

Selected Readings

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**Tuberculosis
Control**

**An
Annotated
Bibliography**



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Contents

Introduction	2
Political will and commitment	3
Case detection predominantly through sputum smear microscopy among patients attending health care facilities	5
Short-course chemotherapy (directly observed, standardized, and free-of-charge)	9
<i>Intermittent Treatment</i>	9
<i>Directly Observed Treatment</i>	14
<i>Treatment of HIV-infected TB patients</i>	17
Regular supply of all essential anti-TB drugs	20
Systematic monitoring and evaluation	21

Introduction

This bibliography is intended as a resource for National Tuberculosis Programme (NTP) Managers and other personnel working in TB control. The bibliography should also be useful for those who teach TB control in schools of public health, medical institutions and allied professional schools. The aim is to provide a selective overview of the main aspects of TB control, providing the scientific basis of the key components of the DOTS strategy. This list is not comprehensive, nor is it representative of all aspects of TB control. It is largely drawn from the scientific literature published in English. The bibliography includes representative examples of scientific papers based on country-level and regional information. We hope that this bibliography will provide answers to many of the questions which health workers may face in the course of their TB control activities.

This is the second edition of the bibliography. Some seminal articles referenced in the first edition (WHO/TB/97.228) have been retained. At the request of readers, additional statistical data from the original articles have been included. The structure of this edition follows that of the DOTS strategy. Comments and suggestions for improvement for future editions of this bibliography are welcomed. Please address correspondence to:

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Political will and commitment

Tuberculosis Research Centre, Chennai. Trends in the prevalence and incidence of tuberculosis in South India. *International Journal of Tuberculosis and Lung Disease* 2001;5:142-157.

Knowledge of epidemiological trends in tuberculosis is helpful in planning, monitoring and evaluating national tuberculosis programmes, especially in high prevalence areas. Results of this large field trial started in 1968-1970, and 15-year follow-up, showed little decrease in annual risk of tuberculosis infection (-2% annually). Incidence of smear-positive tuberculosis cases declined by only about 2.3% per annum (157 to 113/100 000) — approximately the same rate as population growth in this period. Prevalence of culture-positive tuberculosis decreased by only 1.4% per annum (870/100 000 1968-1975 to 694/100 000 in 1984-1986), and, reflecting the lack of effective treatment, there were 3.5 times as many prevalent cases as incident cases. In fact, “the ratio of prevalence to incidence increased steadily over time, a symptom of ineffective treatment and ‘pooling’ of partially treated cases.” Furthermore, even the slight decrease in cases was entirely due to a decrease in the development of TB in persons with abnormal radiographs at baseline, which “was likely due to a greater likelihood that subjects with radiographic abnormalities had received anti-tuberculosis drugs, as treatment became more wide-spread.” The study meticulously documents the continuing burden of tuberculosis and the need for effective control measures; the area has begun implementing the DOTS strategy, and the impact of DOTS on TB epidemiology will be documented in the years to come.

Dye C. Tuberculosis 2000-2010: control, but not elimination. *International Journal of Tuberculosis and Lung Disease* 2000;4:S146-S152.

Worldwide there are 8 million new cases of TB (136 per 100 000 population) and 2 million deaths due to TB per year. India, China, Indonesia, Bangladesh, and Pakistan account for more than half the incidence. The burden of TB can be reduced substantially with DOTS. However, less than one fourth of smear-positive cases received DOTS in the year 2000. DOTS effectively reduces incidence, duration of illness and risk of death. Global implementation of DOTS can cut the disease burden by half. However, because of endogenous reactivation, multidrug-resistant TB, and the increase in HIV incidence in recent years, control strategies need to be improved. Without improvements in application of control methods, the number of cases will rise to 11 million by 2020. Methods and tools for impact assessment, shortening diagnostic and treatment delays, more effective case detection and treatment, and a high efficacy vaccine will be needed for elimination of TB.

Political will and commitment

Tupasi TE, Radhakrishna S, Rivera AB, et al. The 1997 Nationwide Tuberculosis Prevalence Survey in the Philippines. *International Journal of Tuberculosis and Lung Disease* 1999;3:471-477.

Since the previous survey in 1981-1983, TB case rates remained high, and the prevalence of active pulmonary TB cases was unchanged (4200/100 000 population). There were 810 culture-positive and 310 smear-positive cases per 100 000 population. The prevalence was higher in males than females, and similar in urban and rural populations. This continued high prevalence reflects ineffective tuberculosis control; there was a minimal decrease in cases since only 2% of the population was on DOTS in 1996. However, by 2000 the country was rapidly scaling up DOTS.

Nyangulu DS, Harries AD, Kang'ombe C, et al. Tuberculosis in a prison population in Malawi. *Lancet* 1997;350:1284-1287.

A high rate of pulmonary tuberculosis was present (5.1% of prisoners screened). Active TB transmission was suggested by the fact that all prisoners with TB, except one, developed symptoms of pulmonary TB after entering the prison. "As a result of this study, the National Tuberculosis Control Programme has implemented interventions in eight prisons in Malawi to improve tuberculosis control ...".

Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for tuberculosis. *Journal of the American Medical Association* 1995;274:945-951.

The authors implemented a programme of directly observed treatment using short-course chemotherapy, first to selected patients, then to virtually all patients in the city of Baltimore. Case rates declined much more rapidly than in the pre- directly observed treatment period, and significantly faster when virtually all patients received observed treatment than when selected patients received it. Case rates declined more rapidly than in cities without DOTS, even though Baltimore had a high rate of AIDS, and even after controlling for socioeconomic differences. "Baltimore's annual TB case rates dropped the most, both in absolute and relative terms, compared with the other major cities in this study.... Directly observed therapy seems imperative among populations and within regions where the disease has become epidemic. Failure to resolve the age-old TB problem of treatment completion will prove costly in both economic and human terms."

Case detection predominantly through sputum smear microscopy among patients attending health care facilities

Wilkinson D, Newman W, Reid A, Squire SB, Sturm AW, Gilks CF. Trial-of-antibiotic algorithm for the diagnosis of tuberculosis in a district hospital in a developing country with high HIV prevalence. *International Journal of Tuberculosis and Lung Disease* 2000;4:513-518.

A diagnostic algorithm was tested based on sputum smear microscopy, chest radiographs, culture, and clinical assessment. Of the 280 TB patients assessed, 160 (57%) were sputum smear-positive. The 120 smear-negative patients were treated with a trial of antibiotics. Of these, 46 (38%) responded to a 5-day course of amoxicillin, and, of those who did not, 34 (28%) responded to a subsequent course of erythromycin. The remaining 40 (33%) patients who did not respond to either antibiotic were considered smear-negative TB cases. Of these latter 40 patients who had negative smears and no response to antibiotics, 11 (28%) had negative cultures and may not have had tuberculosis. In addition, 24 culture-positive TB patients (45% of all smear-negative, culture-positive cases) responded to either amoxicillin (9, 17% of all smear-negative, culture-positive patients), or to the second antibiotic course, with erythromycin (15, 28% of all smear-negative, culture-positive patients). The sensitivity (89%) and specificity (84%) of the algorithm for culture-positive TB were high. If only amoxicillin had been used in this study, a much greater proportion of smear-negative, culture-positive patients would have been identified (83% vs 55%), although the proportion of identified patients who were culture-negative and who might have been unnecessarily treated for TB would have increased from 28% to 39%. This study suggests that only a single antibiotic course should be used in the diagnostic algorithm, and also suggests that the diagnostic yield of different broad-spectrum antibiotics should be systematically assessed in different communities.

Marciniuk DD, McNab BD, Martin WT, Hoepfner VH. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. *Chest* 1999;115:445-452.

The authors report that the proportion of culture-positive pulmonary patients with normal chest radiographs in Saskatchewan, Canada, is increasing (10% in 1996-1997), probably due to improved case detection and laboratory methodologies. Such patients, however, show symptoms typical of TB, the most common being cough (76%) and sputum production (64%).

Nguyen TNL, Wells CD, Binkin NJ, Becerra JE, Pham DL, Nguyen VC. Quality control of smear microscopy for acid-fast bacilli: the case for blinded re-reading. *International Journal of Tuberculosis and Lung Disease* 1999;3:55-61.

In an unblinded set of slides, 2.9% of positive slides were misread as negative, while none of the AFB-negative slides were re-read as positive. In a blinded set, 18.7% of the positives were misread as negative. In another unblinded set, several scanty positive slides were deliberately mislabeled as AFB-negative. In this unblinded and mislabeled set, 11.3% of the positives were misread as negative. False-negative error is more common than false-positive error as only one negative slide was misread as positive in the three sets. Blinded re-reading is more effective in detecting false-negative errors. Re-reading should be done by a person who did not read the first time, and the results of the first reading should not be known to the second reader. Misclassifications are common in sputum smear microscopy if quality control is performed through unblinded re-reading.

Van Deun A, Portaels F. Limitations and requirements for quality control of sputum smear microscopy for acid-fast bacilli. *International Journal of Tuberculosis and Lung Disease* 1998;2:756-765.

There is a consensus on the need for quality control (QC) of microscopy. This article provides practical observations and suggestions, emphasizing that regular QC with feedback can effectively motivate laboratory technicians in primary health care institutions. It is essential that all slides be properly identified and kept and that QC readers be blind to results of the first reading. "Umpire" re-checking is essential because those performing cross-checking may have higher error rates than some peripheral readers. Clinically significant false positives are rare and often clustered. Re-staining of slides may be important, particularly for apparent false-positives (because carbol may have faded) and for a sample of negative slides to determine if false negatives are present. More sophisticated sampling using blinded re-reading of a randomly selected sample of slides may reduce the work-load of cross-checking while maintaining adequate quality. QC can identify but not correct logistic problems such as insufficient training of staff and poor quality microscopes and reagents.

Jones BE, Ryu R, Yang Z, et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. *American Journal of Respiratory and Critical Care Medicine* 1997;156:1270-1273.

Classically, "primary" tuberculosis and "reactivation" tuberculosis were believed to have distinct radiographic patterns, with cavitation more common in reactivation tuberculosis and mediastinal adenopathy and lower lobe infiltrates more common in primary TB. This article evaluated this theory using data from DNA fingerprinting (RFLP analysis) to classify TB as being primary or reactivation. Contrary to expectations, the authors found that "chest radiographic findings in adults with tuberculosis of recent infection are similar to those in

patients with remote infection.” The authors found increased rates of mediastinal adenopathy and pleural effusion in HIV-infected patients, but found that these patterns were as common in patients with recent as with remote infection, and concluded that “the distinctive chest radiographic findings in HIV-infected patients with tuberculosis are not due to an increased frequency of recent infection”. This study again demonstrates the lack of specificity of chest radiographs in classification of TB.

Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beinr Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clinical Infectious Disease* 1997;25:242-246.

Chest radiograph patterns in TB patients were related to the stage of HIV disease. Radiographs show an increase in the frequency of adenopathy and decrease in cavitation with progression of immunosuppression. Of patients with culture-positive TB, normal chest radiographs were found in 8% of bacteriologically confirmed patients. Patients with negative sputum smears had a normal chest radiograph more frequently (15%) than patients with positive smears (5%). At higher levels of immunosuppression ($CD4^+ < 200/mm^3$), there was more hilar/mediastinal adenopathy on radiography; lesser degrees of immunosuppression ($CD4^+ \geq 200/mm^3$) were associated with cavitation.

Wilkinson D, De Cock KM, Sturm AW. Diagnosing tuberculosis in a resource-poor setting: the value of a trial of antibiotics. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997;91:422-424.

Smear-negative, culture-positive tuberculosis, otherwise identified only through culture, can be diagnosed effectively and cheaply in a resource-poor setting using a combination of Ziehl–Neelsen staining and a trial of antibiotics.

Of 334 patients, 142 (43%) were diagnosed with active TB by culture, of whom 86 were sputum smear-positive. Of the 237 smear-negative patients, 56 (24%) had positive cultures. Half of the smear-negative, culture-positive patients (28) were diagnosed with TB on account of failure to respond to a trial of antibiotic. The remaining 28 (20% of all cases) were not diagnosed with TB, and most (57%) of these were diagnosed as pneumonia and discharged. In addition, 32 culture-negative patients failed to respond to the antibiotic and may have been wrongly diagnosed as having TB (20% of 157 cases with TB). The diagnostic sensitivity of the algorithm was 80%, and specificity was 78%.

Styblo K. *Epidemiology of tuberculosis*. VEB Gustav Fisher Verlag Jena 1984.

“X-ray evidence of clinically active tuberculosis is very unreliable.... The patient himself will remain the focal point from which to start case-finding of tuberculosis. He will not “forget” his disease because the vast majority of serious forms of tuberculosis cause

Case detection

unpleasant symptoms.... Mass indiscriminate radiography will have no place in any future tuberculosis control programme.... Well-organized outpatient chemotherapy, especially if provided free of charge, will attract symptomatic cases from far and wide.... Mankind will only be freed of tuberculosis if a reasonable annual decrease in the risk of tuberculosis infection is achieved in all developing countries.”

Toman K. *Tuberculosis case-finding and chemotherapy*. World Health Organization: Geneva, 1979.

“Most new positive results are obtained from the first and second specimens.” “In new, untreated patients with prolonged chest symptoms and abnormal lung X-ray shadows, two consecutive smear examinations (e.g., of on-the-spot and overnight sputum) were practically equivalent to one culture examination.” X-ray failed to diagnose 10%–15% of culture-positive patients, and diagnosed nearly 40% of patients as having TB who had negative cultures and likely did not have active TB. “Patients without symptoms are not an urgent matter of public health concern. Their prognosis is likely to be favourable and their infectiousness, if any, is slight.”

Garland L H. *Studies on the accuracy of diagnostic procedures*. *American Journal of Roentgenology Therapeutic Nuclear Medicine* 1959;82:25-38.

Review of diagnostic accuracy of X-rays. Readings were discordant for 30% of X-rays read by different experts, and 21% of experts reading the same film at two separate times. Consistency in reading by highly experienced radiologists was only slightly better.

**Short-course chemotherapy
(directly observed, standardized,
and free-of-charge)**

Intermittent Treatment

Khatri GR, Frieden TR. The status and prospects of tuberculosis control in India. *International Journal of Tuberculosis and Lung Disease* 2000;4:193-200.

Reports results of the first 6 years of DOTS implementation in India. Regimens used for Category I, II, and III patients were 2H₃R₃Z₃E₃/4H₃R₃, 2H₃R₃Z₃E₃S₃/1H₃R₃Z₃E₃/4H₃R₃E₃, and 2H₃R₃Z₃/4H₃R₃; 146,012 patients were put on treatment. Quality of diagnosis was good and treatment success was achieved in 81% of new smear-positive patients, 82% of new smear-negative patients, 89% of patients with extrapulmonary tuberculosis, and 70% of re-treatment patients. Treatment success rates are more than double and death rates are less than one fourth those of the previous programme. Since publication, the programme increased coverage to 400 million population by 2001 and had treated more than 500,000 patients. "The key challenge in the years ahead will be to balance the urgent need for rapid expansion with paramount importance of ensuring quality of implementation."

Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *International Journal of Tuberculosis and Lung Disease* 1999;3:S231-S279.

Work in collaboration with centres in Africa, India, Hong Kong, Singapore, Prague, Algeria, Zimbabwe, and Korea is summarized. Controlled clinical trials ensured random allocation of patients to study regimens, treatment supervision, and systematic follow-up. Intermittent drug regimens were tried. These document the need for an initial intensive phase of two months followed by a continuation phase of four months to achieve 95% relapse-free cure among patients with drug-susceptible organisms. Intermittent treatment is equally effective as daily treatment and much more convenient for patients and health workers. These studies have documented the components required for successful TB control programmes, i.e. effective treatment regimens, directly observed treatment, and surveys for monitoring. Selected studies are summarized in the table below.

Intermittent short-course chemotherapy

Studies using short-course chemotherapy

Date of start study and place	Regimen (%)	Patients assessed for relapse	Relapse rate in 2-year follow-up
1973 Singapore	2HRZS/2HRZ	79	11
	2HRZS/4HRZ	78	0
	2HRZS/2HR	77	8
	2HRZS/4HR	80	2
1974 Madras	2HRZS/3H ₂ Z ₂ S ₂	129	5
	2HRZS/5H ₂ Z ₂ S ₂	132	0
	2HZS/5H ₂ Z ₂ S ₂	129	4
			} 18 months
1974 Hong Kong	6HRS143	6	
	2HRZS/4H ₂ Z ₂ S ₂	87	7
	2HRZS/6H ₂ Z ₂ S ₂	87	3
	4H ₃ R ₃ Z ₃ S ₃ /2H ₂ Z ₂ S ₂	71	6
	4H ₃ R ₃ Z ₃ S ₃ /4H ₂ Z ₂ S ₂	83	1
1977 Madras	3HRZS200	20	
	3HRZS/2H ₂ Z ₂ S ₂	187	4
	3HZS/2H ₂ Z ₂ S ₂	199	13
1977 Hong Kong	6HRZE163	1	
	6H ₃ R ₃ Z ₃ E ₃ S ₃	152	1
	6H ₃ R ₃ Z ₃ S ₃	151	1
	6H ₃ R ₃ E ₃ S ₃	166	8
	6H ₃ R ₃ Z ₃ E ₃	160	2
1978 East and Central Africa	2HRZS/4HR	166	3
	2HRZS/4HZ	164	8
	2HRZS/4H	156	10
	2HRZS/6H	123	3
1978 East and Central Africa	2HRZS/4TH	105	3
	2HRZS/4H	100	11

Intermittent short-course chemotherapy

Date of start study and place	Regimen	Patients assessed for relapse (%)	Relapse rate in 2-year follow-up
1978 Singapore	2HRZS/4H ₃ R ₃	97	1
	1HRZS/5H ₃ R ₃	94	1
	2HRZ/4H ₃ R ₃	109	1
1979 Hong Kong	2H ₃ R ₃ Z ₃ S ₃ /4H ₃ R ₃ S ₃	220	3
	2H ₃ R ₃ Z ₃ S ₃ /2H ₃ R ₃ Z ₃ S ₃ /2H ₃ R ₃ S ₃	205	5
	2H ₃ R ₃ Z ₃ S ₃ /4H ₃ R ₃ Z ₃ S ₃	208	3
	2H ₃ R ₃ Z ₃ /4H ₃ R ₃ Z ₃	199	6
1980 Madras	2H ₃ R ₃ Z ₃ S ₃ /4H ₃ R ₃ S ₂	111	2
	2H ₃ R ₃ Z ₃ S ₃ /4H ₃ R ₃ S ₁	111	5
	2H ₃ R ₃ Z ₃ S ₃ /4R ₃ H ₂	101	3
	2H ₃ R ₃ Z ₃ S ₃ /4R ₃ H ₁	116	2
	2H ₃ R ₃ Z ₃ S ₃ /4H ₃ S ₂	151	3
	2H ₃ R ₃ Z ₃ S ₂ /4H ₃ R ₃ S ₂	108	3
	2H ₃ R ₃ Z ₃ S ₂ /4H ₃ R ₃ S ₁	117	4
	2H ₃ R ₃ Z ₃ S ₂ /4R ₃ H ₂	102	6
	2H ₃ R ₃ Z ₃ S ₂ /4R ₃ H ₁	109	7
	2H ₃ R ₃ Z ₃ S ₂ /4H ₃ S ₂	155	10
1983 Singapore	2HRZS(C)/4H ₃ R ₃	46	7
	2HRZS(S)/4H ₃ R ₃	47	0
	1HRZS(C)/5H ₃ R ₃	42	5
	1HRZS(S)/5H ₃ R ₃	46	2
	2HRZ(C)/4H ₃ R ₃	40	8
	2HRZ(S)/4H ₃ R ₃	44	2

Note: The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol, S: Streptomycin. C indicates Fixed-dose combination; S indicates single drugs.

Intermittent short-course chemotherapy

Yuen AP, Wong SH, Tam CM, Chan SL, Wei WI, Lau SK. Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. *Otolaryngology and Head Neck Surgery* 1997;116:189-192.

Compared the efficacy of a thrice-weekly 6-month regimen $4S_3H_3R_3Z_3/2H_3R_3$ with a thrice-weekly 9-month regimen $4S_3H_3R_3Z_3/5H_3R_3$ in the treatment of cervical tuberculous lymphadenopathy. Failure rates were 2% and 1%; cure rates were 89% and 90%. Since there was no significant difference, a 6-month regimen is recommended for tuberculosis lymphadenopathy.

China Tuberculosis Control Collaboration. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. China Tuberculosis Control Collaboration. *Lancet* 1996;347:358-362.

200 000 smear-positive patients were diagnosed. New patients were treated with $2H_3R_3Z_3S_3/4H_3R_3$ and retreatment cases with $2H_3R_3Z_3S_3E_3/6H_3R_3E_3$. The cure rate for new patients was 90% and for previously treated patients 81%. The failure rate in previously treated patients fell progressively from 18% to 6%.

Chaisson RE, Clermont HC, Holt EA, et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *American Journal of Respiratory and Critical Care Medicine* 1996;154:1034-1038.

A fully supervised 6-month thrice-weekly therapy (isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks followed by isoniazid and rifampin for 18 weeks) is highly effective in treating TB patients with or without HIV. Treatment compliance with fully supervised $2H_3R_3Z_3E_3/4H_3R_3$ was 90%, and cure rates were 81% and 87% in HIV-seropositive patients and HIV-seronegative patients, respectively. Relapse rates were 5.4% (HIV-seropositive) and 2.8% (HIV-seronegative) ($p=0.36$). Of HIV-seropositive patients, 33% died within 18 months of diagnosis, generally of non-TB causes; 3% of HIV-seronegative patients died, of unknown causes.

Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. *American Review of Respiratory Disease* 1991;143:700-706.

In 6-month intermittent anti-TB regimens containing rifampicin, isoniazid and streptomycin, pyrazinamide needs to be given only for the first 2 months. There was no additional benefit when pyrazinamide was administered for four or six months (relapse rates at 30 months: 3% for 2-month pyrazinamide, 5% for 4-month pyrazinamide, 3% for 6-month

Intermittent short-course chemotherapy

pyrazinamide). Patients on the three-drug regimens without streptomycin achieved sputum culture negativity less rapidly leading to the possibility of a small risk of failure in these groups. Therefore a fourth drug, e.g. ethambutol needs to be given in the intensive phase of treatment for smear-positive patients.

Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. *Annals of Internal Medicine* 1990;112:407-415.

Trial of the "Denver Regimen," which is 0.5HRZS–1.5H₂R₂Z₂S₂/4.5H₂R₂ given to 125 patients with every dose directly observed. Only two patients (1.6%) relapsed.

Fox W. Whither short-course chemotherapy? *British Journal of Diseases of the Chest* 1981;75:331-357.

Review of evidence for short-course treatment up to 1981. Six month regimens are only acceptable if pyrazinamide as well as isoniazid and rifampicin are used in the initial phase. Regimens of 2HRZS/4HR had relapse rates of 0%–2%. Regimens of 2HRZE/4HR, 6HRZE, and 6H₃R₃Z₃E₃ had relapse rates of 1%–2%. "The advantage of full supervision of every dose of medicament in ensuring that a very high level of success is achieved is obvious, as is the element of uncertainty introduced by depending on self-administered regimens, whatever their duration. It is paradoxical to insist on the importance of 100% success with primary chemotherapy and to use self-administered chemotherapy as a means of achieving it."

Hong Kong Chest Service/British Medical Research Council. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. *Tubercle* 1976;57:81-95.

Reports on toxicity of pyrazinamide when used in daily and intermittent regimens. The incidence of serious adverse reactions was not high. The most common adverse reaction to pyrazinamide, arthralgia, was more in the group receiving daily doses (7%) than in the thrice-weekly intermittent regimen (3%). The majority of the adverse reactions started during the first three months of therapy. The incidence of arthralgia is reduced by administering pyrazinamide intermittently, and by shortening the period of administration.

Mitchison DA, Dickinson JM. Laboratory aspects of intermittent drug therapy. *Postgraduate Medical Journal* 1971;47:737-741.

Results from a series of animal studies on intermittent treatment were reviewed and extended to study the effects of isoniazid and rifampicin on *M. tuberculosis* using cultures and infected guinea-pigs. The efficacy of treatment increased as the interval between

Directly observed treatment

doses was increased (from 1-4 days) for rifampicin, ethambutol, and isoniazid, but not with thiacetazone, ethionamide or streptomycin. This provides the scientific basis of intermittent treatment, which for rifampicin, ethambutol and isoniazid was more effective than daily treatment in this model.

Directly observed treatment

Ollé-Goig JE, Alvarez J. Treatment of tuberculosis in a rural area of Haiti: directly observed and non-observed regimens. The experience of Hôpital Albert Schweitzer. *International Journal of Tuberculosis and Lung Disease* 2001;5:137-141.

Directly observed treatment given by former tuberculosis patients resulted in higher success rates than self-administered treatment (87% vs 58%). Of 281 patients, 138 (49%) were treated by directly observed treatment and 143 (51%) were treated without observation. Default rates were four times higher and deaths were three times higher in the group that was not observed (29% vs. 7% default; 12% vs 4% death). By involving the community, the authors were able to demonstrate that directly observed treatment can be successful even in a scattered rural population with scarce economic resources, high HIV infection, high illiteracy rates, difficult access to transport, and unstable political conditions.

Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet* 2000;355:1345-1350.

Reports that the success of directly observed treatment in 30 programmes reviewed is due to a variety of factors. These include interventions such as incentives to patients, tracing of patients who interrupt treatment, staff motivation, and supervision. The authors note that effective services require “an actively managed programme of tuberculosis control, with a mixture of inputs to improve adherence that include incentives, defaulter actions, and patient-centered designs.”

Balasubramanian VN, Oommen K, Samuel R. DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India. *International Journal of Tuberculosis and Lung Disease* 2000;4:409-413.

Direct observation of treatment increased treatment success from 55% to more than 95%. Patient outcomes were significantly different between those who did and did not receive directly observed treatment. Of patients whose treatment was not directly observed, 45% had relapse or failure compared with 3% of those who were directly observed. Under programme conditions, 86% of all failures and relapses were among patients who did not receive treatment observation. The findings emphasize the importance of ensuring patient-friendly treatment observation for all patients.

Wilkinson D, Davies GR, Connolly C. Directly observed therapy for tuberculosis in rural South Africa, 1991 through 1994. *American Journal of Public Health* 1996;86:1094-1097.

Out of 2 186 patients studied in Hlabisa, South Africa, 1903 (87%) received outpatient directly observed treatment. Treatment was under the supervision of both health workers as well as non-family member volunteers selected by patients themselves. Amongst non-family member volunteers, patients most commonly selected storekeepers as treatment observers (72% of patients observed other than by health workers were supervised by storekeepers). Other community volunteers included employers, teachers, village headmen and laypersons. In this resource-poor setting, community volunteers were effective treatment observers and were well accepted by the patients.

Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. *New England Journal of Medicine* 1995;333:229-233.

Availability of free medication for short-course chemotherapy was associated with cure rates of only 40% and a rapid increase in drug resistance. Application of directly observed treatment doubled cure rates and was associated with a rapid decline in tuberculosis (>15% annually) and in drug resistance (75% in three years). Decreases were greatest in populations (such as children) in which recent transmission of tuberculosis was previously common. The economic savings from directly observed treatment were far greater than the expense of the programme. "New York City's experience demonstrates that tuberculosis can be controlled even in populations in which immunosuppression is common and the prevalence of drug-resistant organisms is high."

Centers for Disease Control and Prevention. Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis [published erratum appears in *MMWR Morb Mortal Wkly Rep* 1993 Jul 26; 42(27): 536]. *Morbidity and Mortality Weekly Report* 1993;42:1-8.

Directly observed treatment "should be considered for all patients because of the difficulty in predicting which patients will adhere to a prescribed treatment regimen.... If the percentage of patients who complete therapy within 12 months is <90% or unknown, the use of DOT should be expanded."

Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis. We can't afford not to try it. *New England Journal of Medicine* 1993;328:576-578.

Default rates of patients on short-course therapy with directly observed therapy were <10% compared with 39% for patients not on directly observed treatment. Observed treatment costs less than non-observed treatment. "We believe it is time for entirely intermittent directly

Directly observed treatment

observed treatment programs... to be used for all patients... By observing that every dose is taken, especially during the initial phase of treatment, when the burden of mycobacteria is highest and the risk of selecting for drug-resistant mutants is greatest, we will have fewer treatment failures and less acquired drug resistance... A program of directly observed therapy cannot be implemented unless a well-organized infrastructure exists to support it... Programs of directly observed therapy are not simple or easy to conduct. They require energetic administration, creativity, and flexibility... We have found that patients from all segments of society, and their physicians, accept directly observed treatment when the issue of public accountability and public health requirements for documentation of treatment are properly explained. Since the costs are equal to or below those of the standard regimens, we believe that every patient with tuberculosis in this country should receive directly observed therapy."

Murray CJ, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet* 1991;338:1305-1308.

Using directly observed, short-course treatment, cure rates of 86%–90% can be achieved. The cost per year of life saved with ambulatory short-course treatment was US\$ 1. "Chemotherapy for smear-positive tuberculosis is thus cheaper than other cost-effective health interventions such as immunisation against measles and oral rehydration therapy."

Manalo F, Tan F, Sbarbaro JA, Iseman MD. Community-based short-course treatment of pulmonary tuberculosis in a developing nation. Initial report of an eight-month, largely intermittent regimen in a population with a high prevalence of drug resistance. *American Review of Respiratory Disease* 1990;142:1301-1305.

A demonstration of the effective use of community volunteers, in this case church-affiliated lay workers, to provide directly observed treatment. A high rate of multidrug resistance was documented, and less than half of patients with multidrug-resistant isolates were cured. Among patients with isolates resistant to none or one drug, 80% had a favorable outcome. This project documents the effectiveness of religious workers as providers of observed treatment in this context. It also demonstrated yet again that community-based active case finding may identify a large number of patients with chronic TB, many of whom do not benefit from treatment.

Sbarbaro JA. The patient-physician relationship: compliance revisited. *Annals of Allergy* 1990;64:325-331.

Approximately one third of patients do not take medications regularly as prescribed, and perhaps one third of patients who do take medications make errors in self-administration. Noncompliance is not related to disease state, age, sex, race, marital status, severity of illness, educational level, adverse effects of medications, or patients' understanding of their disease. In one study of tuberculosis patients, 31% of a select patient group who had

Treatment of HIV-infected TB patients

been pre-judged by the authors to be undoubtedly reliable took less than 70% of their prescribed medicine. Pill count, particularly if not done on surprise home visits, is an inaccurate means of measuring compliance.

Fox W. Self-administration of medicaments. A review of published work and a study of the problems *Bulletin of the International Union of Tuberculosis* 1961;31:307-331.

Review of problems with self-administered treatment, particularly of drugs taken for long periods of time. Studies from the Tuberculosis Research Centre in India summarized: non-adherence was not related to side effects, dosage, or prior receipt of one year of supervised treatment. Non-adherence was as high with placebo as with active drug. Surprise home visits revealed a much greater degree of non-adherence than pill counts or urine tests. "Every effort was made... to obtain and keep the patient's cooperation and much time was spent during several interviews explaining both to the patient and to the family the seriousness of the disease and the necessity for a long course of chemotherapy. The infectious nature of the disease and the radiographic lesion was demonstrated to the whole family.... The patient was warned that he would feel much better after a few weeks of treatment and that he might be tempted to stop taking his medicine, but that to do so might have very serious consequences. Such instruction... was repeated at every monthly examination, and at other visits to the clinic as well as in the patient's home, by the doctors, by the public health nurses, and by the health visitors. Further, an attempt was always made to get another member of the family actually to watch the patient swallow ... [medicine]. The explanation was always given in simple language.... Despite this approach, ensuring self-administration was a major problem."

Fox W. The problem of self-administration of drugs with particular reference to pulmonary tuberculosis. *Tubercle* 1958;39:269-274.

"It will be appreciated that these irregularities have been detected in patients under intensive supervision. The great majority keep up the social side of the relationship with the clinic and attend regularly. Surprisingly, mere attendance at the clinic in no way means regularity in taking medicine."

Treatment of HIV-infected TB Patients

Harries AD, Nyangulu DS, Kang'ombe C, Ndalama D, Glynn JR, Banda H. Treatment outcome of an unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba hospital, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998;92:343-347.

In Malawi, smear-negative pulmonary tuberculosis and extra-pulmonary tuberculosis are more common in TB patients with HIV infection; 75% of TB patients are HIV-positive.

Treatment of HIV-infected TB patients

All smear-positive pulmonary TB and new and retreatment severe extrapulmonary TB patients received 8 months of short-course chemotherapy. New and retreatment patients with smear-negative and not severe extrapulmonary TB received 12 months daily non-rifampicin-containing treatment. Treatment outcomes depend on the HIV status, type of TB and age group. HIV-infected patients had a higher death rate than HIV-negative TB patients (60% vs 6%), and one third of all HIV-positive patients and half of the new HIV-positive smear-negative pulmonary patients died during treatment. Of the 827 TB patients registered, death rates were highest among smear-negative patients (46%), followed by extrapulmonary patients (37%), and lower among smear-positive patients (19%). The reason for high death rates in smear-negative patients is probably due to incorrect diagnosis, as there are many operational difficulties in resource-poor settings in sub-saharan Africa.

Alpert PL, Munsiff SS, Gourevitch MN, Greenberg B, Klein RS. A prospective study of tuberculosis and human immunodeficiency virus infection: clinical manifestations and factors associated with survival. *Clinical Infectious Disease* 1997;24:661-668.

HIV-infected patients with pulmonary tuberculosis were less likely to have positive sputum smears for AFB than were patients with TB who did not have HIV infection (54% vs 75%). Multivariate analysis of the factors associated with survival revealed that HIV-infected patients with higher CD4 cell counts, those who received directly observed therapy, those with drug-susceptible isolates, and those without a history of injection drug use lived longer.

Ackah AN, Coulibaly D, Digbeu H, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire. *Lancet* 1995;345:607-610.

247 consecutive HIV-infected patients with smear-positive pulmonary or clinically confirmed extrapulmonary tuberculosis were compared with 312 HIV-negative TB patients. Mortality during treatment was higher in HIV-infected patients (6% vs 0.4%), and was even higher (10%) in HIV-infected patients with low (<200/ μ L) CD4+ lymphocyte counts. Of patients completing treatment, cure rates were similar in HIV-positive (93%) patients and HIV-negative (92%) patients, and were independent of CD4+ counts.

Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 1995;151:129-135.

Study of severity of AIDS and mortality among HIV-infected patients with and without TB. "Active tuberculosis was associated with an increased risk for death (odds ratio 2.17), even when controlling for age, intravenous drug use, previous opportunistic infection, baseline CD4+ count, and antiretroviral therapy." TB may hasten the development of AIDS in HIV-infected persons.

Treatment of HIV-infected TB patients

Okwera A, Whalen C, Byekwaso F, et al. Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet* 1994;344:1323-1328.

191 HIV-infected patients with sputum smear-positive tuberculosis were randomized to receive either 2HTS / 10HT or 2HRZ / 7HR. Patients receiving thiacetazone were 10 times more likely to have adverse reactions (18.2 vs 1.6 reactions per 100 person years). Patients who received the rifampicin-containing regimen were more likely to have negative cultures after two months of treatment (74% vs 37%), and were 60% more likely to survive. Patients with HIV infection should not receive thiacetazone; short-course treatment hastens cure and prolongs survival in HIV-infected persons.

Alwood K, Keruly J, Moore-Rice K, Stanton D, Chaulk CP, Chaisson RE. Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *AIDS* 1994;8:1103-1108.

HIV-infected patients who received directly observed, intermittent treatment were more likely to complete treatment than were HIV infected patients who received short-course chemotherapy without directly observed treatment. HIV infected patients who received directly observed treatment were also much more likely to survive (85% vs 57%, $p=0.01$). This improved survival was found in multivariate as well as univariate analysis.

Regular supply of all essential anti-TB drugs

Trebucq A, Caudron JM, Pinel J. Requirements for antituberculosis drug tender requests. *International Journal of Tuberculosis and Lung Disease* 1999;3:S358-S361.

Procurement of drugs must ensure low price and high quality, and that drugs are delivered on time reliably. "To obtain the best prices for the programmes, it is necessary to put potential suppliers in competition," but ensuring quality may become difficult with some tendering processes. The ten steps in the tender cycle are: 1. Determine tender scope and format, 2. Define requirements, 3. Select suppliers to participate (e.g., by open competitive process), 4. Release tender documents, 5. Receive and open offers, 6. Collate and compare offers, 7. Evaluate and select bidder, 8. Award contract(s), 9. Monitor performance and quality, 10. Enforce contract terms. "Management of competitive tenders is an important and difficult task....Bioavailability study results for rifampicin should be requested systematically in the procurement documents."

Pecoul B, Chirac P, Trouiller P, Pinel J. Access to essential drugs in poor countries: a lost battle? *Journal of the American Medical Association* 1999; 281:361-367.

Drugs need to be available, affordable, and used correctly in order for treatment to be effective. Problems regarding access to essential drugs in developing countries are poor quality, lack of availability due to fluctuating production and high cost, and consequences of the World Trade Organization (WTO) agreement. The DOTS strategy reached only to 23% of TB patients globally in 1998. Access to all TB drugs to the poor population needs to be improved. Strengthening of the WHO's Drug Strategy by procuring quality drugs, increasing their availability, increasing research and development activities, and humanizing the WTO agreement will increase access to essential drugs.

Systematic monitoring and evaluation

Tuberculosis Research Centre, Chennai. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *International Journal of Tuberculosis and Lung Disease* 2001;5:40-45.

The possibility of increase in drug resistance in patients receiving short-course treatment was explored. If patients resistant to isoniazid develop resistance to rifampicin during short-course treatment, tuberculosis treatment would become much more difficult. This study reports the response to treatment, relapse rates and emergence of drug resistance of several trials at the Tuberculosis Research Centre, Chennai. Patients were treated with: 2HRZE/6HE, 2H₂R₂Z₂E₂/4H₂R₂E₂, 2H₃R₃Z₃E₃/4H₂R₂ or 3H₃R₃Z₃E₃/3H₂R₂. Of 1817 patients, 320 (17.6%) had initial resistance to isoniazid, four (0.2%) had resistance to rifampicin alone and 58 (3.2%) had multidrug-resistant tuberculosis. Response to treatment was not influenced by duration of previous anti-TB treatment. Relapse rates were higher in patients with drug resistance (13% vs 7%). Patients whose isolates were initially resistant to isoniazid had more failures compared to patients with drug susceptible organisms (19% vs 2%). However, of the 320 patients who had drug-resistant organisms 260 (81%) had a favourable response. Emergence of resistance to isoniazid, rifampicin, or both occurred in only 1% of patients with drug susceptible organisms and 11% in patients with organisms resistant to isoniazid. Overall the emergence of resistance to rifampicin was only 2% despite a high level of isoniazid resistance. The study concludes that standard short-course treatment can safely and effectively treat sputum-positive pulmonary tuberculosis patients with minimal emergence of rifampicin resistance.

Tanzania Tuberculin Survey Collaboration. Tuberculosis control in the era of the HIV epidemic: risk of tuberculosis infection in Tanzania, 1983–1998. *International Journal of Tuberculosis and Lung Disease* 2001;5:103-112.

The HIV epidemic caused an increase in the notification rates of smear-positive tuberculosis in adults, from 32 cases per 100 000 in 1983-1987 to 69 cases per 100 000 in 1994-1998, despite the presence of a national tuberculosis programme since 1979. Treatment completion rates increased from 55% in 1980 to 80% in 1990. Three national tuberculin surveys of school children conducted at five-year intervals to assess the annual risk of tuberculosis infection showed that there was no change — and in fact a 2% annual reduction — in the annual risk of tuberculosis over 15 years (-1.1% in 1983-1987; -1.0% in 1988-1992; -0.9% in 1993-1998), despite the increase in notification rates of smear-positive tuberculosis in adults. The study indicates that the presence of an effective DOTS programme curtailed tuberculosis transmission despite a substantial increase in TB due to the HIV epidemic.

Monitoring and evaluation

Marrero A, Caminero JA, Rodriguez R, Billo NE. Towards elimination of tuberculosis in a low income country: the experience of Cuba, 1962–97. *Thorax* 2000;55:39-45.

Reports on the epidemiology of TB and the performance of TB control programmes in Cuba. In Cuba, effective tuberculosis control services resulted in a decrease (by -9% per annum) in the smear-positive tuberculosis notification rate from 58 to 4.4 per 100 000 during 1965–1991. Over the next three years, economic and nutritional hardships resulted in a striking increase (+24% per annum) in the notification rate — to 8.3 per 100 000; subsequent enhanced control activities resulted in a resumed downward trend (-6% per annum) in notifications to 6.9 per 100 000 in 1997. The NTP in Cuba is a good example of political commitment and integration with the primary health care system in controlling TB.

Zhang LX, Tu DH, Enarson DA. The impact of directly-observed treatment on the epidemiology of tuberculosis in Beijing. *International Journal of Tuberculosis and Lung Disease* 2000;4:904-910.

Reports the success of the TB control programme after the implementation of DOTS in 1978. Coverage increased from less than 10% in 1978 to 90% in the 1990s. An independent institution visited patients in their homes at a random time during the course of treatment, and confirmed that >95% of patients received direct observation correctly as per policy. The prevalence of smear-positive cases decreased by 87% between 1979 and 1990, from 127 to 16 per 100 000 (annual rate of reduction of 17.2%). Mortality declined from 11.2 to 2.2 per 100 000 from 1980 to 1996. The notification rate of new smear-positive cases decreased from 18.9 to 7.3 per 100 000 from 1980 to 1996, a decrease of 9% per year. DOTS can reduce the number of TB cases and deaths, with minimal development of anti-TB drug resistance (0.8% in 1996), in a low-income country at a low cost.

World Health Organization. Anti-tuberculosis drug resistance in the world. Report No. 2: Prevalence and Trends. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. Geneva, Switzerland, 2000. WHO/CDS/TB/2000.278.

This second report on the global project on anti-TB drug resistance examined 64 104 TB cases between 1996-1999 from 58 geographical settings, and analysed ecological data from 72 geographical settings. Drug-resistant TB ranged from 2.9% (New Caledonia) to 40.8% (Estonia). The rate of multidrug-resistant TB in new cases was high in Estonia, Latvia, Ivanovo Oblast, Tomsk Oblast, Henang (China), Tamil Nadu (India) and Mozambique. Germany, New Zealand and Ivanovo Oblast showed significant increases in multidrug-resistant TB, while The Netherlands showed a decline. The prevalence of drug resistance was directly related to the proportion of previously treated cases registered (ranging from 0% in four areas to 48.2% in the Islamic Republic of Iran), and inversely related to the proportion of TB cases treated under DOTS. Drug-resistant TB was present in all the geographical settings, highlighting the importance of expanding and strengthening TB control to contain and reduce drug

resistance. This report concludes that prior TB is a strong predictor of drug resistance and recommends that surveillance of drug-resistant TB should be a priority, DOTS should be implemented in an appropriate TB control programme, and that second-line treatment regimen should be considered where multidrug resistant TB is high, but only in well established control programmes: “. . . attempts to introduce second-line drugs for MDR:TB in a setting that is unable to guarantee acceptable cure rates of drug-susceptible TB cases will most likely lead to disastrous consequences.”

Espinal MA, Kim SJ, Suarez PG, et al. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Journal of the American Medical Association* 2000;283:2537-2545.

Of the 6402 culture-positive tuberculosis cases (86% new cases and 14% retreatment), 1148 new cases (20.8%) and 390 (44.5%) retreatment cases had strains resistant to one or more drugs. The overall success rate for susceptible new cases was 83% and for susceptible retreatment cases was 57%. Patients with multidrug resistant isolates had higher failure rates than patients with susceptible isolates (new cases 21% vs 2%, $P < 0.001$; retreatment cases 34% vs 6%, $P \leq 0.001$). Failure rates in single drug resistant new cases were higher in those with rifampicin resistance in patients with other single drug resistance. The study concludes that standard short-course treatment based on first-line drugs is inadequate for treating some TB patients with drug resistance. To prevent drug resistance, rifampicin, the most potent first-line drug, should be administered strictly under direct observation to protect its efficacy. “The introduction of feasible and inexpensive rapid testing for rifampicin resistance should be explored.” “The best way to prevent the development of multidrug-resistant TB is to encourage countries to adopt DOTS and to provide standard SCC to new patients.”

Rabarijaona L, Boisier P, Ratsirahonana O, et al. Replacement of streptomycin by ethambutol in the intensive phase of tuberculosis treatment: no effect on compliance. *International Journal of Tuberculosis and Lung Disease* 1999;3:42-46.

Report on patient compliance, treatment efficacy and tolerance to regimens containing either streptomycin (SHRZ) or ethambutol (EHRZ) in Madagascar. There were no difference in compliance between the two regimens; patient tolerance to ethambutol was significantly better ($p < 0.01$). As ethambutol proved to be cheaper and more comfortable, the EHRZ regimen is suitable for the intensive phase of treatment for smear-positive pulmonary TB. Contrary to the impressions of some doctors, streptomycin did not increase adherence to treatment.

Monitoring and evaluation

Jasmer RM, Hahn JA, Small PM, et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991–1997. *Annals of Internal Medicine* 1999;130:971-978.

In San Francisco, following intensification of tuberculosis control measures, annual incidence decreased by 8.9% per annum from 46 per 100 000 in 1991 to 30 per 100 000 in 1997. Molecular epidemiologic analysis using DNA fingerprinting showed a reduction in the rate of clustered cases from 10.4 to 3.8 per 100 000, indicating decreased transmission in the community. Clustered cases declined three times as fast as non-clustered cases (by -15% vs -5% per annum).

Kenyon TA, Mwasekaga MJ, Huebner R, Rumisha D, Binkin N, Maganu E. Low levels of drug resistance amidst rapidly increasing tuberculosis and human immunodeficiency virus co-epidemics in Botswana. *International Journal of Tuberculosis and Lung Disease* 1999;3:4-11.

Tuberculosis incidence declined from 1986 to 1989 after the implementation of DOTS. Between 1989 and 1996, rates of drug resistance remained low (3.9% primary), but TB increased by 120% because of increasing prevalence of HIV infection. This study found that DOTS can prevent drug-resistant TB in the context of a HIV epidemic in low-income countries, but could not prevent the increase in incidence of TB. This increase is likely due primarily to reactivation of latent tuberculosis infection in HIV-infected persons in this area where the prevalence of HIV in the adult population exceeds 20%.

Nuwaha F. Control of tuberculosis in Uganda: a tale of two districts. *International Journal of Tuberculosis and Lung Disease* 1999;3:224-230.

The use of a single health unit for both the intensive and continuation phase of treatment improved patient compliance (92% in single unit vs 57% in two units). Changing treatment units greatly increased the risk of default (43% vs 8%, odds ratio 17.5). Initial hospitalization during the intensive phase is not necessary for, and in this context significantly reduced the probability of, treatment completion. Treatment compliance was associated with the use of short-course chemotherapy; return for repeat smear; no change of health unit; and no change of district.

Comolet TM, Rakotomalala R, Rajaonariora H. Factors determining compliance with tuberculosis treatment in an urban environment, Tamatave, Madagascar. *International Journal of Tuberculosis and Lung Disease* 1998;2:891-897.

Treatment interruption is the most common problem in tuberculosis control. Identifying risk factors for default can help improve patient compliance. The most common risk factors for treatment interruption were male gender (76% vs 56%, $P < 0.05$) and travel to health units for observed treatment of more than one hour (42% vs 24%, $P < 0.05$). Giving false addresses

(35%) was the most common cause for disappearance. Patient adherence increases if communication skills of the medical staff are effective. Poor communication between the patients and health workers was cited much more often by patients who defaulted than by patients who completed treatment (26% vs 3%, $P < 0.001$). Other common reasons cited by patients for interruption of treatment were: feeling better after two months of treatment (27%), lack of awareness of the required duration of treatment (12%), financial difficulties (10%), and fear of seeing the health team after first interrupting treatment (8%). This study highlights the great importance of convenient, patient-friendly treatment observation in achieving acceptable rates of treatment success.

Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998;352:1886-1891.

An age-structured model assessed the impact of improved case detection and cure. Meeting global targets can cause an 11% decline in the incidence rate of TB per year. With the increase in HIV-1 infection, TB cases will increase by 41% (to 10.6 million cases per year) in 2020. DOTS can prevent 43 million cases and 18 million deaths over the next 20 years. The potential of DOTS in controlling TB is greater in developing countries, but requires improved case detection and cure rates in endemic areas.

Norval PY, San KK, Bakhim T, Rith DN, Ahn DI, Blanc L. DOTS in Cambodia. Directly observed treatment with short-course chemotherapy. *International Journal of Tuberculosis and Lung Disease* 1998;2:44-51.

The number of new smear-positive cases detected increased by 121% (5 579 to 12 942 between 1982 and 1996). Cure rates improved from 40%-50% before 1994 to 84% with DOTS in 1995. DOTS is effective even in a war-stricken country with limited health services. This was possible because of commitment of the government, training and mobilization of health workers, a steady supply of drugs, free food for patients, collaboration with NGOs, decentralization of tuberculosis services, and adequate supervision.

Kumaresan JA, Ahsan Ali AK, Parkkali LM. Tuberculosis control in Bangladesh: success of the DOTS strategy. *International Journal of Tuberculosis and Lung Disease* 1998;2:992-998.

DOTS was begun in 1993, covering 1 million people, and was expanded to a population of 67 million in 1996. Of the 41 525 patients registered, 27 548 (66%) were smear-positive and 11 149 (27%) were smear-negative. Sputum smear conversion at 2 months of treatment was achieved in 85% of patients. Treatment outcomes for 1993–1995 were 75% cured, 4% completed treatment, 2% failed, 6% died, 10% defaulted, and 3% were transferred out. Despite being a low-income country with high TB incidence facing poverty, illiteracy, natural

Monitoring and evaluation

disasters and political instability, the DOTS strategy was successful because of government commitment, staff training, regular monitoring, and decentralization of diagnosis and treatment by utilizing the existing primary health care network.

Cao JP, Zhang LY, Zhu JQ, Chin DP. Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. *International Journal of Tuberculosis and Lung Disease* 1998;2:360-364.

New cases received 2H₃R₃Z₃S₃/4H₃R₃ and retreatment cases received 2H₃R₃Z₃E₃S₃/6H₃R₃E₃. High cure rates were achieved for smear-positive pulmonary TB new and retreatment patients (90% cure of new cases and 80% cure of retreatment cases including relapses). Two-year relapse rates were 3.3% among new cases, 4.3% among relapses, and 6.4% among other retreatment cases. Among retreatment patients, relapse rates were higher among those who did not convert to smear-negative after 2 months of treatment (15% vs 3.3%). Among new patients there was no difference in relapse rates among those who did or did not convert at 2 months (3.3% vs 3.6%). Mortality rates were higher in retreatment cases (8.5% vs 3.3%), but this was attributable to long-term non-infectious sequelae of TB and not to relapse of TB. An important finding of this study was that there was a high prevalence (57%) of non-TB symptoms in retreatment patients after cure. Unless such patients are systematically evaluated, they may be mistakenly assumed to have relapse when in fact they have non-tuberculous sequelae of their prior tuberculosis. DOTS is effective in decreasing mortality in both new and retreatment cases and in reducing the proportion of retreatment cases.

Heldal E, Cruz JR, Arnadottir T, Tardencilla A, Enarson DA. Successful management of a National Tuberculosis Programme under conditions of war. *International Journal of Tuberculosis and Lung Disease* 1997;1:16–24.

The authors compared results of treatment before and after the introduction of SCC (2HRZS/6HT). “The overall success ratio improved by 39% ...in spite of evidence of a deteriorating economy and escalation in civil war” between 1982–1983 to 1988–1990, with 3 462 cases completing treatment (71%). The authors conclude that 80%–90% of all registered smear-positive patients stopped transmitting TB. The study documents the successful implementation of DOTS despite economic crisis and civil war.

Ritacco V, Di Lonardo M, Reniero A, et al. Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires. *Journal of Infectious Disease* 1997;176:637-642.

HIV-associated multidrug resistant TB increased substantially in a referral hospital. Of 272 HIV-positive TB patients, 101 had *M. tuberculosis* strains resistant to at least 5 drugs. These were traced back to a single strain in 68 patients who acquired the disease due to in-hospital exposure. The one-year survival was drastically reduced in multidrug-resistant TB patients with HIV (62% vs 7%, $p < 0.001$) compared with HIV-infected TB patients without multidrug resistant TB. Institutional infection control policies should be improved to prevent the spread of TB in immunocompromised patients.

Wilkinson D, Pillay M, Crump J, Lombard C, Davies GR, Sturm AW. Molecular epidemiology and transmission dynamics of *Mycobacterium tuberculosis* in rural Africa. *Tropical Medicine and International Health* 1997;2:747-753.

Using molecular epidemiological methods, the authors estimated the relative proportion of TB cases arising from recent transmission. Overall, 45% of patients had clustered isolates, and the authors estimated that 29-43% of cases were due to recently acquired infection. The data suggests that most of this acquisition occurred outside of the immediate household. These findings were similar for HIV-positive and HIV-negative patients. This data emphasizes the importance of promoting prompt diagnosis and effective treatment in order to stop TB at the source.

Ledru S, Cauchoix B, Yameogo M, et al. Impact of short-course therapy on tuberculosis drug resistance in South-West Burkina Faso. *Tubercle and Lung Disease* 1996;77:429-436.

A fully supervised short-course treatment (2HRZE/4HR or 2HRZS/4HR) reduced the proportion of patients with primary drug-resistant tuberculosis. Primary resistance to streptomycin was higher than resistance to isoniazid or rifampicin. Resistance to all three drugs decreased from 1986 to 1994 (streptomycin 23.8% to 12.4%; isoniazid 18.8% to 7.6%; rifampicin 7.9% to 2.5%). Of note, this study demonstrates a decrease in primary drug resistance without specific treatment of patients with multidrug-resistant TB.

Monitoring and evaluation

Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine* 1994;330:1179-1184.

After application of universal direct observation of treatment in one area of Texas in the United States, drug resistance and relapse rates decreased markedly (primary drug resistance from 13% to 6.7%, acquired resistance from 14% to 2.1%; relapse rates from 20.9% to 5.5%). No resistance developed in patients on appropriate directly.