS programmes. But the fate of patients who default, who are transferred without follow-up and after treatment, is usually unknown, and some will certainly die.[68,69] Another difficulty is that deaths during treatment are not always caused by tuberculosis, but are nevertheless attributed to tuberculosis in the DOTS cohort system. The bigger problem, however, is that whereas 4·5 million new patients (of an estimated 8·9 million) were registered in DOTS and other control programmes in 2004, and 3·3 million had known outcomes, the treatment results of an estimated 5·6 million smear-positive, smear-negative, and extrapulmonary patients were not known to national tuberculosis programmes. Ultimately, DOTS cohorts should include nearly all tuberculosis cases arising in any country, so that cohort outcomes converge more closely with national death registrations. However, convergence will never be complete unless the number of patients lost to follow-up (default, transfer) can be reduced to zero. With respect to counting tuberculosis deaths, linking and cross-referencing between patient cohorts and vital registration is likely to improve the quality of both types of data. To make the links, each case and death must be uniquely identified in the recording system. This information is not yet collected in most high-burden countries.

Prevalence and risk of *Mycobacterium tuberculosis* infection

Although the prevalence of *Mycobacterium tuberculosis* infection and ARI are not direct measures of disease burden, tuberculin skin-test (TST) surveys have long been used to measure both.[70–74] Because $\lambda=\beta P$, programmes of drug treatment are expected to reduce the risk of infection (λ) at least as quickly as tuberculosis prevalence (P), and even more quickly if there are concomitant reductions in the contact rate (β). Tuberculin surveys are cheaper than disease prevalence surveys and less complicated logistically. Notwithstanding these advantages, there are many practical difficulties in the application of TST, concerning both the measurement of infection and its interpretation.[75,76]

The aim of TST surveys is to measure the current, or at least recent, risk of infection. For this reason, those tested are usually children. The children selected should be neither too young (low prevalence of infection, influence of neonatal BCG) nor too old (longer average time since infection). The compromise usually falls in the age-range 5–14 years, but children aged 10 years have been infected an average of approximately 5 years previously.

People infected with *M tuberculosis* are identified by the size of their TST reaction. Although some infected people are anergic and do not respond to tuberculin (especially if HIV positive), TST seems to be a sensitive test of infection. The problem is low specificity: the positive response to *M tuberculosis* infection can sometimes be obscured by unpredictable cross-reactions from BCG vaccination or environmental mycobacteria, although the effect of BCG given only in infancy wanes substantially by adolescence.[77–81] The lower the ARI, the harder it is to distinguish the population of true positives from the population of cross-reactors. A clear difference was found between infected and non-infected children in South Korea in 1965 (figure 3). The two distributions are so distinct that they can be separated by taking a cut-off point at 9 mm induration, and counting all children above this as infected. The number infected can also be estimated by the so-called mirror-image method: the mode of the symmetrical distribution of positives lies at 18 mm, so the total infected is the number at 18 mm plus twice the number with larger

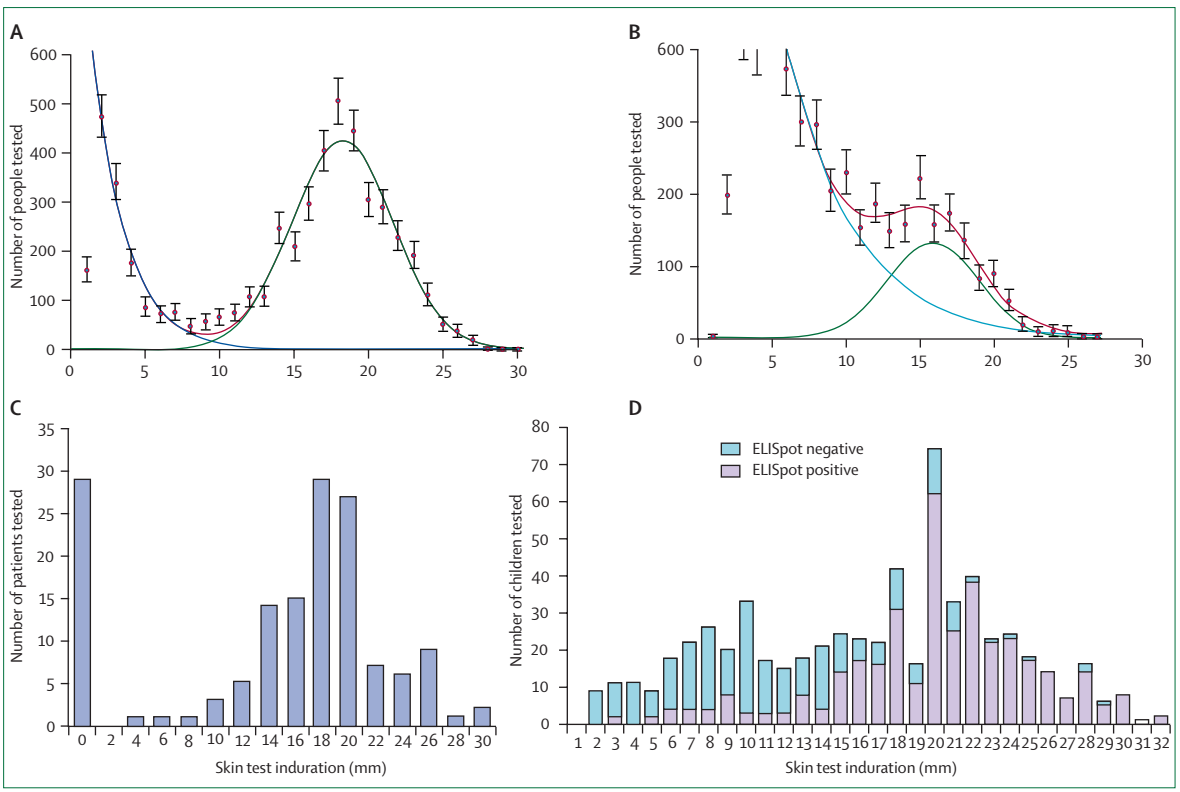

Figure 3: **Use of tuberculin skin test (TST) surveys to estimate the prevalence of infection**
(A) South Korea, 1965: the overall distribution of responders (red points [95% CI], fitted red line) is divided among negatives (exponential, blue) and positives (normal, green) in a mixture analysis.[82,83] (B) Nepal, 2006: the overlapping distribution of positives and negatives is separated by mixture analysis, as in (A).[84] (C) Yemen, 2007: TST among 150 tuberculosis patients. The distribution from 4 mm and above resembles that in (A); 29 patients gave no response, either because of test insensitivity or anergy.[85] (D) The high-specificity ELISpot test was used to calibrate TST, separating probable positives from negatives.[86]

indurations ($N_{18}+2\times N_{\geq 19}$). The most sophisticated procedure is mixture analysis,[82,83,87] which fits two or more distributions (eg, normal and exponential)[79] to the groups of false and true positives. The number infected is the area under the curve that defines true positives (figure 3).[82,83]

If the distributions of true and false positives overlap, as they usually do in contemporary data (figure 3),[88,89] a single cut-off point cannot be used to identify the number of people infected. If the overlap is so great that there is no clear mode of the positive distribution, then neither mirror nor mixture method will be applicable, unless there is an independent way of defining the distribution of positives. Further analytical refinements can help to determine the distribution of positives: for example, by allowing for digit preference (excess of observations at 5 mm, 10 mm, 15 mm, and 20 mm).[90] All statistical methods, however sophisticated, are fundamentally limited by the quality of data.

The essential task is to remove false positives so as to achieve high specificity. One approach is to calibrate TST by testing patients with active disease, assuming that TST indurations have the same distribution among patients (usually adults) and infected individuals (usually children). The frequency distribution of true positives can then be used, with the aid of the mirror method or mixture analysis and related statistical methods, to separate infected and uninfected individuals in the full TST distribution obtained in surveys. In this respect, the most-commonly used tuberculin preparation (RT23, Statens Serum Institut, Copenhagen, Denmark) seems to generate a plausible distribution of induration sizes for patients with a mode at around 18 mm (figure 3), but may not always do so. TST might also be calibrated with highly-specific, interferon-γ release assays (IGRAs), including enzyme-linked immunospot (ELISpot) and ELISA (ie, QuantiFERON-TB Gold, Cellestis Limited, Victoria, Australia; figure 3).[91–94] IGRAs are not yet suitable as replacements for tuberculin in large surveys because they are costly (>$10 per assay), require blood taken by venepuncture (not fingerprick), and need rapid laboratory processing. Also, IGRA and TST responses seem to convert and revert at different rates, so the two tests are unlikely to give the same assessment of infection in any population.[93,95–104]

Although the accurate diagnosis of infection is important for individuals who have been in contact with tuberculosis patients and who might benefit from prophylactic treatment,[105–108] absolute measures of infection have limited value for monitoring epidemic variation and trends. Moreover, Styblo's[15] well-known principle relating infection to disease is no longer widely

applicable.[109,110] Styblo proposed that an increase in ARI of 1% per year corresponds with an increase of 50–60 smear-positive cases per 100 000 per year, with the coefficient usually taken to be 50 (equation 4, panel).[15] This was derived from the observations that each prevalent smear-positive case makes about ten contacts (β) per year that lead to established infections, and that an untreated case remains smear-positive for an average of 2 years.[15] Thus prevalence is twice incidence ($P=2I$), and the ratio of smear-positive incidence (I per 100 000) to ARI (%) is $I/\lambda=(I\times10^5)/(2\beta I\times10^2)=50$. Programmes of drug treatment are expected to shorten the duration of illness and thereby lower the prevalence-to-incidence ratio. Additionally, improved living conditions, HIV infection, and other factors might have reduced the contact rate between infectious tuberculosis patients and other individuals. That two recent reviews found β to be markedly lower than ten in most settings is therefore not surprising. If β is less than ten or $P<2I$, then the ratio of smear-positive incidence to ARI exceeds 50.[109,111] Although it has been suggested that the 1:50 rule does hold at one site in south India,[112] it is likely that the incidence of smear-positive tuberculosis was underestimated in that setting. Therefore, we can no longer assume that the Styblo rule applies generally.

Attempts to measure the exact prevalence or risk of infection require rigorous adherence to recommended procedures.[75,113–115] Even then, doubts about interpretation may persist. For example, tuberculin surveys are mostly done in schoolchildren who may not be exposed to the same ARI as children who are not at school or adults. Uncertainties of this kind add to the view that measures of ARI are best used comparatively, albeit with caveats.[116] One problem is that, when assessing temporal change, the expected rapid fall in ARI caused by drug treatment is superimposed on a relatively static backlog of infection. The slower the decline in infection prevalence, the longer the interval between surveys and the larger the sample size needed to detect changes over time. An alternative approach is to compare infection rates across a range of ages at a single survey, looking for evidence that ARI has been lower on average in younger children. However, the analysis must assume that ARI is independent of age and that age is a proxy for time, which may not be justified.

In short, a tuberculin survey is not guaranteed to give interpretable results in any setting, but is more likely to be useful for measuring time trends and geographical variation, in settings in which (1) the ARI is high (>1% per year), (2) there are data on infection prevalence from previous surveys, (3) there is capacity to ensure strict adherence to recommended procedures, and (4) there is an independent measure of the response of true positives. TST surveys can be done on samples of about 10 000 children, which, at approximately $2–5 per child, gives a total cost of $20 000–50 000 (our data from surveys in India, Somalia, and Tanzania). This is far cheaper than surveys of disease prevalence or deaths.

Assessing the impact of tuberculosis control

Although drug treatment has undoubtedly hastened the reduction in tuberculosis cases and deaths since the 1950s, there are few recent, wholly persuasive, studies of the epidemiological impact of chemotherapy. The central analytical problem is that changes in incidence, prevalence, and mortality are not necessarily attributable to programmes of drug treatment. This is because other variables affect transmission (eg, number of people per habitation, contacts in workplaces) and the progression from infection to disease (eg, undernutrition, diabetes).[117] Because public-health programmes are not done as controlled experiments, the interpretation of trends is rarely free of all ambiguity.

Nevertheless, the measurement of trends in tuberculosis infection, disease, and death can provide strong circumstantial evidence for an impact of chemotherapy in some settings. The rise and fall of case notifications in Peru after the introduction of DOTS probably represent an improvement in case detection followed by a decline in incidence and mortality.[118] The timing of these changes, and the observed annual increases and decreases, are consistent with the expected impact of chemotherapy, and there are other lines of evidence for DOTS impact (eg, on the strengthening of laboratories and diagnostic procedures).[14,72,74,119] Subject to further investigation, recent reductions in the prevalence of infection and disease in south India seem to be attributable to implementation of the so-called model DOTS project, though some of the impact could be caused by the removal of patients found in frequent surveys.[33,120,121] In China, the measured decline in tuberculosis prevalence between 1990 and 2000 was greater in provinces that carried out chemotherapy programmes more effectively under DOTS,[30] and the improvement in treatment is likely to have been accompanied by reductions in mortality.[122] Less clearly, marked reductions in prevalence over several decades in South Korea and Indonesia have been caused by an indeterminate mix of drug treatment plus social and economic development.[29,31]

Many countries have reported falling case notifications over many years, and have reported reduced mortality in cohorts of patients treated under DOTS.[1] With data of this kind, the impact of drug treatment programmes can be estimated from the product of the reduction in incidence and the reduction in case fatality (equation 3, panel).[118] More conservatively, the number of lives saved can be calculated from the number of patients treated multiplied by the reduction in case fatality.[123,124] Such indirect estimates of impact are inferior to direct measures of the number of deaths averted, but do have the virtue of being calculable for most countries.

Conclusions

Despite their imperfections, the measurement methods described here can be combined to assess tuberculosis infection, disease, and mortality, and to evaluate progress towards targets for tuberculosis control. That all countries

Search strategy and selection criteria

Data were identified by searches of PubMed, ISI Web of Science, and the authors' libraries. Search terms used in online databases were, in various combinations, "tuberculosis", "environmental mycobacteria", "incidence", "prevalence", "mortality", "infection", "annual risk of infection", "tuberculin skin test", "mixture method", "mirror-image method", "survey", and "surveillance". Among thousands of papers on this topic, we selected only the key papers in English that were relevant to measurement methods, and that emphasised developments from year 2000 onwards.

will have adequate routine surveillance systems by 2015 seems unlikely, but all should aim to investigate quantitatively the completeness of reporting to obtain a direct measure of case detection, and to show that incidence is falling by 2015.

National control programmes should also be able to show that either mortality or prevalence has been substantially reduced by 2015. With recognition that estimates for the MDG reference year 1990 are mostly based on weak data, the calculated reductions in mortality or prevalence—ideally with measures of uncertainty—should nevertheless be in line with the MDGs. Tuberculosis mortality will ideally be measured by counting deaths in a comprehensive vital registration system. The other, less satisfactory options are to assess changes in the death rate by sample vital registration with verbal autopsy, or by combined analysis of changes in incidence and case fatality.

In countries that currently have weak surveillance systems, a single disease prevalence survey could provide an accurate measure of the national or provincial (in large countries) burden of tuberculosis. Two or more surveys would measure the trend. Repeated surveys of *M tuberculosis* infection can provide supporting information about trends in transmission, especially if the specificity of tests for infection can be guaranteed. Notwithstanding the logic of equations 2–4 (panel), measures of the prevalence of infection and disease, and of mortality, do not generally yield accurate estimates of incidence.

The challenge presented by the MDGs is to measure trends in incidence, prevalence, and deaths. The MDGs do not refer to the absolute burden of tuberculosis, and they do not demand that trends be attributed to programmes of drug treatment. To be able to show that the MDGs have been achieved would be cause for celebration. But to understand why they have been achieved would provide a much firmer basis for tuberculosis elimination.[5]

Conflicts of interest

We declare that we have no conflicts of interest.

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