

Monitoring

53. What is the health, social, and economic burden of tuberculosis?

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The consequences of tuberculosis on society are immense. Worldwide, one person out of three is infected with tuberculosis – that is, 2 billion people in total. Global estimates of the burden of tuberculosis-related disease and death for 1997 indicated that 8 million people developed active tuberculosis every year and nearly 2 million died (1).

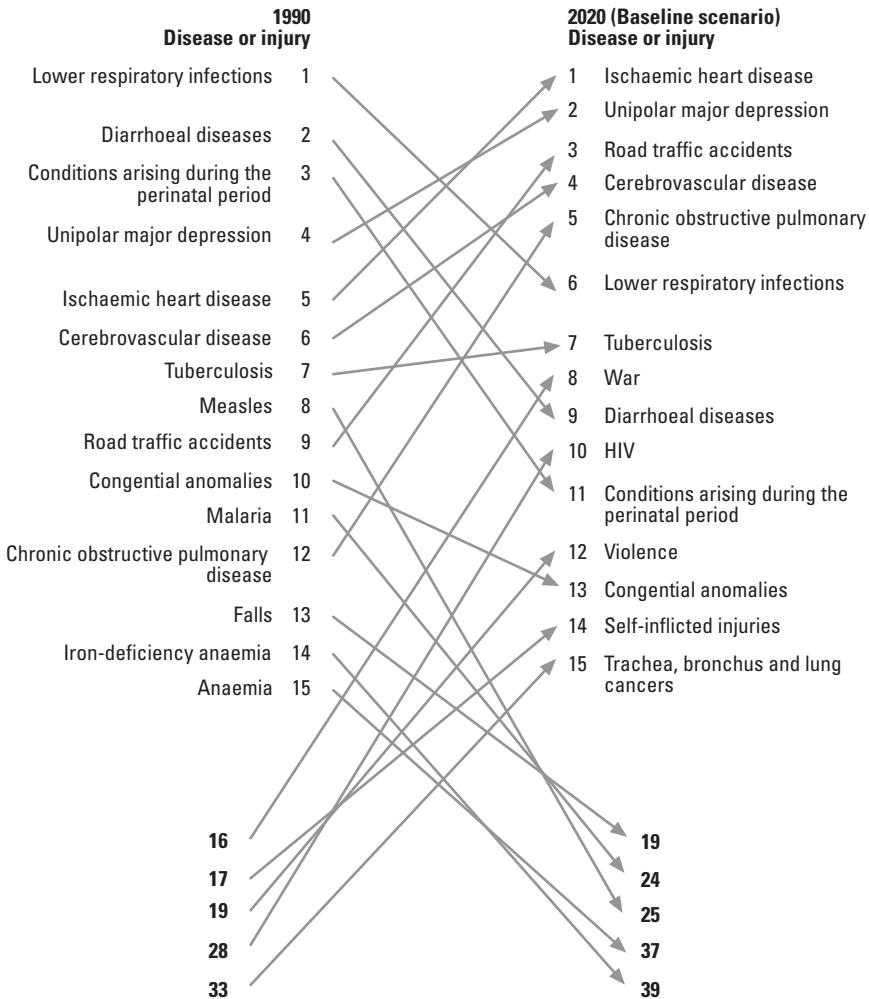
Tuberculosis accounts for 2.5% of the global burden of disease (2) and is the commonest cause of death in young women, killing more women than all causes of maternal mortality combined. As illustrated in Figure 18, tuberculosis currently holds seventh place in the global ranking of causes of death, and, unless intensive efforts are made, is likely to maintain that position through to 2020, despite a substantial projected decline in disease burden from other infectious diseases (3).

Infection with HIV increases the risk of tuberculosis disease (4). Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a sharp increase in tuberculosis, with reported incidence rates increasing two- to four-fold in the 1990s (5).

Drug resistance is an increasing problem in many countries, arising as a result of poor treatment organization. Poorly conceptualized control programmes, irregular drug supplies, and uncontrolled use of tuberculosis drugs in the private sector lead to drug resistance, which can be prevented with effective use of DOTS. WHO and the IUATLD carried out a global survey of drug resistance from 1994 to 1997 in 35 countries (6, 7). Overall, among people with newly diagnosed tuberculosis, there was resistance to at least one drug in 9.9% of cases, and multidrug resistance (resistance to at least isoniazid and rifampicin) in 1.4%. A report on the second round of global surveillance, published in 2000, revealed a similar picture (any drug resistance in 10.7% of new cases, multidrug resistance in 1%). These reports confirm that the strongest risk factor for drug resistance is previous tuberculosis treatment; 23.3% of such cases had resistance to at least one drug, and 9.3% had multidrug-resistant tuberculosis (8). Drug resistance reduces the efficacy of the standard

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Figure 18
Change in rank order for the 15 leading causes of death, world, 1990–2020^a



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treatment regimens recommended by WHO, with failure rates 15 times higher in patients with multidrug-resistant tuberculosis than in those with drug-susceptible disease (9).

Tuberculosis hinders socioeconomic development: 75% of people with tuberculosis are in the economically productive age group of 15–54 years (10). Ninety-five per cent of all cases and 99% of deaths occur in developing countries, with the greatest burden in sub-Saharan Africa and south-east Asia. Twenty-three countries together

Table 55
Estimated household costs of tuberculosis

Cost to patient	Bangladesh (11)	India (12)	South Africa (13)	Uganda (14)
Direct costs (US\$)	130	41	99	68
Lost work	57%	NA	NA	91%
Time loss	14 months	3 months	4 months	10 months
Lost income (US\$)	115	89	272	161
Indirect cost as percentage of annual household income	15	14	NA	NA
Total cost as percentage of annual household income	31	20	NA	NA

account for more than 80% of all cases of tuberculosis. Household costs of tuberculosis are substantial (Table 55).

Although the “direct” costs of diagnosis and treatment are significant for poor families, the greatest economic loss occurs as a result of “indirect” costs, such as loss of employment, travel to health facilities, sale of assets to pay for treatment-related costs, funeral expenses, and particularly lost productivity from illness and premature death. A study from Uganda found that 95% of subsistence farmers with tuberculosis reported a loss in production, and 80% of wage-earners had stopped work (14). A review of studies investigating the economic impact of tuberculosis showed that, on average, 3–4 months of work time are lost if an adult has tuberculosis, resulting in the loss of 20–30% of annual household income, and an average of 15 years of income is lost if the patient dies from the disease (15).

The relation between tuberculosis and poverty is complex, as the disease impoverishes those who suffer from it, and the epidemic is exacerbated by socioeconomic decline. Poverty results in crowded housing with increased risk of transmission and in poor nutrition with increased risk of breakdown from infection to tuberculosis disease. The break-up of the Soviet Union in the early 1990s and the subsequent economic decline and collapse of health and social support structures have led to a rapid rise in tuberculosis, with rates increasing by 7% per year in the Russian Federation, Ukraine and other countries of the former Soviet Union (5). In Cuba over a 3-year period, economic and nutritional hardship resulted in a striking increase (24% per annum) in the tuberculosis notification rate (16). A strengthened programme allowed a renewed trend in transmission reduction, resulting in a renewed reduction in incidence.

Negative social consequences, such as stigma, are a particular problem for women in some societies, restricting options for marriage and employment and even leading to divorce. A study in India indicated that 15% of women with tuberculosis (equivalent to 100 000 women per year nationally) faced rejection by their families (12).

The negative impact carries over to the next generation, as the coping mechanisms of poor families adversely affect their children. The same study from India found that 8% of rural and 13% of urban children (equivalent to 300 000 nationally) were taken out of school when a parent (usually the father) developed tuberculosis. Other long-term consequences include indebtedness; the Indian study showed that more than two-thirds of households went into debt to cover the costs of tuberculosis; the average family debt was US\$ 59, equivalent to 12% of the annual household income. Continued spread of tuberculosis infection condemns the next generation to the avoidable risk of tuberculous illness and death.

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54. What are the global targets for tuberculosis control, and what is the basis of these targets?

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The global targets for tuberculosis control are to cure 85% of the sputum smear-positive cases detected, and to detect 70% of the estimated new sputum smear-positive cases (1). These targets were originally adopted by WHO in 1991. It became clear that the global targets would not be achieved by 2000 as intended, and the target date was put back to 2005 by the World Health Assembly in May 2000.

The numerator for the case detection target is the number of new cases of sputum smear-positive tuberculosis registered in one year, and the denominator is the number of new sputum smear-positive cases estimated to have arisen in the same population over the same period. As the case detection target relies on an estimate for the incidence of tuberculosis, it is difficult to measure accurately in most settings, especially in the context of an epidemic of HIV infection.

The numerator for the cure rate target is the number of patients in a one-year cohort of new cases of smear-positive tuberculosis fulfilling the WHO/IUATLD definition for cure, and the denominator is the number of patients originally registered for treatment in that cohort.

Progress in implementing effective tuberculosis control based on the DOTS strategy has been slow; by 1999, only 40% of estimated new infectious cases were reported to WHO (23% in DOTS programmes, and 17% in non-DOTS programmes) (2). Cure rates for patients registered in DOTS programmes in 1998 were much higher than those in non-DOTS programmes – 73% vs 16%. The addition of patients completing treatment without a smear result to confirm cure gave a “treatment success” rate of 84% in DOTS programmes – close to the global target.

Adoption of the targets is based on two principles – impact and feasibility. First, epidemiological modelling has demonstrated that achieving the targets will result in a significant decline in the tuberculosis epidemic, reducing incidence by about 50% in 8–12 years, in the absence of HIV. A 1991 report by Styblo & Bumgarner showed the effect of differing rates of case detection and cure on the prevalence of tuberculosis, and predicted that cure rates in excess of 75% would lead to a substantial reduc-

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tion in prevalence over time. Increasing case detection without improving cure rates will actually worsen the epidemic (3). This work was influential in defining the targets, and has been confirmed by more recent studies, which suggest that countries achieving the global targets would then see a fall in incidence of 8–12% per year (cases reduced by 50% in as little as 6–9 years) and an even faster reduction in mortality of 9–13% per year (50% reduction in 5 years or less) (4).

These theoretical figures fit past and current experience. Tuberculosis declined rapidly in much of Europe over the last century, but the fall in incidence of infection accelerated from 4–5% to 12–13% per year following the introduction of effective treatment (5). This has been recently confirmed by data from Peru, which suggest that the decline in incidence has reached nearly 8% per year, double the rate before DOTS was introduced (2, 6).

Second, achieving these targets is feasible. Early studies of the sociology and epidemiology of tuberculosis in India revealed that 70% of people with smear-positive tuberculosis had symptoms and sought health care, confirming the feasibility of achieving the target by case detection in health facilities (7). Additional experience in IUATLD-supported national tuberculosis programmes of Benin, Malawi, United Republic of Tanzania, and Viet Nam in the late 1980s showed that cure rates exceeding 80% could be achieved and sustained, demonstrating the feasibility of the cure rate target (8). A survey in the United Republic of Tanzania suggested that 70% detection of new infectious cases could be achieved under programme conditions. By 2000, seven countries had achieved the global targets, and 43 had reported treatment success rates in excess of 70% with estimated case detection rates of over 50% (2).

Significant challenges face the world if the targets are to be met as planned. The tuberculosis epidemic in sub-Saharan Africa is increasing by 10% per year, driven primarily by the HIV pandemic (2). The high death rate in people with HIV-related tuberculosis prevents many affected countries from achieving the global cure rate targets. In addition, neither of the targets for case detection or cure takes HIV into account; effective tuberculosis control services cannot at present prevent an increase in tuberculosis in the context of a significant HIV epidemic (see “Can tuberculosis be controlled?”, page 301).

A second obstacle to achieving the global targets is inadequate case detection and notification. Although 43% of the global population lived in areas covered by DOTS programmes in 1999, only 23% of people with infectious tuberculosis were treated with DOTS (2). Contributing factors are the limited primary health care infrastructure in many countries, the widespread availability of diagnosis and treatment in the private sector in some countries, particularly those of southern Asia that are home to one-third of people with tuberculosis, and the fact that the private sector in developing countries generally does not report diagnosed cases.

Achievement of the global targets depends on the ability of countries to accelerate coverage of the population with DOTS whilst sustaining high cure rates, the effectiveness of strategies to address HIV-related tuberculosis, and the ability of tubercu-

losis programmes to increase case detection through provision of effective services, social mobilization, and involvement of the private sector.

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55. What is DOTS?

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DOTS is the internationally recommended strategy to ensure cure of tuberculosis (1). It is based on five key principles (see Table 56) that are common to disease control strategies, relying on early diagnosis and cure of infectious cases to stop spread of tuberculosis.

The treatment of infectious cases as a strategy for preventing transmission and thereby controlling tuberculosis was highlighted by Crofton in the early 1960s (3), less than 20 years after the first effective drugs were discovered and only 10 years after randomized controlled trials had demonstrated that combined treatment regimens can cure patients and prevent the emergence of drug resistance (4).

The package of interventions that eventually became known as the DOTS strategy was first formulated in national tuberculosis programmes supported by the IUATLD under the leadership of Dr Karel Styblo. Initially in the United Republic of Tanzania, and then later in several other countries of Africa and Latin America, Styblo developed the technical and managerial principles of effective tuberculosis control based on the management unit of the district. The district has the staff and resources to organize diagnostic and treatment services, maintain supplies and monitor programme performance for a population of 100 000–150 000. Styblo showed that short-course treatment was essential to reach adequate cure rates on a programme basis, verified the necessity of directly observed treatment, and developed the principles of recording, reporting, and drug management that are also integral to DOTS.

WHO began to promote this strategy in 1991 (5), and in 1994 produced a Framework for Effective Tuberculosis Control (6) that clearly described the main components of what was later to be known as the DOTS strategy. The Framework was revised and expanded in 2002 (7).

The term “directly observed therapy” had been in use for several years before it was modified to “directly observed treatment, short-course” by WHO in 1995, and used to designate a comprehensive strategy to control tuberculosis (8). Although “DOTS” appears to emphasize the direct observation component of the strategy, all aspects are

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Table 56
Principles and components of DOTS^a

Key principle	Component of DOTS
Organized and sustained intervention	Government commitment to ensuring sustained, comprehensive tuberculosis control activities
Accurate and early identification of infectious cases	Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services
Effective and patient-friendly treatment	Standardized short-course treatment using regimens of 6–8 months, for at least all confirmed smear-positive cases. Effective case management includes directly observed treatment during the intensive phase for all new smear-positive cases, the continuation phase of rifampicin-containing regimens, and the whole re-treatment regimen
Effective drug management	A regular, uninterrupted supply of all essential antituberculosis drugs
Outcome-based monitoring	A standardized recording and reporting system that allows assessment of case detection and treatment results for each patient and of the tuberculosis control programme's overall performance

^a Source: reference 2.

essential, and DOTS is no longer an acronym but the “brand name” of the WHO-recommended strategy for TB control.

Government commitment is an essential component of DOTS, and WHO has emphasized advocacy and social mobilization as means of achieving this commitment. Sufficient funds and administrative support to hire staff, purchase essential items (drugs, microscopes, reagents, printed materials, etc.), and contract for services are necessary for the programme to operate.

The rationale for diagnosis primarily by microscopy among patients in health facilities has been reviewed in detail in the first section of this book.

Direct observation of treatment in which “a trained and supervised person observes the patient swallowing the tablets” is fundamental to the DOTS strategy to ensure adherence to treatment (2). Early WHO documents emphasized the importance of direct observation by health workers (9). Later, experience gained in DOTS programmes around the world demonstrated that trained lay people were at least as effective in observing treatment; these have included community health volunteers in Bangladesh (10), storekeepers in South Africa (11), religious leaders, lay health workers, and community volunteers. Some recent studies have questioned the necessity of direct observation of treatment (12) or proposed reducing the frequency of

observation to once a week (13). However, the benefits for health workers and patients of reducing the frequency of observation may be offset by the potential for increasing rates of drug resistance arising from hidden non-adherence. To be effective, a treatment observer must be accessible and acceptable to the patient, and trained by and accountable to the health service.

The requirement of an uninterrupted supply of tuberculosis drugs is clear. In addition, the quality of drugs should be ensured, particularly if they are provided in fixed-dose combinations, which are more susceptible to problems in manufacture (see “What are the advantages and disadvantages of fixed-dose combinations of antituberculosis drugs?”; page 189).

The reporting system in DOTS, which allows simple and robust monitoring of patient progress and programme performance, is described in “Why is a recording and reporting system needed, and what system is recommended?” (page 270). DOTS records can be easily checked for internal consistency and for consistency between records, and can also be externally verified by reviewing sputum slides, interviewing patients and health workers, and monitoring consumption of drugs and supplies. Operational research designed to continuously analyse and improve the programme is another aspect of systematic monitoring and evaluation.

Modifications to the DOTS strategy have been proposed – for example, to address specific problems such as HIV-related tuberculosis and multidrug-resistant tuberculosis. These modifications to the basic strategy are usually known as DOTS Plus (14). Additional elements that have been proposed for low-incidence countries (Table 57) include active case detection in selected high-risk groups, routine drug susceptibility testing, and expanded use of treatment for latent tuberculosis infection.

Status of DOTS expansion

WHO receives reports on DOTS implementation from national tuberculosis programmes and has published annual global reports on tuberculosis control since 1997. The 2003 report provides information on case detection during 2001 and treatment outcomes for patients registered in 2000. The seven published reports show that the number of countries implementing DOTS has increased from 70 in 1995 to 155 in 2003, with 7.1 million patients reported as treated in DOTS programmes between 1995 and 2000.

By the end of 2002, 61% of the global population had access to DOTS, but only 32% of people estimated to have newly developed sputum smear-positive tuberculosis were registered in DOTS programmes (15).

Constraints to rapid DOTS expansion include financial shortages, human resource problems, inadequate health care infrastructure, lack of secure supply of good-quality antituberculosis drugs, and gaps in public information about the danger of tuberculosis (16). In order to address these concerns, WHO, jointly with high-burden countries, has developed a Global DOTS Expansion Plan, which describes the actions and resources needed to rapidly expand DOTS to reach the global tuberculosis control

Table 57
DOTS in low-incidence countries^a

The required components of the DOTS policy package	Additional elements of tuberculosis control for low-incidence countries
Government commitment to sustained tuberculosis control	Government commitment to tuberculosis control, with the aim of elimination: <ul style="list-style-type: none"> • legal framework including laws on mandatory notification, cohort analysis of treatment results, and drug policy; • tuberculosis control policy based on consensus by national authorities and leading organizations; • maintenance of an efficient network for tuberculosis control by ensuring technical leadership at national level and trained human resources at lower levels.
Sputum smear microscopy to detect infectious cases among people with symptoms of pulmonary tuberculosis attending health care facilities	In the general population, case detection among symptomatic patients. Risk-group management (e.g. active case detection in high-risk groups). Diagnosis confirmed by culture. Drug susceptibility testing, especially in groups at high risk of drug resistance. Outbreak management (e.g. source and contact tracing).
Standardized short-course chemotherapy for all tuberculosis cases, with directly observed treatment for at least the initial 2 months among infectious cases	Directly observed treatment for more than the initial 2 months for high-risk groups and where cure rates are low. Specialized treatment for multidrug-resistant tuberculosis. Preventive treatment for newly infected persons and for some high-risk groups, e.g. HIV-infected individuals.
Regular, uninterrupted supply of antituberculosis drugs (preferably quality-controlled fixed-dose combination drugs)	Regulations on drug use; reserve drugs for drug-resistant tuberculosis available only in highly qualified centres
Evaluation and supervision: use of sputum smear microscopy for evaluation of patient progress towards cure	Surveillance based on a uniform reporting system. Culture and sputum smear examination to assess treatment outcome. Drug resistance surveillance. Quality assurance of tuberculosis control data (e.g. auditing system).

^a Source: reference 1.

targets (17). Successful implementation of this plan will require increased investment of human and financial resources, as well as new strategies and additional resources to address global and local challenges to tuberculosis control, particularly HIV-related tuberculosis.

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56. Is DOTS cost-effective?

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The relative value of different interventions can be assessed by comparing inputs and outputs. For health interventions, this is usually achieved by combining elements of cost and impact. Assessments of cost-effectiveness are useful for prioritizing different disease-specific interventions, for assessing the relative value of different interventions for the same condition, and as a tool for resource mobilization to promote investment.

Costs are directly comparable, as they are generally measured in the same way. However, the impact of one intervention is not always directly comparable with that of another. For example, disability prevented by polio immunization is not directly comparable with deaths averted by DOTS. Some form of standardization of impact is therefore needed for the comparison of interventions.

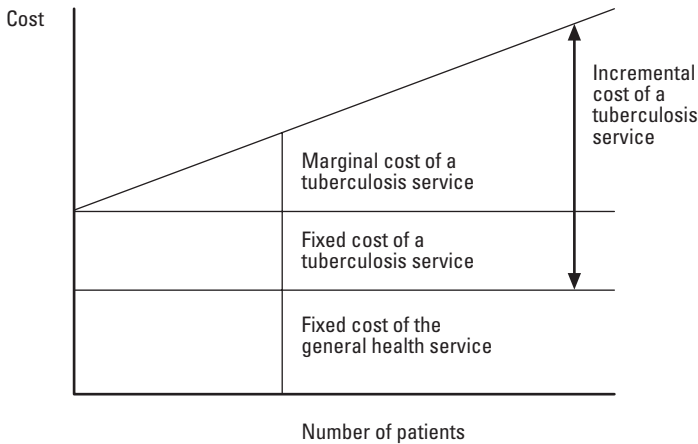
The most widely used analysis of relative efficiency of health care interventions is cost-effectiveness, in which the impact of an intervention is converted to a common health benefit, such as years of potential life saved. However, this indicator may underestimate the value of interventions for diseases that are not life-threatening but that cause considerable disability, such as leprosy. The concept of the disability-adjusted life year (DALY) was therefore developed, as an indicator that incorporates measures of disability and death (1). The cost-effectiveness of an intervention can then be measured in terms of the cost of preventing the loss of one disability-adjusted year of life.

The health service costs of tuberculosis control can be divided into four categories (Figure 19):

- fixed costs of general health services;
- fixed costs of tuberculosis control services – the costs of adding a tuberculosis programme to the general health services, which do not change with increasing numbers of patients, for example, staff salaries;
- marginal costs of tuberculosis control services – the costs associated with each additional new patient diagnosed and treated, for example, costs of drugs;
- incremental costs – this measure combines the fixed and marginal costs of tuberculosis control services.

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Figure 19

Theoretical framework for costing a tuberculosis control service^a

^a Source: reference 2.

Evidence that DOTS is cost effective compared with other health care interventions

In 1993, the World Bank published *Investing in Health*, comparing the cost-effectiveness of different primary health care interventions. The report estimated that effective tuberculosis control cost US\$ 20–57 per death averted and US\$ 1–3 per DALY saved. Thus, tuberculosis chemotherapy was found to be one of the most cost-effective of all health interventions, along with measles vaccination and vitamin A supplementation (1). Since publication of this report, costs of antituberculosis drugs have fallen considerably; a basic course of treatment now costs as little as US\$ 10 compared with US \$40–60 in the early 1990s (3), further increasing the cost-effectiveness of DOTS. However, cost-effectiveness has not been comprehensively reassessed in the context of HIV; by reducing the post-cure survival time of tuberculosis patients, HIV infection is likely also to reduce the cost-effectiveness of DOTS somewhat.

Evidence that DOTS is cost-effective compared with other tuberculosis control strategies

Other strategies for tuberculosis control are BCG vaccination, preventive treatment, and active case detection in the community. Although these strategies are appealing in theory, in practice they are relatively ineffective in controlling tuberculosis compared with DOTS.

BCG vaccination of infants is recommended in high-prevalence countries to prevent serious forms of tuberculosis in children, such as meningitis and miliary tuberculosis. The World Bank estimated that BCG costs US\$ 7 per DALY saved, but

the intervention is cost-effective only if the annual risk of tuberculosis infection is high (i.e. more than 1% per year) (4). However BCG vaccination, since it primarily prevents noninfectious forms of tuberculosis, has little or no impact on tuberculosis transmission.

The World Bank study did not estimate the cost per DALY of preventive treatment, but concluded that selective screening and treatment in high-risk populations (e.g. household contacts of infectious patients and people with HIV infection) was “suspected to be reasonable”, and cautioned that “mass prophylaxis has high cost with limited effectiveness” (4).

On a theoretical basis, active case detection in the community may be effective. However, as discussed in “What is the role of case detection by periodic mass radiographic examination in tuberculosis control?” (page 72), such a strategy has severe practical limitations. It would detect prevalent cases primarily, which can be rapidly controlled with DOTS in any case (see “Can tuberculosis be controlled?”, page 301). Moreover, patients identified through surveys of this nature tend to be unlikely to complete a full course of treatment.

Evidence that DOTS is cost-effective compared with other tuberculosis treatment strategies

Two early studies comparing the cost-effectiveness of different strategies for providing tuberculosis treatment came from experience in countries of Africa – one from Botswana (5), and one each from Malawi, Mozambique and the United Republic of Tanzania (6). Each study compared short-course treatment with “long-course” regimens based on streptomycin, isoniazid, and thioacetazone, and also compared fully ambulatory regimens with inpatient care during the intensive phase. Although the drug costs for short-course treatment were more than three times higher than those for standard treatment, improved cure rates made short-course treatment the more cost-effective option, particularly if treatment was provided on an outpatient basis. Further studies have substantiated this finding, and a review of eight cost-effectiveness studies published between 1982 and 1992 showed that the cost per outcome for ambulatory short-course treatment was 19–41% that of long-course treatment with two-month hospitalization (2).

The cost savings for countries as they implement DOTS can be substantial. An economic analysis of DOTS in India conducted by WHO in 1996 estimated that an additional investment of US\$ 200 million per year would yield an annual return of US\$ 750 million through reduced prevalence of disease, deaths averted, and release of hospital beds (7).

However, the economic benefits of DOTS are even greater for communities than for governments. In many developing countries, the direct costs of tuberculosis diagnostic and treatment services for government health services are considerably lower than the direct and indirect costs for households. A study in Uganda was one of the first to demonstrate this, revealing that, out of a total cost of US\$ 324, the patient con-

tributed US\$ 229 in direct and indirect costs (8). Of these patient costs, lost income equivalent to 3–4 months of work time usually forms the greatest proportion (see “What is the health, social, and economic burden of tuberculosis?”, page 233) (9).

Evidence of the potential economic benefit of DOTS for communities comes from a study conducted in Thailand, which showed that for every US\$ 1 invested by the government in tuberculosis control, the community gains by US\$ 50 over a 20-year period (10).

The per capita incremental cost of implementation of DOTS may be as low as US\$ 0.05 in some low-income countries (11), and would rarely be more than US\$ 0.20 in high-prevalence, low-income countries.

In summary, DOTS is a highly cost-effective strategy, producing significant savings for governments and communities. DOTS is a “good buy” for health planners and policy-makers. In resource-poor settings, DOTS should be one of the highest priorities for health services, and it offers significant advantages over other tuberculosis control strategies and methods of treatment.

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57. How can the progress of treatment be monitored?¹

*T. Santha*²

The three approaches to monitoring progress of patients during treatment are bacteriological, clinical, and radiographic assessment.

Assessment by bacteriology

Bacteriological assessment can be done by smear and culture. Although culture is more specific, it is time-consuming and costly and there is a delay in getting the results. Moreover, appropriate facilities are not universally available. Hence the management of patients is generally based on smear microscopy. Based on smear results, the response to 12-month treatment regimens that do not contain rifampicin can be predicted with 90–92% confidence (1). With short-course treatment, the organisms are killed rapidly, but dead bacilli may be excreted for some time, with the result that smears may be positive in some patients even when they are responding well to treatment (2).

On monthly sputum examination, one of the four patterns shown in Table 58 could be observed. It is evident that, if culture results are not available, serial smears alone clearly show all the different courses. Thus, in monitoring treatment, culture examinations are merely confirmatory. It is exceptional for patients receiving treatment to be consistently negative on smear yet positive on culture: the patient who is smear-positive initially either attains culture negativity or reverts to smear positivity.

It is not necessary to examine the sputum every month. WHO and IUATLD recommend monitoring progress during treatment in smear-positive patients though sputum smears on three occasions: at two months, during the fifth month, and at the end of treatment (3, 4). This allows decisions on treatment management to be made with a minimum of tests.

A laboratory report that states “sputum not obtainable” or “patient does not expectorate” by no means implies sputum smear negativity; it is important that such a report is regarded as unsatisfactory. In patients who do not produce sputum despite careful instruction, tickling the throat with a laryngeal swab or inducing sputum with

¹ Based on the chapter in the previous edition by K. Toman.

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Table 58
Interpretation of the results of sputum examination by smear and culture during tuberculosis treatment

Month	Smear	Culture	Smear	Culture	Smear	Culture	Smear	Culture
0	++	+++	++	+++	++	+++	++	+++
1	++	+	++	+	++	+++	++	+++
2	0	0	+	0	++	++	++	++
3	0	0	+	0	0	+	++	++
4	0	0	0	0	0	+	++	+++
5	0	0	0	0	++	+	+++	+++
6	0	0	0	0	++	++	+++	+++
Response	Favourable		Favourable		Fall and rise		Failure	

saline can provoke a clearing cough and sputum suitable for smear examination. Smear positivity alone, especially if the degree of positivity is declining, need not be cause for alarm.

Clinical assessment

Clinical assessment of progress is largely subjective. Disappearance of clinical symptoms, general well-being, ability to resume normal activities, and weight gain are all pointers to clinical progress. Persistence or reappearance of symptoms plus weight loss – i.e. objective clinical deterioration – indicates the need for further investigations by sputum microscopy. Erythrocyte sedimentation rate and other tests are unreliable and unnecessary in monitoring progress. Clinical assessment is often the only means available for judging progress in extrapulmonary and smear-negative pulmonary tuberculosis: weight gain is a valuable indicator in such cases.

Assessment by radiography

Serial radiography is still preferred by many physicians. However, several studies have demonstrated that this can be very misleading for assessing the progress and eventual outcome of treatment. Patients may show radiographic improvement yet still discharge tubercle bacilli. Bacteriologically quiescent disease may be classified as treatment failure because of residual lesions on the X-ray, including cavitation. Patients with persisting bacteriological negativity could show radiographic changes that would be interpreted as deterioration by expert assessors. In a study of 112 patients with bacteriologically quiescent disease, followed up by bacteriology and radiography for 4 years, radiographic changes in 35 patients (31%) were classified as deterioration. In 12 patients (11%), an increase in cavitation or appearance of cavitation was recorded. Clearly, assessment by radiographic changes alone can be very misleading (5).

Summary

Microscopic examination of the sputum smear is a reliable and inexpensive method for assessing the results of treatment in initially smear-positive patients. Radiographic and clinical evaluations are unsatisfactory for assessing progress. Smear microscopy is also a valuable guide to progress and outcome: Examination of smear-positive patients at 2 months, 5 months, and at the end of treatment will give a good indication of the success of treatment in large-scale treatment programmes. Follow-up smears provide reliable information about patient progress and programme performance. However, the individual patient benefits from bacteriological assessment only if, in the event of treatment failure, another course of treatment with an effective regimen can be provided.

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58. How effective is tuberculosis treatment and what are the needs for the future?¹

*T. Santha*²

The introduction of effective antituberculosis drugs brought about a revolution in the management of tuberculosis. From the era of bedrest, good food, and fresh air in a sanatorium – the best that the pre-chemotherapy era had to offer to a selected few – tuberculosis can now be treated effectively in the patient’s home, without interfering with normal life or work (see “What were the main findings of the Madras study comparing home and sanatorium treatment?”, page 173). Currently recommended regimens can achieve 90–95% relapse-free cure rates, not only in controlled clinical trials but also under programme conditions.

In previously untreated patients who take treatment regularly and completely the following results can be achieved:

- Standard treatment for 18 months, with three initial drugs for 2 months but without rifampicin, has a potential cure rate of 96% and a relapse rate of less than 3%. However, it has generally not been possible to implement this regimen on a mass basis (see “What is the optimum duration of treatment?”, page 144).
- Short-course chemotherapy of 6–8 months’ duration, including rifampicin at least in the intensive phase, can achieve cure rates of 97–99% and a relapse rate of less than 6% (see “What is the optimum duration of treatment?”, page 144).
- Patients who have relapsed can achieve more than 80–90% cure if treated for 8–9 months with five drugs, including rifampicin, during the intensive phase and three drugs in the continuation phase, since more than 80% of the relapses occur with drug-susceptible organisms (1).
- In patients who had incomplete prior treatment, response will depend upon the drugs and dosages given during the prior treatment and the duration of treatment since these factors influence subsequent drug susceptibility (2). In well-performing programmes, 70–80% of these patients are cured (3).
- Smear-positive patients who have failed a directly observed short-course treatment or re-treatment regimen have a low probability of cure with regimens that include

¹ Based on the chapter in the previous edition by K. Toman.

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only first-line drugs, as the probability of resistance to several of the drugs is high. Treatment of these patients with reserve drugs for a long period (18–24 months) can achieve relapse-free cure in two-thirds of them at best (see “What reserve regimens are available and what is their place in tuberculosis control programmes?”, p. 215).

On the whole, the efficacy of current treatment regimens is high: a patient who adheres to treatment has a greater than 98% chance of cure, generally with only one course of treatment. Most patients who default or relapse can be cured with a re-treatment regimen. Thus, there is little potential for new drugs to increase cure rates. However, new drugs could promote tuberculosis control by reducing the duration or frequency of treatment.

Lack of treatment success in practice is most often due to failure to ensure correct treatment, rather than to failure of correctly applied treatment (see “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185, and “How frequently do patients stop taking treatment prematurely?”, page 181). In poorly organized programmes, more than 30% of patients default. Treatment irregularity is common, particularly if drug intake is not observed and if drug supply is not regular, free of charge, and easily accessible to the patient. Death during treatment (all causes) may be high because of HIV infection or delayed diagnosis.

Much can be gained by improving operational aspects of tuberculosis control programmes (see “What is DOTS?”, page 241). However, development of new drugs could substantially facilitate programme implementation. A longer period between intermittent doses (see “What is intermittent treatment and what is the scientific basis for intermittency?”, page 130) would reduce the frequency of patient visits and facilitate observation of drug intake – but two or three highly effective drugs with the same efficacy and half-life are required. More effective drugs, in addition to isoniazid and rifampicin, could shorten the initial intensive phase, overcome drug resistance, and reduce the risk of death during the initial weeks of treatment.

The principal problem remaining today is that available drugs have little or no action on quiescent bacilli (see “How does tuberculosis treatment work?”, page 102). The purpose of the second phase of treatment is to eliminate bacilli that reproduce slowly or occasionally, much like the effect of preventive treatment in persons infected with *Mycobacterium tuberculosis* who do not have disease. A drug capable of acting on latent tubercle bacilli, or an immunomodulator able to improve the capacity to destroy those bacilli, would shorten treatment duration. Shorter treatment would reduce default and increase cure rates and also reduce the work and cost of maintaining patients on treatment.

These are some of the areas of research now being explored. However, with the present technology and good programme organization, most tuberculosis patients can be cured, most sources of tuberculosis infection can be rendered noninfectious in a few days or weeks of treatment, and most tuberculosis patients can be cured. If a

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sufficient proportion of the sources of infection in the community are detected and treated, the prevalence and transmission of tuberculosis, and the resulting mortality, can be reduced rapidly.

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59. Is primary drug resistance a menace to the control of tuberculosis?¹

M. Espinal² & T. Frieden³

In the early days of chemotherapy, regimens were often inadequate, irregularity of treatment was common, and failure rates were high. As a result, the prevalence of patients with chronic pulmonary tuberculosis discharging drug-resistant organisms increased. It was generally feared that these patients would infect the community to such an extent that primary drug resistance (see “What are the different types of drug resistance?”, page 198) might become an epidemiological and clinical problem similar to that of penicillin resistance in staphylococcal disease. Alarming figures of drug resistance in 50% or more of newly attending patients were reported, mainly from developing countries, where, in fact, most of these patients had (concealed) treatment failure and thus had acquired – not primary – resistance.

It was not possible to compare the data from different clinical reports or surveys, mainly because of the considerable differences in laboratory techniques, criteria of drug resistance, and methods of selecting groups of patients for examination.

The WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance overcame these methodological concerns. Epidemiological surveys were conducted between 1994 and 1999 in more than 72 countries/areas using stringent methods, including population-based representative sampling, careful differentiation between new and previously treated cases, standard laboratory methods, and an international proficiency testing programme (1). Trends were available from 28 countries/areas.

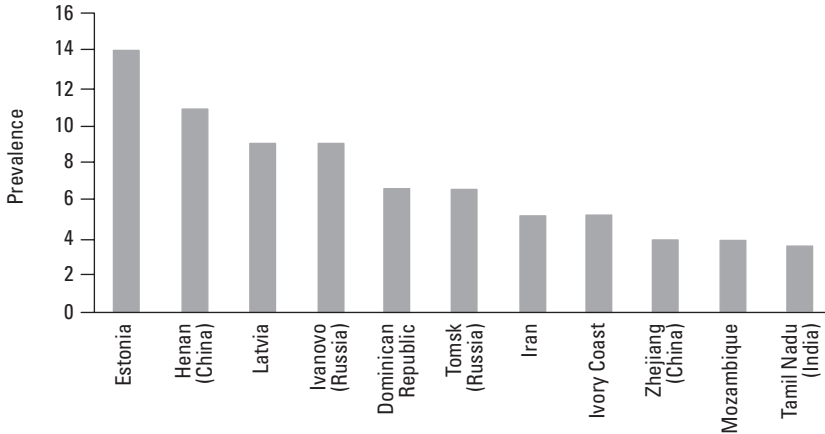
Of 65 of the countries/areas surveyed, 11 showed a relatively high prevalence of multidrug-resistant tuberculosis (see Figure 20). The remaining sites surveyed showed no signs of a major problem, suggesting that multidrug-resistant tuberculosis is far from universal. While a high prevalence of streptomycin resistance was documented in many countries, this finding is of limited significance as the use of streptomycin is being abandoned for treatment of new patients by many of these countries (2). A high prevalence of resistance to isoniazid – but not to rifampicin or ethambutol – was also documented.

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Figure 20
Countries/areas with the highest prevalence of multidrug-resistant tuberculosis within the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance^a



^a Source: reference 1.

Table 59 gives information on the distribution of resistance among new cases of tuberculosis.

Information from 28 countries/sites that had conducted two or more comparable surveys showed no evidence of increasing drug resistance among new cases (i.e. primary resistance) between 1994 and 1999. As far as trends can be observed, there is an indication that the levels are fairly stable in most areas.

Systematic surveillance and mathematical models suggest that the number of new tuberculosis cases found to be drug-resistant, especially multidrug-resistant, will remain low in most parts of the world (4). This prediction follows from the assumption that multidrug-resistant strains of *Mycobacterium tuberculosis* have a relatively low genetic fitness (either less transmissible or less likely to cause infectious tuberculosis if transmitted) compared with drug-susceptible strains. Relative fitness is measured by dividing the odds of finding a resistant strain in a restriction-fragment length polymorphism cluster by the odds of finding a susceptible strain in a cluster. With low relative fitness, multidrug-resistant strains would be, on average, less likely to persist in self-sustaining transmission cycles, and new multidrug-resistant cases are generated mainly as the by-product of low cure rates among drug-susceptible or mono-resistant cases.

High default rates can lead to high rates of multidrug-resistant tuberculosis among new cases as seen, for example, in Estonia, Latvia, and parts of the Russian Federation. Under these circumstances, the main remedy is to ensure high cure rates for drug-susceptible or mono-resistant disease. Reserve drugs would be needed to treat

Table 59
Resistance to one or more drugs in 58
countries/settings surveyed between 1996 and 1999
among newly diagnosed, previously untreated
patients^a

Strains	Median	(Minimum, maximum)
Total examined	474	(41, 12 063)
Total resistant	10.7%	(1.7, 36.9)
Resistant to any one drug	7.0%	(1.3, 17.9)
Resistant to isoniazid	3.0%	(0, 7.9)
Resistant to rifampicin	0.2%	(0, 2.0)
Resistant to streptomycin	2.5%	(0, 14.5)
Resistant to ethambutol	0.5%	(0, 3.0)
Resistant to two drugs	2.5%	(0, 11.9)
Resistant to three drugs	0.6%	(0, 7.3)
Resistant to four drugs	0.1%	(0, 8.5)
Multidrug resistance ^b	1.0%	(0, 14.1)

^a Source: reference 3.

^b Resistance to at least isoniazid and rifampicin.

individual multidrug-resistant tuberculosis cases, but whether they would be needed to contain an epidemic of multidrug-resistant strains will depend on the relative fitness of the specific strains, the characteristics of the host population, and environmental factors (e.g. crowding) that influence transmission dynamics. In an extreme case, a highly fit strain of multidrug-resistant tuberculosis has been reported as having spread rapidly and extensively among severely immunosuppressed AIDS patients hospitalized under conditions of inadequate infection control (5). Similarly, it is likely that certain strains of multidrug-resistant tuberculosis could spread widely among malnourished prisoners housed in overcrowded conditions (6). In such settings, reserve drugs might well be needed to contain an epidemic of multidrug-resistant tuberculosis. In contrast, it is far from certain that strains of multidrug-resistant tuberculosis could cause a self-perpetuating community-wide epidemic, particularly in the absence of significant immunocompromise.

There is now adequate evidence that, with standard treatment, the prognosis for patients with primary resistance to one drug – provided that it is not rifampicin – is almost as favourable as that for patients with susceptible organisms (7). Only a very high level of primary drug resistance in a population can substantially reduce the overall success rate of standard two-phase treatment including an initial phase of four drugs daily. There is thus no reason to assume that primary drug resistance is becom-

ing a greater danger to the community than the current danger of exposure to infection with drug-susceptible organisms.

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60. What are the keys to cure?

*K. Toman*¹

How is it that cure rates in many areas are still low, despite the extraordinary potency of present-day treatment?

Some physicians believe that high success rates can be achieved only in certain outstanding treatment centres and that success rates will remain low unless more effective drugs are introduced. This is a rather superficial view. For more than 25 years, there have been drugs from which nearly 100% effective, inexpensive, non-toxic, and accessible regimens can be composed. Thus, the key to cure lies not in the introduction of new and better drugs or regimens but elsewhere (see “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185).

An important technical requirement for successful treatment is the prescription of adequate regimens, i.e. only those whose efficacy has been established by controlled trials. A regimen should contain at least two drugs to which the patient’s bacilli are susceptible. The chosen drug should be given in the same dosage, at the same rhythm (daily or intermittently), and for the same period as was done in controlled trials. Deviations from this rule that have no scientific basis and that cannot be clearly justified should be regarded as malpractice.

Another technical, almost axiomatic, prerequisite is the regularity of drug intake. Since the advent of treatment, many changes have taken place. Drug combinations and dosages have been varied and the rhythm of administration and duration of treatment have changed, but the need for regularity of drug intake persists. No new regimen or drug has been able to overcome the necessity of long-term regularity, and interruption of the regular rhythm of treatment increases the risk of failure. It must be borne in mind that the main reason for treatment failure is not drug resistance but the irregularity of drug ingestion.

It is illusory to expect that new drugs will solve the main problem of treatment, unless a regimen can be found that needs to be administered in one injection or only for a few days. The success of treatment is determined as much by operational as by technical factors.

¹ Deceased.

Even the most effective regimens currently available, irrespective of the drug combination or duration of treatment, may fail if not administered regularly. Thus, today it is not the lack of knowledge about adequate treatment but its adequate administration (1) that is the crux of the matter (see “Why does treatment fail and what can be done to avoid poor treatment outcome?”, page 185). This is one of the problems that can be solved not by technical or medical means but mainly by organizational measures. Ensuring regular drug intake is a managerial task *par excellence*, and it has rightly been stated that the control of tuberculosis is basically a management problem. Nearly all attempts to ensure adherence through health education – for example, by thoroughly instructing patients about the importance of regularity and the poor prognosis in case of irregularity – have been insufficient to motivate patients to take their drugs regularly as prescribed (see “How frequently do patients stop taking treatment prematurely?”, page 181). Verbal motivation of patients is rarely successful unless applied in an adequate organizational framework satisfying certain operational requirements.

Operational requirements

Treatment services must be easily accessible. Patients who feel very ill may be willing to travel long distances in order to be seen by a reputed physician. However, they can rarely repeat such travel or stay at the place of treatment for a long time. Treatment services should therefore be within easy reach and be free of charge (2, 3).

Treatment services should be acceptable to and utilized by the community. Health staff should be able to communicate with patients in their own language and should be sympathetic to their complaints and needs. Patients should be helped to handle the problems causing default. Services must be compatible with local beliefs, traditions, and habits, and should also be efficient. In short, they should inspire confidence (see “What is the significance of default (treatment interruption) in the treatment of tuberculosis?”, page 263).

Drugs should always be available in sufficient quantities. When patients have to be turned away because drugs are out of stock, the effect on treatment regularity is bound to be detrimental.

Treatment should be directly observed. This means that each dose should be administered under the direct observation of a trained, accountable individual. It is particularly important when rifampicin is included in the regimen, and especially in the intensive phase of treatment when the bacterial load is highest. However, it is not always easy to organize such treatment for every patient. In many instances, individual arrangements for treatment observation will have to be made. Sometimes the observation of treatment will have to be delegated to other institutions or individuals, e.g. to a hospital or health post located close to the patient’s workplace or home.

In summary, treatment must be organized with a view to the patient’s convenience rather than to the convenience of the treatment service.

At present, the key to cure is to be found in the organization of treatment delivery. The success rate of even the best available regimen will be low if treatment

services are not focused on the cooperation of patients. On the other hand, even a second-best regimen may be highly successful if treatment is delivered with adequate organization.

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61. What is the significance of default (treatment interruption) in the treatment of tuberculosis?¹

N. Bock²

The most important cause of tuberculosis *treatment failure* among detected patients is non-completion of treatment, or default. The most important cause of tuberculosis *programme failure* is a low rate of treatment completion, as defaulting patients continue to transmit tuberculosis in the community, sometimes with acquired drug resistance. Treatment success rates of at least 70–85% are necessary to ensure a substantial reduction in the incidence of tuberculosis (1). Systematic cohort analysis frequently reveals that less than half of patients who start treatment actually complete it.

Treatment regimens capable of curing almost every tuberculosis patient have been available for more than 40 years, yet a large proportion of the patients detected have not been successfully treated. In a 1964 report of a community-based tuberculosis treatment programme in southern India using a regimen of isoniazid plus *p*-aminosalicylic acid (PAS), only 64% of 123 patients were culture-negative after 12 months although the regimen was capable of a 90% cure rate (2). The low level of success was attributed to failure of the health delivery services to maintain patient adherence to treatment. By the end of the 12-month period 27% of patients had refused treatment, 10% had died or moved, and fewer than half of the remainder had collected at least 80% of their medication.

A comparison of the results of a triple-drug treatment regimen (streptomycin + thioacetazone + isoniazid) in routine health delivery services versus controlled clinical trials, both in Kenya, indicates the importance of both default in treatment failure and organization of treatment services in treatment success (3). The triple regimen achieved culture negativity at 1 year in 96% of patients in controlled clinical trials, but in only 76% of those in routine health delivery services. The proportion of patients completing 12 months of continuation-phase treatment in the well-organized clinical trial programmes was 91%, compared with 51% of those receiving routine services.

¹ Based on the chapter in the previous edition by K. Toman.

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Treatment interruption is a major challenge in almost all areas. In New York City, for instance, only 11% of patients who started on treatment as inpatients in one hospital in 1988, before improvement in the tuberculosis control programme, were shown to have completed treatment (4). Failure to achieve high completion rates was a factor underlying both the striking increase in tuberculosis in New York City and the emergence of drug resistance in the USA in the late 1980s and early 1990s (4–6). Patient factors that have been associated with default range from inadequate understanding of the treatment regimen (7) and fear of discrimination due to the stigma associated with tuberculosis (8) to financial burden or travel distance to the clinic (9). Health system factors include unreliable drug supply, inconvenient clinic hours, inadequate patient education and support by staff, and poor staff motivation (10).

After 1 or 2 months of effective treatment, the patient feels symptom-free. From that moment it seems pointless to the patient to take medication that may be unpleasant and give rise to minor adverse effects that cause more discomfort than the disease itself. It is only natural to enjoy the recovery and stop taking medication.

Discontinuation of treatment has also been observed in a number of other conditions that require prolonged drug ingestion, such as cardiovascular diseases, rheumatic fever, leprosy, epilepsy, diabetes, and malaria prophylaxis. It is also true of the self-administration of oral contraceptives.

The dictionary definition of default is failure to do something required by duty or law. When default might cause harm to the individual or community, corrective or preventive action should be taken. In the case of a tuberculosis patient, irregularity or premature cessation of treatment usually has serious consequences not only for the patient but also for the community as a whole. It is the moral, if not the legal, duty of the health services to take the necessary precautions. However, since the interruption or self-termination of treatment is a common feature of human behaviour, these precautions must be an essential part of the treatment strategy – a built-in element of treatment organization. Prevention and management of default are integral components of treatment and are thus – principally and undeniably – the responsibility of the doctor or person in charge of treatment. The DOTS strategy shifts the ultimate responsibility for patient cure from the patient to the health system. Therefore, if treatment failure is due to default, it is unjust to hold the patient primarily responsible.

As long as the organizers of treatment services do not accept this responsibility, even the most effective drug regimens will fail to produce the high level of therapeutic and epidemiological success of which they are capable.

However, it is easier to identify than to remedy the causes of default. Many health professionals believe that health education of the sick and of the public is all that is needed to ensure compliance with medical instructions. Unfortunately, experience has shown that such efforts, or even detailed instructions by a doctor, are generally insufficient to motivate patients to take the prescribed regimen.

There is far more to motivation than informing and instructing people: it is a matter of human relations and requires an understanding of the patient's non-medical

problems, way of life, work, beliefs, wants, fears, and attitudes towards traditional and modern medicine. Motivation requires a person to speak the patient's "language" and bridge intellectual and social distances, remove cultural barriers, and change attitudes and habits. Positive motivating factors are efficient professional performance, good working morale, compassion, and staff's identification with the community they serve.

In summary, motivation is a problem of human communication, differing from one patient to another and one community to another. That is why no uniform and generally applicable recipe can be given. Failure to communicate with the patient, a patronizing approach, or disrespectful behaviour will alienate the patient and create distrust, resulting in the rejection of treatment.

The only means of ensuring that treatment is taken as prescribed is by direct observation (see "What are the advantages of direct observation of treatment", page 183). In an effective programme of direct observation, each patient's needs and concerns are addressed and a human bond between the patient and the treatment observer is established so that the risk of default is minimized.

Among 725 275 smear-positive cases reported to WHO in the 1998 cohort and receiving standardized short-course treatment in a DOTS programme, the global default rate was 6% (11). Considering patients who were not evaluated as defaulting, the default rate among those treated in a DOTS strategy programme was less than one-quarter of that among those treated in non-DOTS programmes (11% vs 58%). Thus, the DOTS strategy, if successfully applied, can address the health system organizational problems that are factors in default.

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62. How important is follow-up and what is the frequency of relapse after the completion of treatment?¹

*T. Santha*²

Relapse is defined as “a patient previously treated for tuberculosis who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis” (1).

Before the advent of treatment, the complete cure of smear-positive pulmonary tuberculosis was seen only rarely. Pathologists and clinicians maintained that the disease practically never healed in the strict sense of the term, but could only be arrested, become stabilized, or rendered inactive. Since bacilli almost always persisted in the residua of tuberculosis lesions, relapse was common, and that was the reason for the adoption of a policy of lifelong follow-up of patients who had completed treatment. These patients were kept on a register and examined regularly at intervals of several months, or at least once a year. That routine, however, placed a steadily increasing burden on the health services, absorbing a substantial proportion of staff time and financial resources. The dramatic success of treatment called into question the usefulness of indefinite follow-up and prompted demands for the reassessment of this policy. For that purpose, two questions needed to be answered:

- What is the frequency of relapse?
- How is relapse detected?

In a longitudinal survey and analytical studies, it was found that relapse still accounted for about 15–20% of the annual incidence of newly registered infectious cases (2–4). Controlled clinical trials in which patients were followed up regularly for 2 years or more have shown that the frequency of relapse is around 3–7% with standardized short-course chemotherapy. Similar results were obtained with either a 6-month regimen using rifampicin throughout the treatment period or 8 months if rifampicin was given only in the initial intensive phase of treatment. Approximately 80% of the relapses occur within the first 6 months of stopping treatment (5). More than 80% of relapses occur with organisms susceptible to the tuberculosis drugs used earlier (6) and hence their re-treatment does not pose a problem.

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It was also found that the individual risk of relapse among persons with a history of bacteriologically confirmed tuberculosis varied substantially and was determined mainly by three factors:

- whether treatment had been received or not (in case treatment was not given, the patient would be considered to have recurrent tuberculosis, not to have relapsed);
- whether or not the regimen given was adequate and regularly taken; and
- the time that had elapsed since smear/culture conversion to negative was achieved.

The highest relapse rate is found in patients who have never received any treatment (about 5% per annum) and the next highest rate (about 2%) in patients with prior inadequate treatment (7). After 3–5 years, the risk in both groups diminishes appreciably, to about 1% (7).

The most important finding was the striking effect of adequate treatment on relapse, which falls to a few per million per annum (8, 9). Although the risk is still considerably higher than the risk of disease in persons with no history of previous tuberculosis, it does not warrant lifelong follow-up. Moreover, even with active monitoring, relapses were mostly discovered on account of symptoms rather than during routine follow-up examination. In a longitudinal survey lasting 12 years, each person with a history of tuberculosis was examined bacteriologically every 6 months and by X-ray once a year. Less than half of the relapses were discovered through follow-up examinations, despite a stringent research discipline.

In patients who have been adequately treated, the risk of relapse is too small to justify prolonged follow-up (10). Thus, routine follow-up examinations are generally unnecessary. This conclusion was reached by the Centers for Disease Control of the Public Health Service in the USA (11), as well as by investigators who followed up patients treated in Scotland (12). The former stated (11): “Tuberculosis patients who complete adequate chemotherapy should be considered cured. They have no need for routine lifetime periodic recall for X-ray examination. Indeed, perpetuating life-time follow-up of such treated patients diverts clinic personnel and resources from the crucial task of providing services for those who really need them.”

However, ex-patients should be strongly advised to come for examination without delay if they develop symptoms suggestive of tuberculosis (10). General practitioners and physicians who are likely to encounter patients with a history of previous tuberculosis should be informed about the possibility of relapse and the need to promptly evaluate recurrent respiratory symptoms (such as prolonged cough). However, it should also be understood that, among symptomatic ex-patients, cough is more the result of irreversible, bacteriologically quiescent lung damage than of recurrence of active tuberculosis disease (13).

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63. Why is a recording and reporting system needed, and what system is recommended?

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The recording (patient registration) and reporting system is used to systematically evaluate patient progress and treatment outcome, as well as overall programme performance, and to identify problems that need to be solved (1, 2). It is a fundamental principle of effective tuberculosis control that the programme is responsible for monitoring and reporting outcomes of every patient started on treatment, without exception – “no cheating”. It is common for specialized institutions or individual physicians to believe sincerely that a high proportion of the patients they place on treatment are cured, but for systematic evaluation to reveal that only a minority of patients – not infrequently, a small minority – actually complete treatment (3).

What is the recommended recording system?

The recommended recording system consists of:

- a tuberculosis laboratory register that includes data from all patients who have had a sputum smear examination;
- patient treatment cards that detail the regular intake of medication and follow-up sputum examinations; and
- the tuberculosis register, which lists *every* tuberculosis patient and monitors individual and collective progress toward cure (1, 4) (some countries register only tuberculosis patients who start treatment).

Tuberculosis laboratory register

The laboratory technician records patient details in the tuberculosis laboratory register with a serial identification number. The results of the sputum examination are then recorded in the general health facility where the patient is registered for treatment. From tuberculosis laboratory registers and routine clinic records, the proportion of outpatients (attending health facilities for any reason) examined and the

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proportion of patients examined for diagnosis who are found to be smear-positive can be easily monitored.

Patient treatment card

Each person with a diagnosis of tuberculosis (smear-positive, smear-negative, or extrapulmonary) has a patient treatment card. This card records basic epidemiological data (age, sex, etc.), clinical information (type of patient, category of treatment, smear result, weight), and the administration of drugs. Each card also gives information on the patient's address and treatment centre; this is useful in case the patient does not attend scheduled treatment. The health worker uses the patient treatment card for recording the treatment given and the results of follow-up sputum examinations. During the continuation phase and at the end of treatment, patients submit sputum samples for microscopy to ensure that they become – and remain – negative and are thus declared cured of tuberculosis. These results, along with follow-up patient weight, are also recorded on the treatment card.

Tuberculosis register

The health care worker responsible for supervising each administrative area or institution uses the tuberculosis register to monitor progress and treatment outcome for *all* patients in that district. This provides the district or local health director with rapid, continuous feedback on programme performance in the district. Each patient's address and treatment centre are also recorded, facilitating the tracing of patients who interrupt treatment.

What is cohort analysis?

Cohort analysis refers to the systematic assessment and reporting of standard outcomes of treatment. A cohort of tuberculosis patients consists of patients registered during a certain time period, which is usually a quarter of a year (i.e. 1 January to 31 March, 1 April to 30 June, 1 July to 30 September, and 1 October to 31 December). Sputum smear-positive pulmonary tuberculosis patients (the infectious cases) form a separate cohort from sputum smear-negative and extrapulmonary tuberculosis patients. For smear-positive pulmonary tuberculosis patients, the standard outcomes of treatment reported are cure, treatment completion, treatment failure, death, treatment interruption (default), and transfer out. In smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis patients, cure cannot be assessed systematically because the outcome indicators depend on the sputum smear examination. For these patients, therefore, treatment completion, death, default, failure, and transfer out are recorded in the tuberculosis register. New and previously treated patients form separate cohorts.

Cohort analysis is the key management tool for evaluating the effectiveness of tuberculosis control activities in any area. It enables the identification of problems so

that the programme can institute appropriate action to improve performance. The quarterly report on case detection rapidly identified poor-quality diagnosis, so that diagnostic practices can be promptly improved. The quarterly smear conversion report and quarterly and annual treatment success rates (percentage of patients who are cured plus those who complete treatment) provide any middle- or upper-level manager with timely, concrete indicators of achievements or of problems requiring action. Examples of problems include low cure rate, high default rate, higher-than-expected proportion of sputum smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis, and lower-than-expected case-detection rate.

The recording and reporting system allows for targeted, individualized follow-up to help patients who are not making satisfactory progress, and for rapid managerial assessment of the overall performance of each institution, district, region, or country. The system ensures systematic accountability, and its inherent internal and external cross-checks make false reporting difficult to perform and easy to detect. For example, the laboratory number appears on the tuberculosis laboratory register, the patient treatment card, and the tuberculosis register. These three records are often kept in different health units, which would make false reporting logistically difficult, particularly as the tuberculosis and laboratory registers may contain hundreds or even thousands of records.

What is the recommended reporting and monitoring system?

Monitoring of treatment outcomes by cohort analysis takes place about 3 months after all patients in the cohort should have completed their course of treatment. The tuberculosis officer should perform cohort analysis of treatment outcome every quarter and at the end of every year. Quarterly reports on treatment outcome are forwarded to the intermediate level (e.g. region). The tuberculosis officer at this intermediate level verifies that local reports are correct, complete, and consistent, compiles cohort analysis reports on all patients in the area, and submits the report to the central unit of the national tuberculosis control programme. The national programme compiles cohort analysis reports on all tuberculosis patients registered nationally. The World Health Organization collects and publishes summary, consolidated data annually and, in some regions, quarterly (5, 6).

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64. When should tuberculosis patients be hospitalized, and how infectious are tuberculosis patients while on treatment?¹

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For most tuberculosis patients, successful treatment can be given entirely in an outpatient setting, without significant risk of tuberculosis transmission within the community. In situations where this is possible, a policy of routine hospital admission for tuberculosis treatment is unnecessary – and even anachronistic.

There is a solid body of evidence that outpatient treatment is as effective as inpatient treatment, even for patients with extensive disease and living in poor conditions. In the classic Madras study (see “What were the main findings of the Madras study comparing home and sanatorium treatment?”, page 173), 163 patients with pulmonary tuberculosis were randomized to care either in their homes or in a sanatorium (1). Conditions in the sanatorium included prolonged bedrest, nutritious diet, nursing services, and a well-ventilated and clean environment, which had been advocated as conducive to healing tuberculosis. After 1 year of treatment with isoniazid and *p*-aminosalicylic acid, compliance and clinical, radiographic, and bacteriological responses were equivalent in the two groups. A total of 126 patients were followed for 5 years and no difference in the rate of relapse was observed between the home-treated and sanatorium-treated patients (1).

Following this and other controlled trials in both developed and developing settings (2–4), there has been increased emphasis on outpatient management of tuberculosis (5). Nevertheless, hospitalization of tuberculosis patients remains a common practice in some settings (6, 7), and may even be increasing (8, 9). A reason often cited for initial hospitalization is concern that the patient is infectious and must therefore be isolated from family and community. It is currently impossible to determine exactly when an individual patient becomes non-infectious. However, most patients with disease due to drug-susceptible organisms become non-infectious within several days to weeks after treatment is started, and the risk of infection to contacts is therefore greatly reduced (10). During the 5-year follow-up period of the Madras study, close

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contacts of the tuberculosis patients were observed for skin-test conversion and the development of tuberculosis (11). The tuberculin-negative contacts of patients treated at home were no more likely to convert to positive than the contacts of those in the sanatorium. Moreover, tuberculosis developed no more frequently in contacts of home-treated patients (10.5%) than in contacts of patients treated in the sanatorium (11.5%). Most cases of tuberculosis developed within the first 3 months, suggesting that infection occurred before the start of treatment (11). Additional studies support this landmark finding (12, 13).

There are national and international guidelines that recommend hospitalization for tuberculosis patients who cannot be managed on an outpatient basis (10, 14, 15).

Occasionally tuberculosis is diagnosed while a patient is in hospital, whether or not symptoms of tuberculosis led to the admission; in other words, tuberculosis may be an incidental finding. The indications for admission to or continued stay in hospital related to tuberculosis are similar to those for any other disease. These include potentially life-threatening conditions such as miliary/meningeal disease, adult respiratory distress syndrome, intravascular coagulation, severe haemoptysis, and severe reaction to drugs. Infectiousness is not now, in itself, an indication for confinement in the hospital, except in rare cases (16). However, while it may be appropriate to return a patient to home and family, special circumstances – such as army barracks or crowded correctional facilities – make isolation (in a hospital or elsewhere) advisable until the patient is asymptomatic and has negative or decreasingly positive acid-fast bacilli smears (17). Some programmes recommend that, if patients would be discharged to congregate living situations (e.g. shelter, nursing home, jail, prison, or group home), and in other selected situations, they remain in hospital until they are smear-negative (18).

In a few select circumstances, hospitalization or institution-based treatment may be preferable to outpatient treatment. For example, there are limited data to determine when patients with isoniazid- and rifampicin-resistant (multidrug-resistant) tuberculosis become non-infectious after the start of appropriate reserve drug treatment. In a series of multidrug-resistant tuberculosis patients who responded to treatment at the National Jewish Hospital, the interval from start of treatment to the first of a series of negative cultures ranged from 1 to 8 months (median 2 months) (19). Contacts of infectious multidrug-resistant tuberculosis patients who become infected with multidrug-resistant strains and who develop active disease require longer and more costly treatment, have a lower likelihood of cure, and are at greater risk of death (20–22). Given that multidrug-resistant tuberculosis patients may be infectious for longer, hospitalization may have a role in treatment when multidrug-resistant tuberculosis patients are likely to have close contacts, particularly young children and immunocompromised persons.

Good infection control policies and practices must be in place in facilities where such patients are treated (see “What is nosocomial transmission of tuberculosis and how can it be prevented?”, page 278). Outbreaks of multidrug-resistant tuberculosis

can occur in hospitals in both developed and developing countries if good infection control policies are not practised (2–25). Reported outbreaks, mostly among patients infected with the human immunodeficiency virus, resulted in high mortality.

The American Thoracic Society (26) has said: “In summary in this era of chemotherapy, tuberculosis should be treated in whatever setting most appropriately meets the needs of the patient and the community. Some patients can be entirely treated at home. Others may require some short period of hospitalization in a general hospital followed by ambulatory care. Still others may require longer-term care in an institution mainly because of their other medical and social problems. The fact of tuberculosis should not be the primary determinant of the local care, nor should it act as a constraint. Continuity and completion of chemotherapy are the keys to recovery wherever the care is provided.”

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65. What is nosocomial transmission of tuberculosis and how can it be prevented?

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Nosocomial transmission of tuberculosis is the spread of *Mycobacterium tuberculosis* from a patient with active tuberculosis to other patients or health care workers in a health care setting. Investigation of large outbreaks of multidrug-resistant tuberculosis in hospitals in the USA in the late 1980s and early 1990s (1–5) found that transmission occurred because of delays in diagnosis and treatment of patients with active tuberculosis and lack of appropriate infection control measures. In addition, many of the patients were infected with HIV, and there was a very high mortality rate. HIV-infected persons who are exposed to and infected with *M. tuberculosis* may progress rapidly to active tuberculosis. Delays in the diagnosis and treatment of these secondary cases facilitated further transmission and contributed to the poor outcomes in these patients.

Several studies have demonstrated an increased risk of nosocomial transmission of *M. tuberculosis* to health care workers in Africa, South America, and Asia (6–12). These health care workers included nurses, physicians, nursing and medical students, and laboratory technicians. The risk was greatest among those who had the closest and longest duration of contact with tuberculosis patients. The studies suggest that the greatest risk for nosocomial transmission is from the patient whose tuberculosis has not yet been diagnosed or treated.

Transmission of *M. tuberculosis* can be prevented or reduced by implementing certain infection control measures (13). There are three levels of control:

- administrative controls to help reduce exposure of patients and health care workers to *M. tuberculosis*;
- environmental controls to reduce the concentration of organisms in the air; and
- personal respiratory protection to help protect workers in certain settings when the concentration of organisms cannot be sufficiently reduced by administrative and environmental controls.

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Administrative controls are by far the most important; environmental controls and personal respiratory protection will be ineffective in the absence of good administrative controls.

Administrative controls should receive the highest priority in any tuberculosis infection control programme. Some basic administrative controls should be implemented in all health care facilities, and additional controls are recommended for larger, referral-level facilities. The most important administrative control in all settings is having appropriate policies and procedures in place to facilitate early diagnosis and treatment. Tuberculosis should be suspected in patients who have symptoms of, or risk factors for, tuberculosis. When tuberculosis is suspected, a diagnostic evaluation should be initiated promptly and the results should be returned in a timely fashion so that treatment can be initiated. Ensuring that all medications are taken under direct observation and that treatment is continued and completed after hospital discharge is essential to prevent disease recurrence and subsequent readmission of patients with infectious tuberculosis.

Additional administrative controls recommended for all settings include:

- assessing the risk for transmission in different areas of the facility;
- developing an infection control plan;
- training health care workers in tuberculosis, its transmission, and their role in implementing infection control measures to reduce the risk of transmission;
- educating patients about the importance of covering their mouths when coughing;
- collecting sputum in well-ventilated areas;
- prioritizing patients with suspected tuberculosis in outpatient settings to reduce exposure in waiting areas; and
- reducing exposure in the laboratory.

In addition, the implementation of these interventions should be evaluated periodically.

For referral-level facilities, additional measures are recommended. One effective way to reduce the risk of transmission in these facilities is to promote outpatient management of tuberculosis patients. Two means of doing this are early discharge and avoidance of hospitalization altogether. Hospitalization can be avoided by ensuring prompt and appropriate referral to outpatient tuberculosis care. When hospitalization cannot be avoided, infectious tuberculosis patients should be placed in a separate ward, area, or (ideally) building of the facility. This can reduce transmission to other patients in the facility, especially when used in conjunction with administrative controls for early diagnosis and treatment. In larger facilities, two wards in a separate building, one for patients with suspected tuberculosis and one for tuberculosis patients on treatment, would be optimal. True isolation is usually not feasible because it requires expensive engineering controls. Policies and procedures for enforcing and discontinuing isolation/separation should be developed and evaluated. Consideration

should also be given to collecting data on the number of health care workers in the facility who are diagnosed with tuberculosis and information about risk factors.

Environmental controls are most appropriate for referral-level facilities. They are used to remove and dilute air contaminated with *M. tuberculosis* in tuberculosis patient areas. The simplest and least expensive environmental control is maximizing natural ventilation through open windows. Obviously, this will not be feasible in some climates. The direction of airflow can be controlled to prevent contaminated air from a tuberculosis ward from reaching other parts of the facility, but this requires more expensive measures such as window fans or exhaust ventilation systems. Ultraviolet germicidal irradiation can clean the air by killing airborne *M. tuberculosis*. Lamps are placed near the ceiling to irradiate the air in the upper part of the room without exposing patients and workers in the rest of the room, but there must be good mixing of air in the room for this to be effective. High humidity may reduce effectiveness, and precautions must be taken to ensure safe installation (13).

Respirators are special masks made of material that filters small particles (95% filter efficiency for particles 0.3 µm in diameter) and fit well. Personal respiratory protection is a lower priority than administrative or environmental controls. However, in referral-level facilities, respirators can be used as a supplement to administrative and environmental controls in certain high-risk settings, such as isolation rooms, and rooms where bronchoscopy, sputum induction, spirometry, or autopsies are performed.

These precautions are particularly important where HIV infection is common. Without them, tuberculosis can spread rapidly in AIDS wards and similar settings. HIV-infected health care workers are at risk of tuberculosis, and ideally should not be exposed to infectious tuberculosis patients.

Implementing a tuberculosis infection control programme with an emphasis on administrative controls will help to reduce transmission of *M. tuberculosis* within health care facilities, protecting not only other patients but also health care workers who are vital resources in the fight against tuberculosis.

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66. Where is tuberculosis usually spread and how can spread be reduced?

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The risk of being *exposed* to *Mycobacterium tuberculosis* depends principally on three factors:

- the number of cases capable of transmitting *M. tuberculosis* in a community (principally sputum smear-positive cases);
- the duration of infectiousness of such cases; and
- the number and duration of encounters between a source of infection and susceptible individuals.

The risk of becoming *infected* with *M. tuberculosis*, after exposure, depends on three other factors:

- the number of infectious droplet nuclei produced by an infectious case;
- the volume of air in which these droplets are contained; and
- the period over which a susceptible individual inhales air containing such droplet nuclei.

Spread of *M. tuberculosis* will therefore be most common in communities and population groups in which the prevalence of infectious tuberculosis is high, where cases remain infectious for a prolonged period of time, and where people interact frequently. Transmission is most likely to occur where the concentration of bacilli in the air is high and exposure to that air is prolonged. It will be highest where there is prolonged direct contact between infectious sources and susceptible individuals.

The risk of becoming infected after exposure outdoors differs from that following indoor exposure. Outdoors, infectious droplet nuclei rapidly disperse in an essentially infinite volume of air (and are rapidly killed by sunlight); indoors the droplet nuclei are trapped, particularly if ventilation is poor. Household contacts of an infectious case are thus at higher risk than community contacts, and among household contacts, intimate contacts are at highest risk (1).

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M. tuberculosis is thus most likely to be spread whenever the above conditions are met – in prisons, hospitals, schools, offices, aeroplanes, etc. However, the relevant epidemiological question is what settings are of major public health importance. Household contact is certainly the most frequent event: almost always when a new case emerges, a household member will have been exposed, and often in a closed environment (the house, the bedroom, etc.). At the other extreme, infection on an aeroplane (2) will be a rare event because the likelihood of an incident infectious case on board is small, duration of exposure is limited, and ventilation on aeroplanes is usually good (3).

Special populations such as health care workers are more frequently exposed to infectious cases than the general community, and are often in close and prolonged contact with cases who have not yet been identified and hence have not yet started treatment. Health care workers are thus at increased risk of tuberculosis (4). Similarly, many prisons have a high incidence of tuberculosis. In countries where a substantial proportion of the population might be sentenced to prison, contact is prolonged, the environment closed, and diagnosis of infectious cases often delayed, the transmission risk is high (5).

The means of reducing the spread of tuberculosis can be derived from the above principles. With existing technology, little can be done on a mass basis directly to prevent the emergence of incident infectious cases. The duration of infectiousness can be curtailed, however, by prompt identification and complete treatment of such cases through an effective network of diagnostic and treatment services. This is the major intervention for reducing the spread of *M. tuberculosis*. In special settings known to carry an increased risk of spread, such as prisons and health care facilities, administrative and engineering measures to improve ventilation (and thus reduce the concentration of infectious droplets) might be done at affordable cost.

The key intervention for reducing spread is the same, regardless of the setting: tuberculosis cases must be identified as swiftly as possible when they present at health care facilities with respiratory symptoms; they must be placed on effective treatment; and treatment with the required frequency and for the required duration must be ensured, so that cure is effected. This strategy most efficiently reduces the risk of exposure and infection in the community, and leads ultimately to a reduction in the emergence of new infectious cases.

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67. What are the principles and requirements of a controlled clinical trial?¹

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Conscientious physicians treat patients only with methods in which they have confidence. However, different physicians often treat the same disease in different ways. If patients recover, physicians understandably ascribe the success to their choice of treatment. How subjective and changeable these judgements are can be seen from the large number of treatment methods that are given prominence, praised by sincere advocates, and eventually consigned to oblivion. It may take a long time for the value of a certain treatment method to be determined. Gold salts, for example, had been in use for almost 20 years as a specific treatment for tuberculosis, as recommended in some 200 published papers, before it was recognized that they were useless, if not actually harmful (1, 2).

In the first half of the 20th century, innumerable therapeutic methods, diets, and compounds were used in the treatment of tuberculosis – tuberculin, other biological agents such as bacterial extracts, attenuated mycobacteria, antisera, and antitoxins, gold salts, cod-liver oil, vitamin C, calcium injections, creosote, salt-free diets, radiation therapy, and various climates (hot and dry, high altitudes, seaside locations) all had their passionate advocates (3). In addition, a host of therapeutic interventions were tried – pneumothorax, diaphragmatic paralysis, pneumoperitoneum, oleothorax, pneumonolysis, plombage, cavity drainage, thoracoplasty, and finally resectional surgery. While this is far from a complete account, it serves as a reminder of the confused of the past.

Determined efforts have been made over the past 50 years to use scientific techniques to evaluate the treatment of tuberculosis. An important advance has been the development of an assessment method known as the controlled trial. Many controlled trials have been carried out and have made it possible to establish the efficacy, toxicity, and applicability of currently recommended treatment regimens. However, some physicians still do not appreciate the value and scope of this method. There are also some authors who refer to their investigations as controlled trials without observing

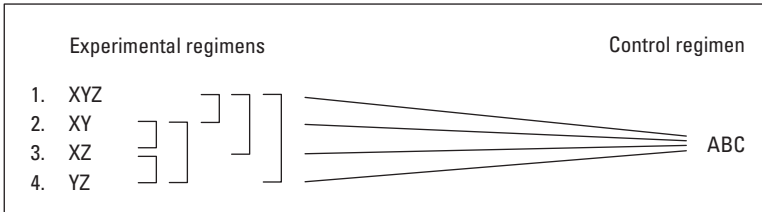
¹ Based on the chapter in the previous edition by K. Toman.

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Figure 21

Example of comparison of treatment regimens in a controlled trial

The new drugs of which the experimental regimens are composed are X, Y, and Z, the symbol for the control regimen being ABC. Four regimens are constructed from different combinations of drugs X, Y, and Z.



the essential requirements. Therefore, it might be worth recalling the main features of the method.

The method

In a controlled trial, two or more equivalent groups of patients are formed. One group – the controls – remains untreated or receives a treatment of known effect, while the other – experimental – groups receive the treatments to be studied. (It is unethical to have an untreated group for a disease if effective treatment is available.)

Nowadays, the control group usually receives a standard robust regimen, with almost 100% efficacy and minimal relapse rates. If a control regimen is not included in the study, the protocol must specify which regimen – of known effectiveness – will be used as the control.

By using certain study schemes known as factorial designs, it is possible not only to measure the effects of the tested regimens, but also to identify the separate contribution of each drug provided that the drugs do not interact (4). See Figure 21.

Using such a design, 10 different comparisons can be made. Each experimental regimen can be compared with the control regimen. Comparing the experimental regimens with one another allows the individual contributory effect of each drug or factor, as well as the relationships between them, to be studied in terms of bacteriological and radiographic response, adverse effects, emergence of drug resistance, and relapse rate. The comparisons may also reveal synergistic or antagonistic interactions between the drugs or factors under study.

Ethical considerations

There are critics who reject controlled trials with generalizations such as: "Conducting controlled therapeutic trials is experimenting on people and is thus unethical." However, such statements disregard the fact that the prescribing of any treatment that

is not supported by quantified evidence of the benefits and risks is effectively experimenting on people. Moreover, it is experimentation with a treatment whose effects will remain uncertain. Unless the disease treated is known to be fatal, unavoidable bias may easily result in errors, and it is now widely accepted that it is neither ethical for the doctor nor safe for the patient to use a new treatment that has not been tested in a controlled trial.

There must always be an important reason for a trial, such as the need for a treatment of higher efficacy or acceptability, or for reducing the duration of treatment, the level of toxicity, the relapse rate, or the cost. Furthermore, there must be good justification for taking risks. The possible risks from the experimental treatment should be balanced against the risks to the patient and the community if the disease were left untreated or treated in the usual manner. Doctors participating in the trial should be given the assurance, laid down in the protocol, that they may withdraw a patient from the trial or break the code whenever continuation of the treatment might, in their view, cause serious harm. This must be ensured, even at the risk of nullifying the whole trial. Thus, the administration of a new treatment with strict observance of the principles of the controlled trial safeguards medical ethics and ensures scientific research of a high standard.

The protocol of a controlled trial

An essential requirement of a controlled trial is that it be planned and conducted according to a meticulous plan and working programme – the protocol. After the decision has been made to conduct a controlled trial, the protocol is drafted by a team of experts including not only physicians, but also representatives of other disciplines involved in the trial, e.g. a bacteriologist, a statistician, a nurse, a sociologist, a biochemist, an immunologist, and an administrator. The objectives, methods, working procedures, and schedules, are defined in the protocol, as well as the responsibilities of the parties involved in the trial. Every individual involved in the trial is strictly bound to adhere to the protocol, which should be consulted for instruction and guidance throughout the trial. The slightest deviation from the protocol must have the consent of the coordinating centre, otherwise the whole trial may be seriously impaired or invalidated. Thus, a protocol needs to be prepared with care, expertise, and responsibility. An unplanned trial, i.e. a trial without a protocol, is not a controlled trial, and the results of a trial with a deficient protocol are unconvincing, if not void.

Preliminary test runs

Before a protocol is completed, preliminary (pilot) studies may have to be conducted to obtain information rapidly, e.g. on the feasibility or operational efficiency of certain procedures, on unknown effects, or on the acceptability of certain policies. Sometimes it is useful to have a short test run of the protocol to see whether it contains any flaws.

All the investigators have the right to ask for amendments before participating in the trial and should feel that the protocol is their own, for which they will share responsibility and recognition. The final version of the protocol should be agreed upon by all authorized participants before the trial starts.

In the protocol, instructions and definitions can usually be found under the following headings:

1. Aim of the trial
2. Treatment to be studied (with justifications, ethical considerations, and related studies)
3. Study population and requirements for admission
4. Allocation to treatment groups
5. Management of treatment
6. Monitoring of progress
7. Recording and reporting
8. Analysis of data, assessment, and interpretation of results

Aim of the trial

The problem must be clearly defined and the objective of the study stated, i.e. what is to be proved or how the study is intended to solve the problem.

Example

The problem. Six-monthly treatment regimens are too long for many patients to complete.

The objective. To reduce the duration of treatment to 4 months. The study is to prove (or disprove) that this is feasible and that the additional resources required are commensurate with the benefits. The study must be conducted in such a way as to show the advantages of one regimen over the other in clinical, epidemiological, and economic terms.

Although it is theoretically possible to investigate many problems in a single trial, it is wise to address only a few.

Most controlled trials in the field of tuberculosis are designed to explore clinical aspects of treatment, such as duration, efficacy, or the toxicity of various dosages of drugs, or the efficacy, adverse effects, and relapse rate of various drug combinations (see "What is intermittent treatment and what is the scientific basis for intermittency?", page 130). Present knowledge of the treatment of tuberculosis is based almost entirely on controlled trials. Not only is the controlled trial a device for measuring the effects of drugs, but it has also been successfully employed to establish the value of certain policies for treatment and general management of tuberculosis patients. The best-known example is the classic Madras study (5) comparing home and sanatorium

treatment (see “What were the main findings of the Madras study comparing home and sanatorium treatment?”, page 173).

Thus, controlled trials have a wide spectrum of objectives.

Treatments to be studied

The drugs, dosages, and method of administration used in the trial should be described precisely, so that the treatment can be replicated elsewhere and the results verified. Both the protocol and the report should therefore make clear: the compound that is to be used (e.g. streptomycin = streptomycin 1 g/0.75 g sulfate base powder, diluted with sterile distilled water); the form of preparation (e.g. powder, granules, tablets, enteric-coated granules); the exact quantity per dose; and details of administration (e.g. single dose or divided doses, time of the day, dosage intervals, before or after food, directly observed or not). The control regimen, whether it is a standard regimen or not, must be similarly well described. No doubt or ambiguity should be left on any important point, since that might lead to confusion and potentially harmful errors.

The significance of the research, previous studies, and ethical considerations should be analysed and discussed.

Study population

The criteria for admission to a trial should be laid down clearly and should define not only the types of patients eligible, but also those to be excluded.

Example

Eligible for admission: patients of both sexes, 15 years of age and above, living within 5 km of the treatment centre, with sputum positive for tubercle bacilli by microscopy and culture, and with organisms susceptible to isoniazid and rifampicin.

Not eligible: patients who have been treated for tuberculosis before, weigh less than 40 kg, have diabetes or jaundice, are pregnant, or are migrants likely to move out of the area within the next 2 years.

It is useful, for the purpose of assessment, to keep the characteristics (age, sex, severity of disease, etc.) of patients in the various treatment groups as uniform as possible.

The number of patients to be admitted to the trial, based on calculations of required sample size, is an important question. It will depend largely on the nature and objective of the trial, the number of treatment groups, the estimated magnitude of expected differences in results, and the precision required for valid comparison of the results. A competent statistician should be consulted.

A controlled trial does not necessarily require vast numbers of patients. In fact, if strictly comparable groups can be constructed, the statistician may find that groups of 100 or fewer patients are adequate. Large numbers in themselves are often worse than useless if the groups are not comparable – and may create false confidence in potentially invalid results.

However, if large numbers of patients are required, so that the period of intake to the trial would be very long, or if the numbers are larger than one treatment centre can cope with, the trial should be decentralized. It is one of the advantages of a controlled trial that it can be conducted simultaneously in a series of centres in one or more countries or even continents. In this way, the intake period can be substantially shortened and all patients, though treated in different places, can be handled uniformly according to the protocol.

Allocation to treatment groups

The allocation of patients to the various treatment groups is critical for the correct conduct of a controlled trial, the aim being to ensure statistical comparability of the groups. Groups must therefore be similar in every respect except treatment: only then can the differences between results be measured and effects attributable to the various treatments identified.

Allocation must be strictly randomized. Proper randomization procedures – designed by competent statisticians, laid down in the protocol, and rigidly followed – will ensure that group differences in the results obtained will be due only, or probably, to differences in the regimens studied and not to differences (variations) in the groups of patients. If the randomization is deficient, the whole trial may be null and void.

Some randomization procedures still in use leave much to be desired. For instance, randomization by alternation – allocation of every second or third eligible patient to a particular regimen, or allocation according to the year of birth (odd or even number) – is unsatisfactory. The allocated treatment can be easily identified and the investigator or assessor will be biased, consciously or unconsciously. Moreover, allocation by alternation invites manipulation. For instance, if several patients happen to be admitted to the trial at one time, the order of admission can be arranged so that certain of them are allocated to the treatment that is thought preferable by the person in charge.

In many trials the so-called envelope system is used: the investigator is given a number of serially numbered sealed envelopes, each containing an indication of the treatment to be given to a patient admitted to the trial. At admission, a serial number must be assigned to each patient *before* the corresponding envelope is opened; otherwise, if several patients are to be allocated at the same time, the envelopes may be opened first, and treatments could then be allocated according to the investigator's prejudice. Correctly implemented, the envelope system works satisfactorily. The code remains confidential, and can be broken only in case of emergency or for assessment purposes.

A satisfactory randomization method that is frequently used involves a secret list of serial numbers accessible only to a neutral party (usually a statistician) or person with no vested interests in the trial. Each serial number in the list corresponds to a certain treatment, the sequential order of the treatments being arranged according to a table of random sampling numbers. When investigators admit a patient to the trial, they communicate the patient's particulars to the neutral party, and are then informed of the treatment (or coded treatment in double-blinded trials) to be given. Such an arrangement avoids almost all prejudice.

In summary, randomization is essential to avoid biased selection and to obtain equivalent groups in terms of smear positivity, extent of disease, age, sex, etc. Correct random allocation ensures that each person admitted to a study has an equal chance of being allocated to any of the trial groups. Thus, like can be compared with like.

Ideally, trials are double-blinded, meaning that neither the patient nor the investigator knows which treatment the patient is receiving. This is impractical, for example, with trials of daily versus intermittent treatment. However, it could be used in a trial of a vitamin (e.g. pyridoxine) supplement to be given in addition to standard treatment. In this case, a placebo that is physically indistinguishable from the drug to be prescribed would be given; neither the patients nor the investigators know who is receiving the drug and who is receiving the placebo.

Management of treatment

After the requested pretreatment examinations have been carried out as prescribed by the protocol and the necessary forms have been completed, treatment is started and administered precisely as laid down in the protocol. If a patient has to change, interrupt, or stop treatment, this should be done, whenever possible, with the consent of the coordinating centre. Complete protocols will include criteria and procedures for handling most such situations. The centre also decides whether such patients should be excluded from or kept in the trial for follow-up and assessment. Every exclusion for any reason – including “lost sight of the patient” and the refusal of treatment or of important examinations – should be considered carefully, since the results of the trial may be substantially biased through exclusions from assessment.

Monitoring of progress

A special section of the protocol should be devoted to the various monitoring measures and their timing. All routine examinations, as well as special examinations requested only on certain occasions (e.g. in the case of adverse effects), should be described in detail. The uniformity of all monitoring procedures should be ensured. It may be useful for examinations requiring specialist skills and accuracy to be performed in a central (reference) laboratory.

Recording and reporting

The importance of the design of recording forms and of an efficient system for the routing of information is too often underrated. A form (record or report) should be as self-explanatory as possible; its use should not require lengthy instructions. Only questions demanding clear-cut answers, preferably "Yes/No", should be posed.

Before the design of a form is finalized, it may be necessary to test whether the staff concerned find it easy to understand and complete. Sometimes it is advisable to include "trick" questions for cross-checking the correctness of certain recorded data. However, a record should be used only for the collection of information relevant to the operation and assessment of the trial.

Clearly, tuberculosis trials involving long periods of observation require the collection and processing of a huge amount of data, which calls for well organized administrative and clerical procedures.

A continuous check must be kept on the completeness and accuracy of data and reports, and reminders should be sent out promptly to the reporting centres, if necessary. Large-scale multi-centre trials will require computerized data management; all data should be entered in duplicate by two different individuals, the two data sets automatically compared, and all discrepancies investigated and corrected.

Analysis of data and assessment

Before each analysis, whether interim or final, the data should be rechecked for completeness and correctness. An important interim analysis may include, for example, periodic tabulation of bacteriological results and adverse effects according to regimen, duration of treatment, and regularity of drug intake. This provides up-to-date information on the merits of experimental regimens and, occasionally, early warning of the risks involved. If interim analyses are repeated periodically, the final analysis can usually be produced soon after the final data have been entered, thus speeding up completion of the final report.

Analysis, tabulation, and interpretation of results should always be done in close collaboration with the statistician(s). There is generally no disagreement on the factors to be analysed to establish the efficacy of drugs or regimens. However, the classification, and thus the assessment, of response to treatment in bacteriological, radiographic, or clinical terms may easily vary from one centre to another unless clear-cut criteria have been established in the protocol and applied rigidly. Definitions of terms such as "quiescence", "favourable response", "cavity closure", "improvement", "failure", "doubtful", "default", and "relapse" should therefore be foolproof.

If radiographic assessment is required (though this is of minor importance) and the extent of lung involvement (size and number of cavities) at various times has to be compared, the reader(s) should use a uniform nomenclature. Because the interpretation of radiographic findings is unavoidably influenced by individual reading error, the assessment of chest radiographs should be undertaken by a panel of inde-

pendent readers, if possible. However, it is difficult to organize multiple readings in large-scale trials. Therefore, all films are generally read by a single reader who is not otherwise involved in the trial. Such a solution is usually satisfactory since the principal aim is to compare the initial and subsequent radiographic status. In any case, radiographic assessment must be undertaken without knowledge of the patients' particulars or of the treatment that patients have received. Whenever possible, bacteriological and other findings should also be assessed blindly.

The analysis of failures, relapses, and deaths occurring during the entire observation period is just as important as the study of efficacy and success. In addition, all patients whose treatment has been changed because of adverse effects, or who have had major interruptions – even if these seem to have been entirely unrelated to the treatment – should be studied in detail, irrespective of the outcome. Premature cessation of treatment or self-discharge because of drug toxicity may be a shortcoming of the therapy. Often a relatively high frequency of “drop-outs” or irregularity in taking a particular regimen may indicate an acceptability problem that requires special investigation.

Presentation of the report on the trial

In reporting the results of a trial, it is important to provide an overview of the plan and conduct of the study. The report should therefore contain the essentials of the protocol, particularly the criteria for admission, regimens studied, method of randomization, management of patients, and methods of assessing response to treatment. The total number of patients admitted to the study and allocated to the various treatment groups and reasons for exclusion from the main analysis must be specified. All measures taken to eliminate bias should be described so that the reader can judge the validity of the individual decisions.

To show the comparability of the various treatment groups, the report should include tabulated data on the initial status (such as age, sex, weight, bacteriological status, drug susceptibility, radiographic extent of the disease, and cavities) of the patients allotted to the various treatments.

In the evaluation of treatment results, due consideration should be given to the analysis of variables other than the treatment that might have influenced the response or the relapse rate. The authors should give good reasons for ascribing certain effects to the regimens applied and others merely to chance variation.

The report should be presented in such a way that readers can understand what was done and how, and thereby assess the merits of the trial. Readers should be able to draw their own conclusions based on scientifically established facts and findings. That is why the results of well-conducted controlled trials are so convincing and why they are so often readily and widely accepted.

Conclusions

The controlled trial method has not met with universal approval. It is often argued that it is invalid to generalize results because the groups studied are too small, because people are not alike and individual differences may be so great that generalization becomes misleading, or because each individual's response to a drug is variable and therefore unpredictable.

It is true that age, sex, metabolism, genetic and immunological factors, living conditions, physical and mental stress, and a host of other external factors that determine the course and outcome of a disease may differ from one individual to another. On that basis, opponents of the controlled trial conclude that it does not compare like with like, and that such a comparison is invalid. However, this conclusion disregards the very principles of the method.

From biostatistics it is well known (6) that variability is an essential characteristic of living matter and, as such, is natural or normal. However, this variability is within a certain range that can be defined by statistical techniques. For instance, when a series of observations is made on a certain variable in a randomized group (sample), it may be found that the values obtained are grouped with increasing frequency around a certain value. The characteristics of this distribution may be expressed in measurable terms, enabling comparisons to be made between one series of observations and another. The information thus obtained is fully valid for the samples studied. In controlled trials, the results obtained are group results, i.e. results valid for the group as a whole. It is impossible to predict precisely from those results how a particular individual will respond to a treatment previously tested in a certain group, but the response of a group similar to the trial group can be stated with reasonable certainty. Only the controlled trial method can neutralize the effects of individual differences between human beings in their illnesses and responses to treatment. Thus, these differences do not invalidate the method but justify it.

On the other hand, it is known that judgements based on personal impressions may often be deceptive. Clinical experience based on personal impressions can undoubtedly be valuable, but an assessment – of a therapeutic regimen, say – based merely on intuitive impressions cannot be accepted without reservation or scepticism.

Many physicians are guided in their daily work by previous clinical impressions of their own or by school doctrines founded on the impressions of others. Such doctrines, particularly when they are perpetuated in textbooks and repeatedly quoted by reputed teachers, can easily become fixed formulas in the minds of some people – just as if they were proven facts. Traditional ways of learning and teaching have meant that authoritarian judgements and statements have come to be respected and adopted without criticism. Graduates or postgraduates frequently accept them without ascertaining whether they have been subjected to scientific test.

The treatment of the sick must be based on the best scientific knowledge available. The past five decades have shown clearly that the controlled trial is by far the quickest way of obtaining conclusive and reliable information on the efficacy and risks of

a new treatment. The dramatic progress made in the treatment of tuberculosis has been due largely to the fact that the regimens currently in use have first been tested by means of controlled clinical trials. These trials have laid the foundation for the standardization, and hence the worldwide application, of tuberculosis treatment.

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68. What is molecular epidemiology and what is its role in tuberculosis control?

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What is molecular epidemiology?

Molecular epidemiology combines laboratory-based molecular methods for identifying individual strains of bacteria with conventional epidemiological field methods to investigate the determinants and distribution of disease (1). DNA fingerprinting of *Mycobacterium tuberculosis*, using techniques such as restriction fragment-length polymorphism (RFLP) analysis, allows investigators to determine the genetic relatedness of clinical isolates. Patients infected with identical strains may have been infected from each other or from a common source. In the context of epidemiological data it is possible to provide evidence for transmission between persons with active tuberculosis.

There are limitations to this technology. It is still not possible to track transmission between persons when a culture of *M. tuberculosis* is not available from each individual. DNA fingerprinting analysis requires a high degree of sustained quality control, consistency, and proficiency in laboratory techniques. More importantly, the hypotheses to be tested, the study design best suited to test the hypotheses, and the sampling schemes need to be clearly stated and correctly implemented. For example, only limited information is gained from DNA fingerprinting analysis of a case series of specimens if complementary epidemiological information is not available.

What is the role of molecular epidemiology in tuberculosis control?

Molecular epidemiological techniques were first used in outbreak investigations of tuberculosis to confirm suspected epidemiological links and to demonstrate the effectiveness of control measures. In an outbreak investigation of tuberculosis in a facility for persons infected with HIV, DNA fingerprinting analysis of the strains from different patients supplemented information from patient interviews and an outbreak curve to unambiguously identify the source case and the chain of transmission. More

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importantly, molecular analysis supported recommendations for, and allowed objective monitoring of, the impact of specific, targeted public health interventions such as screening and early detection of cases, their isolation from other susceptible contacts, and the use of preventive treatment of infected contacts. Continued surveillance in the facility, after the initial outbreak was identified and control measures were implemented, demonstrated that the chain of transmission had been interrupted (2).

Tuberculosis outbreak investigations in recent years have used DNA fingerprinting techniques to demonstrate new sites and routes of tuberculosis transmission. Molecular epidemiological techniques have demonstrated significant tuberculosis transmission in settings such as commercial bars (3), clandestine bars (4), crack houses (5), prisons (6–9), and shelters and other sites used by the urban homeless (10, 11). DNA fingerprinting can also quickly exclude the possibility of an outbreak, thereby avoiding expensive, time-consuming epidemiological investigations and inappropriate interventions. The importance of treating every infectious case of tuberculosis, even “difficult”, non-adherent patients, and of implementing rapid, efficient contact-tracing practices was illustrated by mini-epidemics and incident cases linked to index cases detected many years earlier (12). These techniques have also been used to demonstrate tuberculosis transmission in health care settings, such as transmission between patients, transmission from patient to health care provider, and transmission from health care providers to patients (13, 14). Tuberculosis transmission by inadequately sterilized equipment, such as bronchoscopes, has also been documented (15, 16). The value of this information is that it points to specific public health and institutional interventions that can be implemented to reduce or stop tuberculosis transmission. Effective interventions can reduce the rates of both transmission and incidence.

Population-based molecular epidemiological studies are difficult, labour-intensive, and expensive. Nevertheless, they provide otherwise unavailable insight and add new knowledge of the dynamics of tuberculosis transmission in a community. For example, a 7-year population-based study of tuberculosis in San Francisco, USA, showed that a decline in tuberculosis transmission rates was partially attributable to specific public health interventions that reduced transmission as demonstrated by a reduced rate of clustering, or shared strains, among the USA-born population (17). Although foreign-born cases account for more than 65% of the reported tuberculosis cases in San Francisco, this study demonstrates that there is limited transmission from foreign-born to USA-born persons, and that most of the transmission in the city is among USA-born persons with risk factors such as HIV infection, substance use, and homelessness (18). A 5-year, population-based, molecular epidemiological study in southern Mexico showed that incidence rates, degree of recent transmission as measured by clustering, and initial drug resistance levels declined in a high-prevalence area as DOTS was implemented (unpublished observations, García-García M, Instituto Nacional de Salud Pública, Mexico).

Molecular epidemiological techniques can be very useful to illustrate laboratory cross-contamination (19), which may account for 1–4% of positive cultures even in otherwise well-performing laboratories. In addition, these techniques have revealed exogenous reinfection (20, 21), and simultaneous infection with more than one strain of *M. tuberculosis* (22), phenomena that were thought to occur but were proved only when DNA fingerprint analysis of isolates of *M. tuberculosis* became available. At present, several research sites are trying to determine the amount and role of reinfection in countries with a high prevalence of tuberculosis. The potential impact of public health interventions will be defined by the proportion of tuberculosis that arises from recent infection and reinfection; this can be established by molecular epidemiology.

Molecular epidemiological techniques have also demonstrated that transmission by sputum smear-negative pulmonary tuberculosis cases does occur and can account for as much as one-fifth of the ongoing transmission in a low-prevalence community (23). Combined with conventional techniques, such as tuberculin skin testing, molecular epidemiology has pointed to super-infectious and pathogenic strains of tuberculosis (24).

How will molecular epidemiology be used in the future?

It is likely that molecular genotyping techniques, such as RFLP analysis, will continue to be used for investigating laboratory cross-contamination and suspected point-source outbreaks, and to differentiate relapse from exogenous reinfection (25). However, if preliminary molecular epidemiological analysis confirms that there are strain-specific differences in tuberculosis, it is possible that these differences can be exploited to improve tuberculosis prevention and control efforts, and the role of molecular epidemiology in tuberculosis control may be greatly expanded. For example, molecular epidemiological techniques may be used to identify strain-specific differences in the degree of infectivity and pathogenicity of *M. tuberculosis*. Comparative genomic analysis of *M. tuberculosis* may identify the genetic determinants of bacterial virulence, aerosolization, infectivity, pathogenicity, drug resistance, and other steps in the pathogenesis of tuberculosis. Molecular epidemiology and functional genomics may contribute to established approaches for new diagnostic techniques, drugs, and – eventually – a vaccine.

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69. Can tuberculosis be controlled?¹

*T. Frieden*²

In some quarters there is a firm belief that tuberculosis, like the weather, can be described but not controlled. Tuberculosis declines if socioeconomic conditions improve (1, 2). This fact has led some observers to conclude mistakenly that tuberculosis can be controlled *only* if living conditions improve. However, it was predicted on theoretical grounds (3), and has now been convincingly demonstrated in practice, that tuberculosis can be controlled in almost any socioeconomic circumstances (4–6).

Five aspects of disease control—disease burden, mortality, prevalence of disease, rate of infection, and incidence of disease – are considered below, in declining order of amenability to control.

Disease burden

The burden of tuberculosis disease – including illness, disability, and direct and indirect costs of the illness – can be reduced rapidly through prompt diagnosis and effective treatment. In addition to the rapid decline in mortality considered below, duration of disease is drastically reduced by effective treatment. Untreated, patients remain ill with tuberculosis for an average of at least 2 years. An effective programme detects most patients within a month of the onset of significant symptoms, and the application of directly observed short-course treatment generally restores complete function within 1 or 2 months. The duration of illness can therefore be reduced from an average of 24 months or more to about 2.5 months – a 90% reduction. If the global target for case detection is met (see “What are the global targets for tuberculosis control and what is the basis of these targets?”, page 238), this would result in an overall reduction in tuberculosis morbidity in the community of about two-thirds, even without taking into account the decline in incidence considered below.

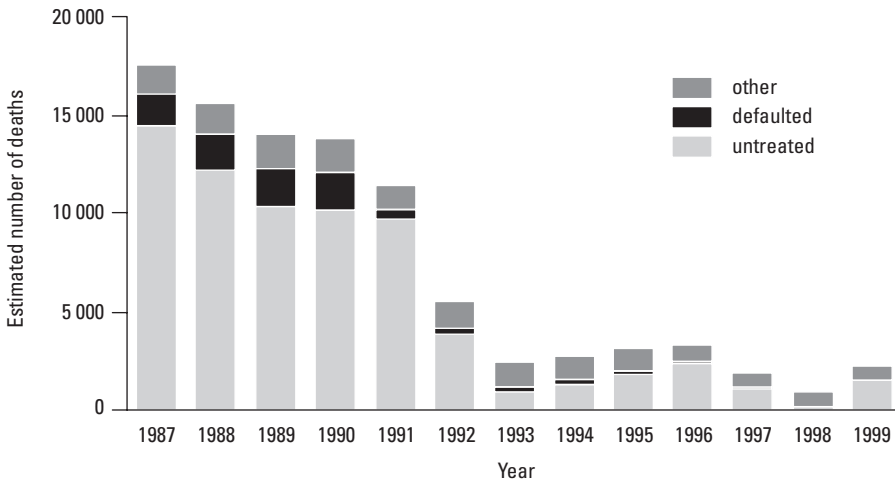
Mortality

Directly observed treatment of tuberculosis rapidly reduces mortality. This was seen even in the first days of tuberculosis treatment: treatment with a single drug resulted

¹ Adapted and reprinted with permission from *International Journal of Epidemiology*, 2002, 31:894–899.

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Figure 22
Reduction in deaths from tuberculosis Peru, 1990–1999^a



^a Source: reference 5.

in dramatic, albeit fleeting, reductions in mortality. Current regimens, given under appropriate management conditions, are nearly 100% curative for patients with drug-susceptible organisms; the reduction in mortality is dramatic and sustained. Untreated, 50–80% of patients with smear-positive tuberculosis will die of their disease (7). In a poorly implemented tuberculosis programme, as many as 30% of patients with smear-positive tuberculosis die (8). In contrast, death rates in DOTS programmes throughout the world are generally less than 5%: of 725 275 new smear-positive patients treated in DOTS programmes in 1998, only 3.8% were reported to have died (9).

In countries where baseline data exist, it is possible to make a reasonable estimate of the reduction in mortality achieved through DOTS implementation. Peru has been able to implement a highly effective DOTS programme (5), with a striking 80% reduction in mortality within just 3 years (Figure 22). This has been achieved by reducing the case-fatality rate among treated patients by prompt diagnosis and effective and directly observed treatment, and because a greater proportion of patients are treated. In India, mortality among smear-positive patients in the previous programme was 20–30%, compared with 4% in the DOTS programme – an approximately sevenfold reduction (8). Considering both smear-positive and smear-negative cases, DOTS reduces the case-fatality rate by about 18%, even if neither the increased detection rate nor secondary cases and their mortality are taken into account. By early 2002, the Indian DOTS programme had treated more than 2 million patients, thereby saving more than 350 000 lives. In China, national coverage with DOTS would prevent more than 50 000 deaths per year (10).

Prevalence of disease

Prevalence of tuberculosis can also be reduced rapidly. In a poorly functioning tuberculosis control programme, the ratio of incidence to prevalence may be as high as 1 : 3.5 (11). Achievement of the global targets for tuberculosis control, even if only a small proportion of prevalent cases are treated each year, will result in a rapid reduction in prevalence. This point is illustrated in a simple model (Figure 23). In this model, there are 100 new smear-positive cases per 100 000 population at the outset and the ratio of incidence to prevalence is 1 : 3.5. The model assumes that targets for case detection (70% of new smear-positive cases) and treatment success (85%) are met, that about half as many prevalent smear-positive cases as incident smear-positive cases are treated each year (12), that 85% treatment success is achieved, that the proportion of patients who fail treatment is as per the global averages in DOTS programmes (9), and that there is a 5% decrease in incidence per year (see below). As can be seen, prevalence declines very rapidly, being reduced to less than half of its previous level within 3 years.

The validity of this theoretical model has been confirmed under programme conditions in both developed and developing countries. In Kolín, in the former Czechoslovakia, an intensive surveillance and control programme in a population of 100 000 reduced the prevalence of chronic tuberculosis by more than 33% per year – to less than one-fourth of its earlier rate in 3 years (13). In New York City, the number of patients with persistently positive cultures fell by two-thirds in 3 years – more than 30% annually (14, 15). This could be documented because the monitoring system identifies almost every patient with bacteriologically proven tuberculosis (4). In Beijing, as documented by community surveys, the prevalence of smear-positive cases declined by 87% between 1979 and 1990, from 127/100 000 to 16/100 000 – a 17% annual decrease sustained over 11 years (16).

Rate of infection

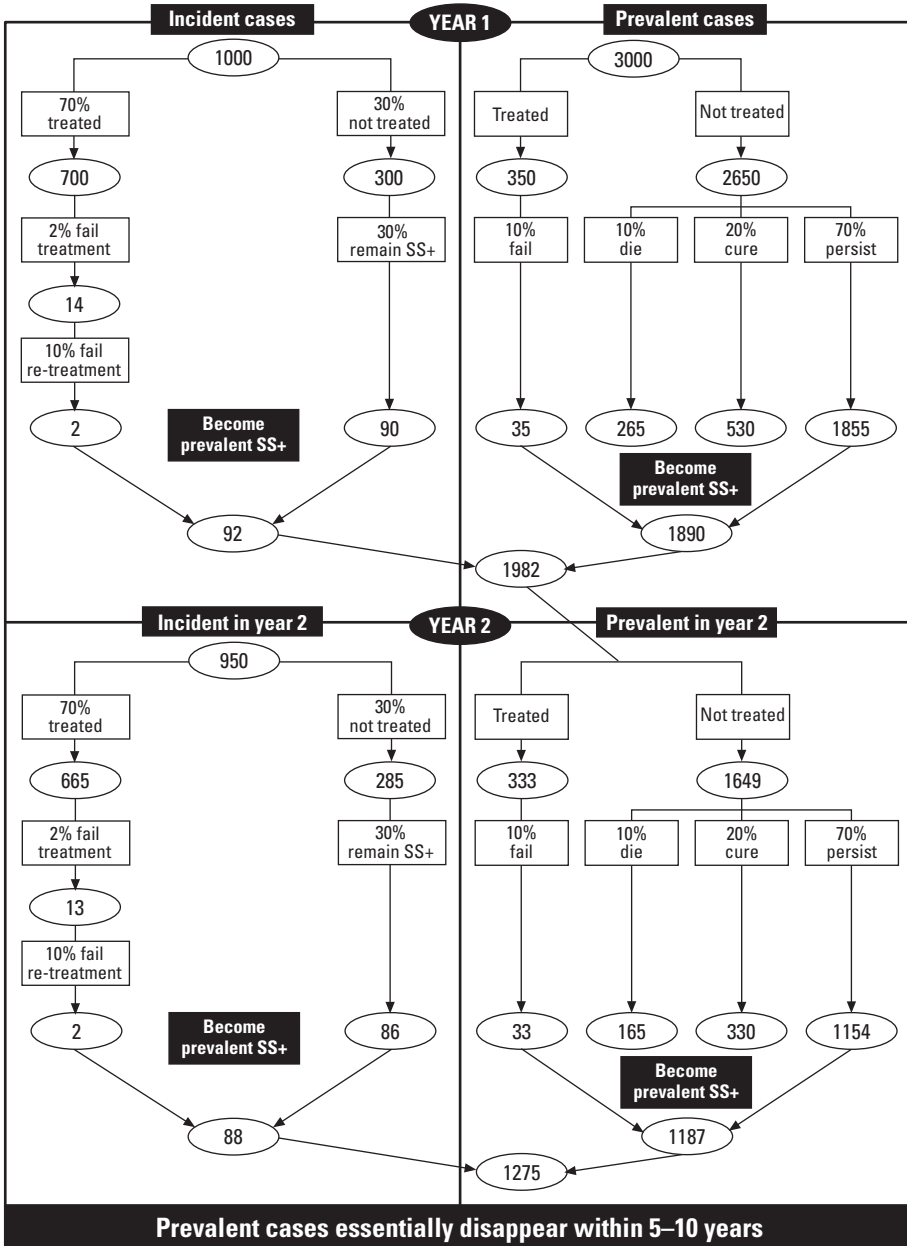
The rate at which individuals become infected with *Mycobacterium tuberculosis* determines the course of the epidemic in a community. For the long-term control of tuberculosis, it is therefore essential that infection rates decline. In industrialized countries, the risk of infection with tuberculosis bacteria declined by approximately 5% or more per year, even before the introduction of chemotherapy. With the introduction of effective treatment, the rate of infection declined by 15% or more per year (17). In developing countries, in contrast, there is little or no decline in the annual risk of tuberculosis infection unless effective tuberculosis treatment services are in place.

Effective diagnosis and treatment of tuberculosis can rapidly reduce the risk of infection. On theoretical grounds, it should be possible to reduce the risk of infection even in developing countries by 10% or more per year (3). However, few studies have attempted to document this in developing countries. Such studies are logistically

Figure 23
Dynamics of smear-positive tuberculosis if global targets are met

SS+ = sputum-smear positive

(1 million population; incidence of smear-positive tuberculosis = 100/100 000)



difficult and are further complicated by difficulties in the interpretation of tuberculin tests in the same population over time. One such survey in the Republic of Korea found an annual reduction in the risk of tuberculosis infection of 8–14%, even though treatment success did not quite reach 85% (18). At a constant rate of BCG vaccination, the incidence of tuberculous meningitis in infants is a reflection of the annual risk of infection. In Beijing, tuberculous meningitis fell from 2.1 to 0.1 per 100 000 between 1986 and 1996, a reduction of 26% per year (16). However, some of this reduction may have been the result of improved vaccination practices.

Incidence of disease

The incidence of tuberculosis is the combination of:

- recurrent tuberculosis in patients who have had previous episodes of disease;
- rapid progression to tuberculosis disease among individuals infected or reinfected within a relatively short period (e.g. 2 years) of infection; and
- reactivation of tuberculosis infection contracted many years previously.

Recent developments in molecular epidemiology, along with conventional epidemiological investigations, have helped to determine the relative proportion of cases arising from each of these groups – which will vary from population to population, and, within one population, over time. For example, in a comprehensive study of tuberculosis epidemiology in southern India in 1972, only 37% of all smear-positive cases of tuberculosis arose from individuals who had a normal X-ray at the outset of the survey. Within 12 years, this fraction had increased to two-thirds, and the proportion of cases arising from individuals who, at survey outset, had X-rays consistent with tuberculosis with negative cultures decreased from 33% to 8%. This corresponded with a reduction in the annual risk of development of tuberculosis among persons with highly abnormal X-rays from 7.0% per year to 3.2% per year, presumably reflecting the greater likelihood that such patients had received at least some, although partial, tuberculosis treatment (11). A recent survey in Norway has shown that fewer than one in five patients developed tuberculosis as the result of recent infection; the overwhelming majority of cases arose from remote infection or recurrent tuberculosis (19).

The amenability to control of tuberculosis incidence – with or without HIV infection – depends to a great extent on local epidemiology. At one extreme are situations in which the vast majority of tuberculosis cases arise from remote infection. Most such cases will not be prevented with current technologies. Many individuals with remotely acquired infections will not be candidates for preventive treatment, and, even if preventive treatment is attempted, its success is far from assured (see “What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?”, page 220). At the other extreme are populations in which as many as half of all tuberculosis cases arise from infection or reinfection within the preceding 2 years. In such a context, the application of effective tuberculosis control measures can result in a

very rapid decline in tuberculosis cases. In New York City, for example, the incidence of tuberculosis among persons born in the USA declined by 25% annually over the 5-year period 1992–1996; incident cases of multidrug-resistant tuberculosis, which were mostly linked to ongoing transmission in health facilities, declined by 34% annually in the same time period (20). Similarly, an elegant study in San Francisco documented that more than one-third of cases resulted from recent transmission. With improved control measures, the overall case rate declined by 7% per year; the rate of clustered cases declined by 15% per year, while non-clustered cases declined by only 5% per year (21). In New York City, molecular epidemiological studies similarly documented a 26% annual decline in the estimated incidence of clustered tuberculosis between 1991 and 1997 (22; and New York City Department of Health, unpublished data, 1997).

A limited number of representative surveys in developing countries suggest that the proportion of new cases caused by recent infection may range from 29% to 48% (23–26). Such cases can be rapidly reduced by effective treatment. In addition, the proportion of cases arising from reactivation of tuberculosis may decline steadily over a longer period of time. Thus, on theoretical grounds, it should be possible to control incidence even in developing countries. This prediction has been borne out by experience.

In developing countries where effective treatment practices have not been implemented, the incidence of tuberculosis remains essentially static (11). In contrast, rapid declines in tuberculosis incidence have been documented in the developing world when effective tuberculosis control measures are applied. In Beijing, during a period when the notification rate was believed to be high and constant, a 9% annual decrease in new smear-positive cases was documented between 1986 and 1996 (16). In Cuba, with directly observed treatment and efficient treatment organization achieving high rates of treatment success, the rate of new smear-positive cases decreased by 10% annually over a 26-year period (6). In Peru, cases of tuberculosis declined by approximately 8% per year (5). An 8–10% annual reduction will cut the number of cases by half in 7 years. Thus, in the absence of an HIV epidemic, the incidence of tuberculosis can be significantly reduced even in developing countries.

Tuberculosis control in the context of HIV

The HIV epidemic undermines tuberculosis control. In the context of HIV, the tuberculosis burden of disease, mortality, prevalence, and, possibly, rate of infection can still be controlled by an effective tuberculosis control programme. However, this can be done only with significantly increased effort and with a very low margin for error.

Because of the increased risk of reactivation in patients who are already infected with the tuberculosis bacteria, as well as the risk of rapid and widespread dissemination of tuberculosis in HIV-infected populations, the incidence of tuberculosis will inevitably increase in most areas of the world if the rate of HIV infection in the adult population is 5% or more. However, an effective tuberculosis control programme can

blunt the impact of this increase, and can also prevent the related emergence of multidrug-resistant tuberculosis. Not only is there an increased incidence because of cases arising from infection acquired many years previously, but each individual tuberculosis patient is likely to give rise to an increased number of secondary cases because of immunosuppression in close contacts. Tuberculosis has increased explosively in areas of the world where HIV is endemic; these increases have been significantly less in areas with effective tuberculosis control services (27).

Experience in the United Republic of Tanzania is somewhat encouraging in this regard. Although the country is in the midst of a substantial epidemic of HIV, systematic surveys for annual risk of infection over the past 15 years have documented continued stable or even slightly declining (by 2% annually) rates of tuberculosis infection (28). This suggests that an effective tuberculosis control programme can, by means of prompt diagnosis and effective treatment, limit the number of secondary infections and cases.

Theoretically, preventive treatment for HIV-infected patients who also have tuberculosis infection could dramatically reduce the impact of HIV on tuberculosis epidemiology. However, since most individuals with HIV infection in developing countries do not know their infection status, and because of the logistic difficulties of giving treatment to a large number of patients who have no clinical symptoms (see “What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?”, page 220), the practical applicability of treatment of latent tuberculosis infection may be limited to individual rather than public health interventions.

New York City demonstrated that it is possible to control an outbreak of tuberculosis even in the context of HIV, and even in an area where multidrug resistance had become common (4). This was achieved by ensuring prompt diagnosis, high-quality laboratory work, standardized treatment regimens, direct observation as the standard of care, and rigorous cohort reporting with accountability for every case diagnosed. In addition, the spread of tuberculosis in hospitals was curtailed (see “What is nosocomial transmission of tuberculosis and how can it be prevented?”, page 278). However, the prevalence of HIV infection among adults in New York City probably did not exceed 3%, in contrast to the more than 30% among adults in some countries of Africa.

Conclusions

Control is a more modest goal than elimination or eradication. Elimination has been defined arbitrarily as no more than one new case per million population per year, or a prevalence of tuberculosis infection of below 1% in the general population (29). This may be achieved in some developed countries even without additional technological advances within the next 20–50 years. However, migration and continued high rates of tuberculosis in many countries may prevent this from occurring unless a concerted effort is made to control tuberculosis in all countries. Eradication, which is applicable to only a small number of disease entities, is defined as the

achievement of a status whereby no further cases of a disease occur anywhere and control measures are unnecessary. Tuberculosis is not currently a candidate for eradication efforts.

Thus, the answer to the question, "Can tuberculosis be controlled?" is "Yes" – if scientific principles are followed, effective clinical and public health management is ensured, and there are committed and coordinated efforts for control from within and outside of the health sector. Tuberculosis control is a winnable battle.

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70. Can effective case detection and treatment prevent and reverse drug resistance in a community?

*M. Raviglione*¹

The prevalence of multidrug-resistant tuberculosis (MDR-TB) in 35 countries was surveyed by WHO in 1994–1997. The prevalence of MDR-TB was found to be related to the quality of tuberculosis control programmes (1). Countries were classified as having “better” or “poorer” tuberculosis control, with better control being defined as full coverage with DOTS, or coverage of at least one-third of the national territory, or a tuberculosis notification rate below 10 per 100 000 population. Any country that had not adopted DOTS or that had a coverage of less than one-third of its territory was defined as having poorer tuberculosis control. The analysis revealed that countries with better control had a lower combined prevalence of MDR-TB than those with poorer control (1.6% vs 3.9%; $P < 0.05$). The prevalence of MDR-TB in countries with better tuberculosis control was also lower among previously treated cases (7.7% vs 17%), while the prevalence of MDR-TB among new cases was similar to that in countries with poorer control.

In a second assessment, the relationship between programme performance and prevalence of drug resistance was studied in countries with reliable data on both drug resistance and treatment outcome (2). The treatment success rate, as the best expression of the performance of tuberculosis control programmes, should be inversely related to the prevalence of MDR-TB. Indeed, countries achieving a high rate of treatment success had low primary MDR-TB prevalence, and the relationship was statistically significant ($r^2 = 0.5$, $P = 0.003$). In some countries where treatment success was high at the time of the survey, such as Peru and Viet Nam, MDR-TB prevalence was still moderately high (2–3%). This was probably due to the persistence, after implementation of DOTS, of MDR-TB created by previously weak programmes.

These observations suggest that proper tuberculosis control, as achieved in effective DOTS programmes, minimizes the emergence of MDR-TB where it does not yet exist. African countries such as Benin, Botswana, and Kenya, which started using rifampicin in their standardized short-course treatment regimens at the time of implementation of good tuberculosis control practices (1983, 1986, and 1993, respec-

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tively) and have achieved high cure rates, have been successful in minimizing the emergence and spread of MDR-TB. Similarly, some Latin American countries, such as Chile, Cuba, and Uruguay, with traditionally excellent control programmes curing most patients, today have very low levels of MDR-TB. On the other hand, countries such as Côte d'Ivoire, Dominican Republic, Estonia, Latvia, Russian Federation, and Thailand, which used rifampicin widely before strengthening their programmes, have a higher prevalence of MDR-TB. Thus, effective tuberculosis control prevents MDR-TB. The situation might be different, however, in settings where MDR-TB is already common.

It is believed by some that adoption of the standard regimens recommended by WHO and the IUATLD for countrywide use will lead to a slow decline in prevalence of MDR-TB. In fact, many patients will be cured even though they are infected with multidrug-resistant strains: some (25–30%) will undergo spontaneous cure as part of the natural history of the disease, and some will die quickly and thus stop infecting others. Available data from the USA (3) suggest that specialized and individualized treatment can cure a relatively high proportion of patients with primary MDR-TB, thus removing them from the infectious pool. However, the duration of infectiousness before sputum conversion or death is also high. Therefore, the assumption that a large number of MDR-TB patients are either cured or die quickly (and therefore stop spreading infection) is unwarranted. In the USA, where these assessments were made, expensive individualized regimens and surgery are more readily available than in most other countries. In developing countries using standard short-course treatment as part of DOTS, however, a much larger number of patients are affected. It appears that most cases of tuberculosis resistant to isoniazid or streptomycin alone can be cured using standard first-line regimens in programme settings. The failure rate of 6-month treatment in tuberculosis cases resistant to isoniazid has been reported as only 1%, with a relapse rate of 11% (4). Similarly, very low failure rates, 0–2%, were observed in clinical trials when regimens of at least 6 months were used to treat patients with strains resistant to either isoniazid or streptomycin (5).

Recent data reported to WHO from national control programmes, as distinct from controlled trials, show that, in patients with strains resistant to a single drug (not including rifampicin) who are treated with short-course regimens, cure rates are not significantly lower than in patients with fully susceptible strains. In Peru, 90% (1029/1145) of patients with susceptible strains and 87% (105/121) with resistance to a single drug were cured with first-line drugs ($P = 0.27$). In the Republic of Korea, the figures were 85% (1668/1968) and 80% (104/129; $p = 0.11$), respectively. These data suggest that standard short-course regimens may cure most cases with monoresistance. Inevitably, however, treatment success rates of rifampicin-resistant and MDR-TB cases are lower. In Peru and the Republic of Korea, success rates of 58% and 56% have been documented in MDR-TB cases, which are significantly lower rates in susceptible cases ($P < 0.001$ in both countries).

In a multi-centre study involving six areas (Dominican Republic, Hong Kong

Special Administrative Region of China, Italy, Peru, and Republic of Korea, and the Ivanovo Oblast in the Russian Federation) average treatment success rate was 52% among new MDR-TB cases, with an average failure rate of 21%. The death rate was generally below 10% (6). Thus, some response to standard first-line drugs is indeed possible, although the failure rate is very high. The question remains of whether achieving a treatment success rate of about 50% among new MDR-TB cases and a relatively low case-fatality rate, but allowing a high failure rate, is sufficient to eliminate MDR-TB.

Countrywide trends of MDR-TB prevalence in good DOTS programmes could provide a direct answer to this question. Few data are currently available from developing countries, but trend data from the Republic of Korea are illustrative (7–9). The estimated number of all resistant cases fell slowly from 1965 to 1980, and then more steeply from 1980–1985 onwards. The number of MDR-TB cases increased between 1975 and 1985, but was lower in 1990 and 1995. The fall in all resistant cases, and in MDR-TB cases, coincides with a rapid increase in cure rates in the Republic of Korea, especially between 1980 and 1985. This is not sufficient to prove that first-line treatment given in a good programme can reverse MDR-TB, but these data do suggest that effective treatment can influence the decline of MDR-TB by preventing the emergence of new MDR-TB cases.

Drug resistance trends have also been studied in Algeria (10). In the region of Algiers, from 1965 to 1990, drug resistance decreased from 15% to 5.2% among new cases and from 81.9% to 21% among re-treatment cases. This decline coincided with two important policy changes: the introduction of standard regimens in the late 1960s and of rifampicin-containing treatment in 1980. However, whether the decline would have occurred regardless of these changes is not known, as there are no data on previous trends. The trend of MDR-TB over time has been reported among cases eligible for a re-treatment regimen: there was no change in either numbers or percentages (11% and 11.5%, respectively) between the periods 1980–1985 and 1986–1990.

Taken together, the experiences from Algeria and the Republic of Korea suggest that MDR-TB can possibly be reduced, but not eliminated, by the use of properly administered regimens with first-line drugs. A recent study from Bobo-Dioulasso, Burkina Faso, shows that introduction of short-course treatment and improved supervision and treatment observation policies in 1989 resulted in a lower prevalence of drug resistance, including rifampicin resistance, in a 1992–1994 survey compared with previous surveys in 1978 and 1986. Unfortunately, no trend data are available for MDR-TB (11).

Evidence from the New York City experience suggests that MDR-TB can be rapidly controlled (12). Between 1991–1992 and 1994, following the implementation of effective control measures, the total number of MDR-TB cases nearly halved (44% decrease); MDR-TB cases decreased by more than 85% between 1992 and 1997. Control measures included directly observed treatment, which ensured high completion rates; infection control interventions in congregate settings such as hospitals, jails,

and shelters for the homeless; and the adoption of adequate treatment regimens for cases with both susceptible and MDR strains (treated with reserve drugs in order to achieve high success rates).

New York City's experience can be summarized as follows. Well-organized treatment with first-line drugs increased the cure rate among non-MDR cases, "turned off the tap" and stopped the generation of acquired MDR-TB. This reduced the spread of MDR-TB strains, contributing to the decline in primary MDR-TB. In addition, existing MDR-TB cases were cured with reserve drugs ("emptying the pool"). This, combined with effective hospital infection control, dramatically reduced the spread of MDR-TB.

Clearly, without reserve agents it will not be possible to achieve a cure rate substantially above 50% among MDR-TB cases. Unless high cure rates are achieved, it is unlikely that transmission of MDR-TB will stop rapidly or be eliminated within a few years.

In conclusion, the information available today on the efficacy of short-course treatment regimens for tuberculosis demonstrates that the emergence of drug resistance can be minimized by programmes that administer drugs correctly to patients and achieve cure. However, the treatment regimens recommended as part of DOTS cannot rapidly reverse MDR-TB if it has already emerged as a significant problem. The crucial factor for elimination is treatment success: at a high cure rate for both susceptible and multidrug-resistant cases, the emergence of MDR-TB will be reversed. High cure rates of susceptible cases ensure that MDR-TB is not created; as a result, "primary" MDR-TB will also decline. At the same time, an increased cure rate of existing MDR-TB will eliminate the sources of transmission in the community.

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71. What are the indicators of an effective tuberculosis control programme?

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Indicators can measure process, outcomes, or impact. They measure the essential elements needed to carry out activities, the extent and quality of those activities, and the results, and should be limited to markers of the most important elements of the programme. Since epidemiological (impact) indicators change slowly and are difficult to measure, operational indicators of process and outcomes are often used to assess effectiveness.

Process indicators

The primary aim of the tuberculosis programme is to detect and cure infectious tuberculosis cases in order to reduce transmission, morbidity, and mortality. To achieve this, a programme requires trained staff and supplies such as antituberculosis drugs and microscopes in a network of general health facilities and laboratories accessible to the population. Relevant process indicators of administrative aspects include the coverage of programme activities (such as proportion of population having access to, and the proportion of health facilities implementing, the recommended policies for diagnosis and treatment), availability of supplies (e.g. frequency of drug stock-outs), availability of trained staff, frequency of supervision, completeness of reporting, and quality of interventions (e.g. quality of sputum smear examination, proportion of pulmonary cases confirmed by positive sputum smears among diagnosed pulmonary cases, indicating the use of microscopy as a diagnostic tool). Another important indicator is the proportion of patients identified as smear-positive in the laboratory register who are registered and treated as documented in the tuberculosis register.

Outcome indicators

The main outcome indicator of an effective programme is the cure rate – the proportion of patients cured out of those diagnosed, analysed in cohorts of patients. Since cure can be confirmed only through bacteriology – in most countries sputum

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microscopy – and the priority is the sputum smear-positive sources of infection, the cure rate is analysed mainly in new smear-positive pulmonary tuberculosis cases. Some patients complete treatment with clinical improvement but without bacteriological confirmation of cure (completion rate); this should be a small proportion. A good programme can achieve a cure/completion rate (also called success rate) of more than 85%, except in HIV-endemic areas. In most such areas, at least 10% of patients die before completing treatment (generally of causes other than tuberculosis), making an 85% cure rate practically unattainable. The cure/completion rate and the case detection rate are the main outcome indicators for monitoring programme effectiveness.

Complementary indicators are the proportion of failures (1–2%, usually the result of inadequate regimens or drug resistance), of defaulters (a good programme should have less than 5%), of transfers without information regarding outcome (often influenced by migration), and of death due to any cause (often due to late diagnosis, HIV/AIDS, or non-tuberculosis causes). The same analysis can be done for re-treatment cases as a group, and independently for relapses, defaulters who are re-treated, patients who fail initial treatment, and other cases.

Treatment outcome indicators must include the *entire* cohort of registered cases in a period, usually 3 months, and can be analysed only after giving time for all the patients to complete treatment, usually 1 year. An early proxy for the cure/completion outcome is the proportion of smear-positive cases who have negative smears after receiving 2–3 months of treatment (sputum smear conversion rate). This indicator reflects the capacity of the programme to maintain patients on treatment, obtain follow-up smears, and reduce patients' bacterial population through treatment.

A second operational priority for the programme is to detect infectious cases for treatment, mainly through sputum smear microscopy in outpatients attending general health facilities. The main indicators are the number of new infectious cases detected as a percentage of expected incident cases (case-detection rate), the percentage of outpatient suspects examined by sputum smear, and the percentage of these who are smear-positive. Incidence can be estimated only roughly at country level (on the basis of studies of prevalence of tuberculosis infection, mortality, and notification) and not at all at district or local level. The proportion of outpatients examined by smear microscopy and the trend of notified new smear-positive cases are more useful and practical at district or health centre level. Additional indicators reflecting case-detection activities are the number of patients examined for diagnosis and the proportion of contacts of tuberculosis cases examined, diagnosed, and placed on treatment.

Impact indicators

The epidemiological impact of an effective programme is measured by the reduction of mortality, morbidity, and transmission (*I*). Reduction in tuberculosis mortality can be monitored through death certification trends over several years. However, these data may not always be available, or may often be imprecise so that changes are seen

only after several years. The most evident impact on mortality is the reduction of deaths in patients under treatment (health facility data).

Reduction in the prevalence of tuberculosis in the community can be detected directly through periodic population surveys – which are expensive and complex – or indirectly through a reduction in the prevalence of smear-positive patients attending health facilities, and through a diminishing trend in notifications if case detection is maintained at a constant level. Diminished prevalence reduces transmission, which can be measured through surveys of prevalence of infection in children, repeated every 5 years. Surveys of the prevalence of infection allow the annual risk of tuberculosis infection and its trend to be estimated.

Reduction in incidence is difficult to measure because operational factors affect case detection and notification. At a constant level of case detection, the trend of notification is a proxy for the trend in incidence. The maximum annual reduction in incidence and transmission expected as a result of a good programme is around 12–15% per year (e.g. Germany, Netherlands, New York City); in developing countries 7–10% per year is very good (Brazil/ Rio Grande do Sul, Chile, Cuba, Peru) (2–6). Reduction in transmission results in a more rapid decrease of incidence in children and young adults and changes the age and sex distribution of cases. Notified incidence of tuberculosis and of tuberculous meningitis in children under 5 years of age reflects the reduction of transmission as well as the protective effect of BCG vaccination; at constant vaccination coverage these are good indicators of the programme impact on transmission.

Prevalence of drug resistance – particularly multidrug resistance, indicating the negative impact of poor quality treatment programmes – is a complementary indicator. A high rate of primary multidrug-resistant tuberculosis interferes with achievement of high cure rates through an increase of failures (drug resistance) and of case-fatality, besides increasing mortality, prevalence, and transmission.

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72. What are examples of effective tuberculosis control programmes?

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An effective tuberculosis control programme detects at least 70% of new sputum smear-positive cases and successfully treats at least 85% of cases detected. An effective programme prevents the creation and spread of drug-resistant forms of tuberculosis by ensuring that cases are detected quickly and placed on proper regimens. A stricter definition of an effective programme, however, should be based on the ultimate capacity of the programme to stop tuberculosis transmission and, as a result, to reduce incidence progressively until tuberculosis is eliminated as a major public health problem. This may not be achieved by curing 85% of detected cases if insufficient cases are detected.

In order to achieve these outcomes, an effective programme ensures guidelines, training, and resources for good tuberculosis case management and gives priority to detection and treatment of the sources of infection. Such a programme monitors both process and impact. Effectiveness is measured indirectly in terms of impact on mortality, morbidity, and transmission; programme quality can be measured directly in terms of case-fatality, cure, and coverage.

As of early 2002, about 155 countries worldwide had adopted a tuberculosis control strategy following the WHO recommendations. However, only 102 of them had achieved full population coverage, thus guaranteeing potential access to all people living in the country. Only fifteen countries had achieved the global targets by early 2002. An additional 54 countries had a detection rate of at least 50% and a treatment success rate of at least 70% (1).

Probably one of the best recent examples of a country with an effective tuberculosis control programme is Peru. After implementing a new strategy of tuberculosis control following WHO recommendations, Peru reached the WHO targets in 1995 and has maintained its performance since then. The estimated case detection rate was more than 90% in 1999. Of all cases analysed in 1998, 90% were successfully treated.

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More importantly, there is now evidence of a decline in notification of new pulmonary tuberculosis cases following 2 years of increase immediately after the implementation of the revised programme in 1991. This decline has averaged 7.5% per year nationally, despite a 10-fold increase in diagnostic effort. Compared with previous trends, the implication is that some 16% of expected cases and 70% of expected deaths were averted between 1991 and 1999 (2). This was achieved through decentralization of diagnostic capacity to well-equipped health centres around the country and effective case management based on direct observation of treatment. As a result, default rates have been minimized and more than 90% of cases have been cured.

Health services in Peru have been equipped with the necessary diagnostic tools; general health staff have been intensively trained and retrained on tuberculosis case management; an effective supply system has ensured continuous supply of drugs; an adequate information system has allowed programme performance to be monitored and corrective action taken; and a general information campaign has brought knowledge and awareness of tuberculosis to all levels of the community. The programme has been fully supported by the commitment of the government to fight tuberculosis. Local areas monitor standard as well as important locally defined indicators (e.g. delay in diagnosis, causes of default, proportion of symptomatic patients examined). A capable management system has been put in place and maintained over the years at national and regional levels. This is a recipe for effective tuberculosis control in developing countries.

Similar successful programmes were set up in other Latin American countries such as Chile, Cuba, and Uruguay, as well as in Morocco and Viet Nam. Other programmes that have achieved remarkable results in terms of high cure rates are those of Benin, Cambodia, China, Malawi, Nicaragua, and United Republic of Tanzania (3–10). In these countries, however, there is no definitive nationwide evidence yet that incidence has decreased as a result of the tuberculosis control efforts.

One of the best-documented effective programmes in a developing country is the tuberculosis control programme of Beijing, China (11). This programme has used direct observation of treatment since 1979, and has documented a substantial and progressive decline in tuberculosis cases (87% reduction in prevalence from 1979 to 1990), deaths (80% reduction), and chronic cases. Drug resistance has remained minimal. One interesting aspect of this programme is the systematic, independent verification that treatment is being directly observed as per policy.

Effective tuberculosis control is reflected by the very low notification rates (as a proxy for incidence rates) in many European countries and in the USA (1). In the USA, a strengthened notification system, the establishment of clear standards of care, the use of special measures for HIV-infected individuals and recent immigrants, and infection control measures, especially in congregate settings, have all contributed to reversing the increasing trend observed between the mid-1980s and 1992 (12). In the USA, one of the best examples of an effective tuberculosis control programme is that of New York City. There, the number of tuberculosis cases rose dramatically in the

1980s until 1992, and began decreasing after the implementation of a revised control programme. The experience in New York City shows that multidrug-resistant tuberculosis can be reduced rapidly even in the context of an HIV epidemic. Within six years, the programme reduced multidrug-resistant cases by 80% and USA-born tuberculosis cases by more than 60%. Control measures included proper short-course regimens and directly observed treatment, which allowed the achievement of high completion rates; infection control interventions in congregate settings, such as hospitals, shelters for the homeless, and correctional institutions; and the adoption of adequate treatment regimens for cases with susceptible and multidrug-resistant strains (13).

An ideal programme not only meets the targets for case detection and cure, but also ensures *patient-friendly* services that make patients feel respected and valued, thereby further increasing the likelihood of high detection and cure rates. Furthermore, an ideal programme demands rigorous accountability from health workers while also ensuring their input and involvement in improving the programme. Such a programme also ensures the continuous and accurate analysis of data to allow objective evaluation and progressive improvements in performance, creating a self-sustaining positive feedback loop. Finally, an optimal programme makes efficient use of resources, generates and documents cost savings, and leverages available human and financial resources in order to ensure long-term sustainability.

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73. What are the relative priorities for a tuberculosis control programme, and what activities should not be undertaken?

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Priority-setting in a tuberculosis control programme is based on programme objectives, the effectiveness of interventions, and the resources available. The first priority is to identify, cure, and document cure among patients seeking care in health facilities. A reasonable target is 85% cure of new sputum smear-positive patients. Once this is achieved, programmes can expand coverage to detect more cases and to detect cases earlier. These first priorities aim to directly cut the chain of transmission and reduce mortality. This is achieved by accurate and prompt diagnosis, free provision of drugs, regular intake of drugs, and systematic monitoring of successive cohorts of pulmonary smear-positive patients. For this to occur, a programme must ensure:

- Organization of outpatient treatment for tuberculosis patients (all forms, both new and re-treatment), including guidelines, training, supplies, registration, sputum smears, monitoring, and supervision. This includes directly observed treatment decentralized to peripheral health workers and community volunteers who are convenient to the patient.
- Organization of diagnosis, including the laboratory network, publication of guidelines, training, quality control, registration, monitoring, and supervision.
- Implementation of case detection in outpatient health facilities, including training and monitoring. This also includes information to the community regarding free availability of tuberculosis diagnosis and cure and the need for prompt evaluation for diagnosis of persons with prolonged cough.

Secondary priorities, which should be incorporated gradually once the basic package is producing satisfactory results, include:

- Enhanced quality control of drugs.
- Expansion of case detection and treatment to nongovernmental institutions and private practice.

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- Expansion of the laboratory network for culture and development of susceptibility testing at the national laboratory. Use of culture for diagnosis in smear-negative patients suspected of having tuberculosis.
- Formulation and implementation of diagnostic and treatment guidelines for children and extrapulmonary cases, associated tuberculosis and HIV/AIDS, tuberculosis in prisons, migrants and other special groups.
- Surveillance of case notification, drug resistance, tuberculosis/HIV, meningitis in children, prevalence of infection, and mortality (if death registration is available).
- Operational research, with emphasis on descriptive epidemiology; risk factors for delayed diagnosis, default, treatment failure, and death; monitoring of cost-effectiveness of interventions and rationalization of care (hospitalization, surgery, referral system, specialized care, integration with other control activities within general health care).

Depending on availability of resources and the epidemiological context, the following activities may also be undertaken:

- Expanded examination of contacts and high-risk groups for diagnosis and preventive treatment (e.g. those living in congregate facilities, high-prevalence groups, HIV-infected persons, persons with incompletely treated tuberculosis in the past).
- Expansion of the tuberculosis package of care to drug-resistant cases. This activity has a much higher priority in areas with high rates of initial multidrug-resistant tuberculosis that also have large populations of immunosuppressed persons, particularly where there are congregate settings (e.g. AIDS wards, prisons, mines).

Staff and other resources of the tuberculosis programmes and of the health delivery system should *not* be used for activities of low yield and little benefit for the community.

Some examples of unnecessary, inadequate, or damaging interventions

Case detection

- “Active” case detection through mass miniature radiography in the general population (see “What is the role of case detection by periodic mass radiographic examination in tuberculosis control?”, page 72).
- Screening – with tuberculin, X-ray, or bacteriology – of low-risk populations such as students, teachers, food handlers, etc.
- Active promotion of services that are not available to the community; for instance, promotion when there are insufficient or irregular supplies of drugs or the treatment services are poorly organized and are achieving low cure rates.
- Use of mobile units specifically for tuberculosis, isolated from permanent health facilities or staff able to provide regular treatment until cure.

- Establishment of tuberculosis diagnostic centres isolated from general health care – most patients with symptoms consult general facilities, without knowing that they have tuberculosis.
- Diagnosis on a clinical basis only, or on the basis of radiology alone. Because of low specificity, many patients without tuberculosis or with healed lesions will be put on treatment unnecessarily, risking harm and wasting resources.
- Request for smears on different successive days, with multiple visits by the patient (three smears can be collected in two visits, spot – early morning – spot).
- Centralized diagnosis or confirmation of diagnosis at specialized institutions (e.g. tuberculosis dispensaries). Most patients with respiratory symptoms first consult the outpatient departments of general hospitals, primary health centres, and private physicians.
- Use of complex inappropriate technology, for instance, use of the polymerase chain reaction in control programmes.

Treatment

- Centralized treatment only at specialized institutions. Although the knowledge of tuberculosis and of clinical complications is usually better and there may be more diagnostic resources, central facilities lose a higher proportion of patients because of greater distance from patients' homes. Except in some urban settings, these facilities should be used only for referral of difficult cases for diagnosis or management of complications, and patients should be referred or transferred to an easily accessible treatment point as soon as possible.
- Asking the patient to buy the missing drugs because of irregular drug supply. This leads to monotherapy and drug resistance, loss of confidence in the service, and treatment default.
- Prolongation of treatment. Very few patients benefit from longer treatment, and there is no justification for extending treatment for all. There is no evidence that longer treatment for meningitis or other forms of tuberculosis is of additional benefit.
- Addition of costly vitamins, nutritional supplements, minerals, and other medication, unless there is a specific deficiency. The nutritional status of the patient improves as a consequence of reduced bacterial load. Nutrition is an important risk factor for breakdown from tuberculosis infection to disease, but has no impact on cure when short-course, high-efficacy regimens are used. Food (for the patient and the family) can, however, be a highly effective incentive to improve treatment adherence.
- Monthly follow-up with X-rays.
- Use of surgical masks by health personnel. These masks are not useful in preventing inhalation of bacilli, they alienate staff from patients, and give the staff a false impression of safety.

Monitoring (including research)

- Monitoring large numbers of process indicators such as number of patients on treatment at any point in time. Standard indicators (diagnostic quality, conversion rate, cure rate, estimated annual detection rate) are revealing and should not be diluted by less important information.
- Extensive monthly reports. Quarterly reporting is generally sufficient for prompt and effective monitoring.
- Combining tuberculosis data collection (quarterly reporting) with the general health information system. On the other hand, quarterly reporting information should be disseminated to as wide an audience as possible – through the general health information system and otherwise.
- Use of excessive resources in pilot projects or operational research, making the tested intervention inapplicable or not sustainable for expansion to the whole country.

74. What is the impact of HIV on the epidemiology of tuberculosis in a community?

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HIV infection reduces cell-mediated immunity and is a powerful risk factor for the development of tuberculosis (1, 2). The impact of HIV on the epidemiology of tuberculosis depends on the extent of overlap between the population infected with HIV and that infected or at risk of becoming infected with *Mycobacterium tuberculosis*. At present, about 70% of people in the world co-infected with HIV and *M. tuberculosis* live in sub-Saharan Africa (3).

The annual risk of developing active tuberculosis disease in a co-infected person ranges from 5% to 15%, depending on the degree of immunocompromise (1). There is also good evidence that HIV infection favours rapid progression from exposure to *M. tuberculosis*, through infection, to active tuberculosis. Among severely immunocompromised patients hospitalized with the complications of AIDS and exposed to infectious patients, the median time between exposure and disease was 12 weeks (4).

Impact of HIV

HIV has its greatest impact on tuberculosis in sub-Saharan Africa, although in parts of India, Myanmar, and Thailand the association between these two infections is becoming increasingly apparent. There are many aspects to the impact of HIV, described below.

Tuberculosis case numbers

In the past 10–15 years, tuberculosis case numbers have increased 300–400% in high HIV-prevalent countries of Africa, mainly because HIV increases the risk of disease reactivation in people with latent *M. tuberculosis* (5). Along with the increase in case numbers, there has been a disproportionate increase in cases with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis (1).

Increased case numbers place an immense burden on tuberculosis control efforts: more staff are needed, particularly tuberculosis programme officers and laboratory

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personnel; there is an increased need for laboratory resources, drugs, sputum containers, and stationery; where patients are hospitalized for the initial phase of treatment, wards become overcrowded, making consistently good nursing care impossible and increasing the risk of nosocomial infection.

Hot spots for tuberculosis transmission

Hot spots for transmission, fuelled by concurrent HIV infection, may occur in places where people are crowded together, such as prisons, refugee camps, mines, health care institutions, and boarding schools. In such situations, active case detection may sometimes be required to curtail tuberculosis transmission.

Increased case fatality

HIV-positive tuberculosis patients experience HIV-related morbidity during tuberculosis treatment. Adverse reactions to antituberculosis drugs, particularly thioacetazone-induced cutaneous reactions, are more frequent, leading to interruptions of treatment and occasional fatalities (6). It is not surprising that HIV-infected patients have a much higher mortality during and after tuberculosis treatment compared with HIV-negative patients. In sub-Saharan Africa, approximately 30% of HIV-infected, smear-positive tuberculosis patients will die within 12 months of starting treatment, and about 25% of those who complete treatment will die during the subsequent 12 months (1).

The high death rates in HIV-infected, smear-positive tuberculosis patients mean that treatment is less cost-effective in terms of years of life saved than previously calculated for HIV-negative patients. In the pre-HIV era, smear-negative pulmonary tuberculosis was a disease with a good treatment outcome. Evidence is slowly accumulating in sub-Saharan Africa that the prognosis for HIV-infected, smear-negative pulmonary tuberculosis patients may be worse than that for patients with smear-positive pulmonary tuberculosis (7).

Recurrence of tuberculosis after completion of treatment

Recurrence rates (defined as return of clinical evidence of active tuberculosis, positive sputum smears, or positive cultures of *M. tuberculosis*) are higher in HIV-infected patients. The use of non-rifampicin-containing regimens and treatment interruptions as a result of drug reactions are associated with an increased risk of recurrence of tuberculosis (1). Recurrence includes both true relapse and recurrent disease following reinfection. The proportion of tuberculosis recurrence due to disease reactivation versus reinfection is unknown.

Drug resistance

Outbreaks of multidrug-resistant tuberculosis have been reported from both industrialized and developing countries in patients with HIV infection. HIV itself does not

cause multidrug-resistant tuberculosis, but it fuels the spread of this dangerous condition by accelerating the progression from infection to disease.

Global targets for tuberculosis control

The overall objective of tuberculosis control is to reduce mortality, morbidity, and transmission of the disease. At present, the best way to achieve this is to focus on new cases of smear-positive tuberculosis, curing at least 85% of detected smear-positive cases, and detecting at least 70% of new infectious cases. HIV makes the targets for cure and detection rates difficult to reach. Cure rates of 85% in smear-positive tuberculosis cases are almost impossible to achieve because of high HIV-related mortality. The case detection target of 70% is also impossible to verify because a method for estimating the total number of such cases with certainty (for use in the denominator) has not yet been found, particularly in the context of a high prevalence of HIV.

Implications

HIV inexorably reveals any weakness in a tuberculosis control programme. Low detection rates lead to rapid spread of infection and disease from untreated patients. Low cure rates, if combined with high default rates, may result in the rapid emergence and spread of drug-resistant strains. And ineffective infection control facilitates rapid and potentially extensive institutional spread of tuberculosis. Tuberculosis rates will generally rise for as long as HIV prevalence rises. If the prevalence of HIV in the adult population reaches 5% in a developing country, current technology cannot contain the increase in cases. DOTS can, however, prolong the lives of individual patients, prevent drug resistance, and blunt the increase in cases. Increased cases result from the increased risk of active tuberculosis in HIV-infected patients, hot spots for tuberculosis transmission, and increased recurrence rates. Ultimately, HIV prevalence will reach a plateau, and it is then likely that tuberculosis case notifications will also plateau, although at rates several times higher than those seen in the pre-HIV era. The control of tuberculosis in high HIV-prevalent areas will depend to a large extent on the control of HIV.

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75. How can tuberculosis control services be promoted and sustained?

*T. Frieden*¹

Challenges and advantages

Effective tuberculosis control requires sustained political and administrative commitment at national and local levels. An effective tuberculosis control programme must therefore initiate, build, and sustain this commitment – a challenging task. Most tuberculosis patients are economically disadvantaged and exert little political influence. Moreover, the disease tends to alienate patients; tuberculosis patients do not naturally form associations or support groups to lobby for more services and resources. Finally, tuberculosis control is a long-term struggle that requires continued support.

Approximately 2 billion people alive today are infected with tuberculosis bacteria, and at least 100 million of them are likely to develop active tuberculosis at some point in their lives. Thus, even if the spread of tuberculosis could be completely stopped and an effective vaccine to prevent tuberculosis in uninfected persons were discovered and applied widely, tuberculosis control services would be needed for at least another 40–50 years.

In addition, the HIV epidemic has drastically increased tuberculosis caseloads, generally in countries with limited resources. Health services in many developing countries are undergoing reform, raising new challenges for tuberculosis control. Although health sector reform can potentially improve efficiency and increase community involvement, in practice it often translates into user fees, reduced services, and limitations in the ability of specific disease control programmes, such as tuberculosis control, to function effectively (1).

Despite these substantial challenges, tuberculosis control programmes have several advantages. First, tuberculosis is a curable disease, and the tuberculosis epidemic is a winnable battle – in contrast to many other health and social problems. Second, tuberculosis control services are highly accountable, and are therefore appealing to many decision-makers. A tuberculosis control programme can track the exact number of patients examined, diagnosed, treated, and cured, make a reasonable estimate of the number of deaths prevented by these activities, and report this information to those

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who fund and support the programme. Third, tuberculosis control is highly cost effective (see “Is DOTS cost-effective?”, page 246). Fourth, many people living in high-prevalence areas recognize tuberculosis as an important cause of sickness and death, and rightly perceive effective tuberculosis control services as a critical indicator of good governance. Fifth, the DOTS strategy can be implemented successfully in almost any context, as it relies on relatively simple interventions. Finally and perhaps most importantly, DOTS is rooted in reliable scientific evidence – including data to support the diagnostic strategy as summarized in the case detection section of this book; randomized controlled clinical trials demonstrating efficacy of practical, short-course treatment regimens reviewed in the treatment section; and a recording and reporting system that allows individual and aggregate evaluation to identify problems rapidly (see “Why is a recording and reporting system needed, and what system is recommended?”, page 270).

Promoting tuberculosis control services

In general, effective tuberculosis control services are best promoted at national level by a tuberculosis programme that is adequately staffed and supported. The programme’s overall strategy should be to establish sound technical policies, make maximum efforts to involve and convince key decision-makers of the importance of implementing these policies, and engage individuals, groups, and communities from outside the government in promoting effective tuberculosis control. Most programmes require the authority to hire staff, purchase goods and equipment, and contract for services. These functions can be performed effectively only if there is political and administrative commitment from within the country or area.

Sustaining tuberculosis control services

Tuberculosis control is a long-term battle. In several countries, initial success in the control of tuberculosis led to complacency, a subsequent resurgence of cases, and the emergence and spread of drug resistance (2, 3). The term “U-shaped curve of concern” has been used to describe the phenomenon of declining interest, commitment, and support for tuberculosis control, followed by an increase in disease burden resulting from poor programme performance (4). The most important strategy to preserve tuberculosis control services is to ensure that they are implemented effectively and that this success is systematically documented and publicized widely to those who allocate funds. Effective implementation requires ongoing analysis of programme data to objectively evaluate and continuously improve services. A key strategy is to identify and maintain the support of key external constituencies within the country. Public sector management tends to be driven by constraints rather than tasks (5). To limit the impact of this inevitable tendency, programmes must seek support from individuals, institutions, and nongovernmental groups. In the case of tuberculosis control, these include individuals and groups interested in ensuring that effective tuberculo-

sis control services remain available in the community. Individuals and groups outside government can therefore play a critical role in promoting and sustaining effective tuberculosis control services.

Ultimately, the establishment and maintenance of high-quality tuberculosis control services reflect effective national leadership and service.

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