FACTORS ASSOCIATED WITH TREATMENT OUTCOMES IN PULMONARY TUBERCULOSIS IN NORTHEASTERN THAILAND

Siriluck Anunnatsiri[1], Ploenchan Chetchotisakd[1] and Christine Wanke[2]

[1]Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand;
[2]Department of Medicine and Community Health, Tufts University School of Medicine, Boston, Massachusetts, USA

Abstract. Tuberculosis and HIV/AIDS are both prevalent in Southeast Asia and Thailand. Factors related to treatment outcomes in smear-positive pulmonary tuberculosis were evaluated in 226 adult Thai patients. Of these, 31% had a cure or a completion of therapy, 7% had treatment failure or death, and 31% had treatment interruption. The prevalence of co-morbid diseases was 52%, including 19% with HIV. Sputum cultures for *Mycobacteria* were carried out in 86 cases (38%), 36 of these (42%) were culture positive for *Mycobacterium tuberculosis*. The rate of drug resistance was 14% (5/36) of culture proven tuberculosis and the mortality rate was 4.6% (7/153) of patients with known outcomes. Of the 7 fatalities, 3 were HIV positive and 1 had multi-drug resistant tuberculosis. Factors that were significantly associated with treatment failure/death were old age (OR 44.1; 95%CI 2.0-983.7), HIV co-infection (OR 27.5; 95%CI 1.3-560.0), and previously treated tuberculosis (OR 9.7; 95%CI 1.6-59.1). These high rates of drug resistance and treatment failure in this area suggest that initial sputum cultures and drug susceptibility testing for *Mycobacteria* should be performed in all patients who have been previously exposed to anti-tuberculous drugs, and HIV testing should be performed on all patients with tuberculosis.

INTRODUCTION

Tuberculosis (TB) remains a common and deadly disease in the world and has an enormous economic impact on many countries. Nearly one-third of the world's population or 1.86 billion people are infected with *Mycobacterium tuberculosis*, 1.87 million people die each year from the disease (Dye *et al*, 1999). The World Health Organization (WHO) defined a strategic approach to TB control in 1995 which is based on directly observed therapy (DOTS), short course chemotherapy, and global TB monitoring and active surveillance to monitor cases and treatment outcomes. Many high burden countries of TB have implemented DOTS, but overall, the progress in global TB control remains very slow (WHO, 2002). The major constraints are poor adherence to the guidelines, economic and infrastructure constraints, and a high prevalence of HIV co-infection. Infection with HIV/AIDS in TB patients is associated with active disease and the development of resistance to anti-tuberculous drugs, and is therefore a major contributor to poor TB control in many high burden countries in Africa, Eastern Europe and Southeast Asia (Nunn, 2001). The success of treatment is a main determinant of TB control, but there is limited data from such endemic areas to determine the extent of adherence to WHO guidelines and factors that relate to the outcome of TB treatment.

Thailand is one of 23 countries with a high burden of TB and is now facing an increasing problem of drug resistant TB. It is estimated that one million Thai people are now living with HIV/AIDS, and the rate of TB is high, at 140 cases per 100,000 population (WHO, 2002). Physicians in Thailand are encouraged to follow WHO guidelines for the treatment and management of TB,

Correspondence: Dr Siriluck Anunnatsiri, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Tel: 66-43-363664; Fax: 66-43-202476
E-mail: asiril@kku.ac.th, or
Dr Christine Wanke, Department of Family Medicine and Community Health, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA.
Tel: 01-617-6360921; Fax: 01-617-6363810
E-mail: christine.wanke@tufts.edu

but the actual rate of adherence is unknown. Our study determined to evaluate TB management at a tertiary hospital in northeastern Thailand and assessed the factors associated with treatment outcomes in patients with smear-positive pulmonary TB.

MATERIALS AND METHODS

A retrospective survey was conducted at Srinagarind Hospital, Khon Kaen Province, northeastern Thailand. All adult patients (≥15 years) who presented from 1999 to 2001 were included in the study if they had smear-positive pulmonary TB in accordance with the WHO case definition (WHO, 1997). Srinagarind hospital has a regional governmental medical school and an 800-bed tertiary care center serving the population of Khon Kaen and nearby provinces, with a cachement area of 7,376,988 km^3. The patients evaluated for the study sought care at the outpatient clinic, emergency room or were admitted as inpatients to the hospital. The exclusion criteria were incomplete medical records or patients who had acid-fast bacilli (AFB) identified in tracheal aspirates or bronchial washings/ brushings but not in the sputum. The study protocol was approved by the Ethics Committee for Research on Human Subjects, Faculty of Medicine, Khon Kaen University, Thailand.

Data collection

Demographic data included sex, age, educational level, place of residence, and employment. Patients were grouped by place of residence whether they lived in Khon Kaen Province or outside the province (a range of 322 km). The clinical data recorded included the presence of co-morbid diseases, clinical symptoms related to pulmonary TB, the presence of lung cavitation on chest radiographs, a history of previous TB treatment, the presence of extrapulmonary TB, types of physicians providing care (pulmonary physicians or others), HIV risk factors, sputum cultures and drug susceptibility testing for *Mycobacteria* and rates of HIV testing.

Definitions

All definitions were taken from the WHO guidelines (WHO, 1997). Patients were considered to have smear-positive pulmonary TB if they fulfilled any of the following criterion; (1) at least two sputum specimens were positive for AFB; (2) at least one sputum specimen was positive for AFB and radiographic abnormalities were consistent with pulmonary TB or (3) at least one sputum specimen positive for AFB with culture proven *M. tuberculosis*.

TB patients were classified as a 'new case' if they had no history of previous treatment for TB or had taken anti-TB drugs for less than four weeks. Following the initiation of anti-TB treatment, patients were classified into 5 groups according to outcomes as 'cure' if they were smear-negative at, or one month prior to, the completion of treatment and on at least one previous occasion; as 'treatment completed' if patients completed treatment but did not have proof of cure; as 'treatment failure' if patients remained or became again smear positive at five months or later during treatment; as 'death' if a patient died for any reason during the course of treatment; as 'treatment interrupted ' if the treatment was interrupted for 2 months or more; and 'transfer' if they were transferred to another facility.

Statistical analysis

Statistical analyses were performed using the statistical program SPSS version 11. Demographic, clinical, and laboratory data were compared among the different groups for treatment outcomes. One-Way ANOVA with Bonferroni multiple comparison test was used for normally distributed data. Categorical variables were analyzed by chi-square or Fisher's exact test. Simple and multiple logistic regression analysis were used to evaluate factors associated with treatment outcomes. Odds ratio (OR) and 95% confidence intervals (95%CI) were calculated by logistic regression model and used as a measure of the strength of the association between the outcome variables and their predictors. Collapsibility was examined in categorical variables. Backward likelihood ratio selection was used for the purpose of multivariate analysis.

RESULTS

During the 3-year period (1999-2001), there were 355 patients with AFB positive sputum

smears recorded in the microbiology laboratory database. Of these, 226 cases (60.1%) fulfilled the study criteria and were included in this analysis. There were 150 males and 76 females and their mean (SD) age was 47.2 (17.7) years (Table 1). The majority of the patients (61.1%) were residents outside Khon Kaen Province and the overall rate of unemployment was 26.9%. The average educational level was less than high school, found in 62.1% (n=87) of patients with a known educational status (n=140).

The treatment outcomes of all patients were classified into 4 groups as shown in Table 1: cure/treatment completion (n=69, 30.5%), treatment failure/death (n=15, 6.7%), treatment interruption (n=69, 30.5%), and transfer (n=73, 32.3%). Patients with cure/treatment completion were significantly younger than the transferred group [mean (SD)=41.8 (15.6) *vs* 52.8 (18.2) years, p=0.001)] while patients in the other groups had similar age distributions. Among these 4 patient groups, there were significant differences in the distributions by gender (p=0.02), level of education (p=0.01), resident areas (p=0.02), previous TB treatment (p=0.04), and medical care provided by pulmonary physicians (p<0.001).

There were 7 deaths and 8 treatment failures contributing to a 4.6% mortality rate and a 5.2% treatment failure rate among the patients with known treatment outcomes (n=153). The causes of death in the 7 fatal cases were opportunistic infections associated with HIV co-infection (n=3), acute myocardial infarction, hospital-acquired infection, postoperative DIC, and MDR-TB.

Baseline clinical characteristics

The majority of patients had newly diagnosed pulmonary TB (n=195; 86.3%). Thirty-one cases (13.7%) had received previous unsuccessful anti-TB therapy for pulmonary TB as a relapse, treatment failure, or an interrupted treatment outcome. Co-existing diseases were found in 51.8% of the patients (n=117) of which HIV/AIDS (n=43) and diabetes mellitus (n=38) were the two most common. Other less common co-morbid diseases were malignancy (n=13), cirrhosis/chronic liver disease (n=11), steroid treatment (n=6), chronic renal failure (n=4), and chronic obstructive pulmonary disease (n=2), and 1 patient each with paroxysmal nocturnal hemoglobinuria, idiopathic thrombocytopenia, asthma, nephrotic syndrome, rheumatoid arthritis, renal transplantation, unclassified connective tissue disease, and aplastic anemia.

The overall rate of extrapulmonary TB in all the groups was 24.3% (n=55). Among the 4 patient groups, there were no significant differences in the proportion of cases with pulmonary cavitation, co-morbid diseases, diabetes mellitus, HIV infection, or extrapulmonary TB (Table 1).

Patient management

Ninety-three patients (41.2%) had care provided by pulmonary physicians and 133 cases (58.8%) were cared for by non-pulmonary physicians (Table 1). Clinical assessment for HIV risk factors was documented in only 35 patients (15.5%). Of 43 cases with HIV/AIDS infection, 24 were detected on first presentation. The utility of HIV testing in this study calculated from 202 patients with unknown HIV status was 27.7% (n=56), 1/3 of them were HIV positive (n=19, 33.9%). All 19 HIV positive cases had clinical signs and symptoms of symptomatic HIV infection.

Sputum culture and drug susceptibility testing for *Mycobacteria* were performed in 86 patients (38.1%) and 36 of them (41.9%) grew *M. tuberculosis.* Drug resistant *M. tuberculosis* was identified in 5 cases or 13.9% of positive culture samples and MDR-TB was present in 1 case (2.8%). Details of the 5-drug resistant cases are summarized in Table 2. Four had acquired drug resistance and one had primary drug resistance. Diabetes mellitus was the only co-morbid condition and was present in only one case. One drug resistant case was cured and one case was fatal. The period of treatment in these patients ranged from 140 to 580 days.

The majority of all patients (n=183; 81%) received a short course of combined chemotherapy with isoniazid, rifampicin, pyrazinamide, and ethambutol as an induction regimen and was followed by isoniazid and rifampicin as maintenance drugs. The median (IQ range) duration of

Table 1
Characteristics of patients with pulmonary TB classified according to treatment outcomes. Data are shown as numbers of patients and (%).

Characteristics	Cure/Treatment completion	Treatment failure/ death	Treatment interrupted	Transfer	Total
No. of patients	69	15	69	73	226
Age (y); Mean ± SD	41.8 ±15.6	49.4 ± 15.7	46.3 ± 18.1	52.8 ± 18.2	47.2 ± 17.7
Male	33 (55.9)	9 (60)	55 (79.7)	48 (65.8)	150 (66.4)
Previous TB treatment	5 (7.2)	5 (33.3)	8 (11.6)	13 (17.8)	31 (13.7)
None/low education (n=140)	18/39 (46.2)	3/6 (50)	27/46 (58.7)	39/49 (79.6)	87 (62.1)
Non-Khon Kaen resident	32 (46.4)	11 (73.3)	45 (65.2)	50 (68.5)	138 (61.1)
Co-existing diseases	28 (40.6)	10 (66.7)	39 (56.5)	40 (54.8)	117 (51.8)
Diabetes mellitus	11 (15.9)	4 (26.7)	6 (8.7)	17 (23.3)	38 (16.8)
HIV/AIDS (n=80)	9/26 (34.6)	4/7 (57.1)	20/30 (66.7)	10/17 (58.8)	43 (53.8)
Extrapulmonary TB	15 (21.7)	3 (20.0)	22 (31.9)	15 (20.5)	55 (24.3)
Cares by pulmonary physicians	42 (60.9)	9 (60.0)	18 (26.1)	24 (32.9)	93 (41.2)
Assessment of HIV risk factors	11 (15.9)	1 (6.7)	15 (21.7)	8 (11.0)	35 (15.5)

Table 2
Clinical data on cases of pulmonary TB with drug resistance.

Case	Age (years)	Sex	Case definition	Underlying diseases	Duration of treatment (days)	Drug resistance	Clinical outcome
1	63	M	Treatment after interruption	DM	156	H	Transferred out
2	73	M	Relapse	No	580	R	Treatment interruption
3	59	F	New	No	272	E	Cure
4	34	M	Treatment after interruption	No	140	K	Treatment interruption
5	32	M	Treatment after interruption	No	304	H, R, E, S, O	Death

H=isoniazid, R=rifampicin, E=ethambutol, O=ofloxacin, S=streptomycin, K=kanamycin, DM=diabetes mellitus

treatment in patients with the cure/treatment completion was 212 (90.5) days; in patients with treatment interruption, the median duration of therapy was 26 (104.5) days, and in the patients who died, it was 51 (295) days.

Factors related to outcomes

The three known treatment outcomes (treatment failure/death, treatment interruption and cure/treatment completion) were evaluated in relation to the patient demographic data, baseline clinical characteristics and clinical management (Table 3). Factors influencing either the treatment interrupted group or the treatment failure/death group were compared with the cure/treatment completed group by univariate analysis. Factors that were associated significantly with treatment interruption were age over 60 years (OR 3.1, 95%CI 1.1 to 8.7), male gender (OR 3.2, 95%CI 1.5 to 6.8), living outside Khon Kaen Province (OR 2.2, 95%CI 1.1 to 4.3), presence of HIV infection (OR 3.8, 95%CI 1.3 to 11.4), and care provided by non-pulmonary physicians (OR 4.4, 95%CI 2.1 to 9.1). There were two factors that were significantly associated with treatment failure/death: age greater than 60 years (OR 11.6, 95%CI 1.2 to 114.1) and past history of anti-TB treatment, regardless of the treatment outcome (complete treatment, treatment failure, or treatment interruption) (OR 6.4, 95%CI 1.6 to 26.2).

In the multivariate analysis, independent factors that were associated significantly with

Table 3
Univariate analysis of factors influencing treatment interruption and treatment failure or death in patients with smear-positive pulmonary TB.

Factors	No. of treatment interruptions/ No. of patients (%)	Crude OR (95%CI)	No. of treatment failures or deaths/ No. of patients (%)	Crude OR (95%CI)
Age group (years)				
15-30	15/36 (41.7)	1	1/22 (4.5)	1
31-45	23/43 (53.5)	1.61 (0.66-3.93)	5/25 (20.0)	5.24 (0.56-48.73)
46-60	11/30 (36.7)	0.81 (0.30-2.19)	4/23 (17.4)	4.41 (0.45-42.92)
>60	20/29 (69.0)	3.11 (1.11-8.70)	5/14 (35.7)	11.64 (1.19-114.07)
Sex				
Female	14/45 (31.1)	1	6/37 (16.2)	1
Male	55/93 (59.1)	3.20 (1.51-6.81)	9/47 (19.1)	1.22 (0.39-3.81)
Education				
No school and Elementary school	27/45 (60.0)	1	3/21 (14.3)	1
Higher	19/40 (47.5)	0.60 (0.26-1.43)	3/24 (12.5)	0.86 (0.15-4.79)
Residence				
Khon Kaen Province	24/61 (39.3)	1	4/41 (9.8)	1
Other provinces	45/71 (58.4)	2.17 (1.09-4.30)	11/43 (25.6)	3.18 (0.92-10.97)
Employment				
No	17/34 (50.0)	1	3/20 (15.0)	1
Yes	51/100 (51.0)	1.04 (0.48-2.27)	10/59 (16.9)	1.16 (0.28-4.70)
Co-existing diseases				
No	30/71 (42.3)	1	5/46 (10.9)	1
Yes	39/67 (58.2)	1.90 (0.97-3.74)	10/38 (26.3)	2.93 (0.90-9.49)
Diabetes mellitus				
No	63/121 (52.1)	1	11/69 (15.9)	1
Yes	6/17 (35.3)	0.50 (0.18-1.45)	4/15 (26.7)	1.92 (0.52-7.13)
HIV infection				
No	10/27 (37.0)	1	3/20 (15.0)	1
Yes	20/29 (69.0)	3.78 (1.25-11.44)	4/13 (30.8)	2.52 (0.46-13.80)
Extrapulmonary TB				
No	47/101 (46.5)	1	12/66 (18.2)	1
Yes	22/37 (59.5)	1.69 (0.79-3.62)	3/18 (16.7)	0.90 (0.23-3.61)
Types of case:				
New case	61/125 (48.8)	1	10/74 (13.5)	1
Previous TB treatment	8/13 (61.5)	1.68 (0.52-5.42)	5/10 (50.0)	6.4 (1.57-26.15)
Types of physicians:				
Pulmonary physician	18/60 (30.0)	1	9/51 (17.6)	1
Others	51/78 (65.4)	4.41 (2.14-9.08)	6/33 (18.2)	1.04 (0.33-3.24)

treatment failure/death were age greater than 60 years (OR 44.1, 95%CI 2.0 to 983.7), presence of HIV-co-infection (OR 27.5, 95%CI 1.3 to 560.0), and history of previous TB treatment (OR 9.7, 95%CI 1.6 to 59.1). Patients whose care was provided by a non-pulmonary physician (OR 7.4, 95%CI 0.79 to 69.6) and patients with co-existing diabetes mellitus (OR 7.2, 95%CI 0.9 to 55.0) had the trend to be more likely to experience treatment failure/death as an outcome, but these associations were not statistically significant. Male sex (OR 2.6, 95%CI 1.2 to 5.7) and care provided by a non-pulmonary physician (OR 3.8, 95%CI 1.8 to 8.0) were independent factors significantly associated with treatment interruption.

DISCUSSION

Tuberculosis is a major global public health problem and data from many developing countries suggests that TB is associated, to some extents, with poverty and poor health education (Accorsi *et al*, 2001; Tekkel *et al*, 2002). In the present study, 1/4 of the patients had no income and 1/3 had a low educational status. Although the majority of our patients were newly diagnosed cases (73%), they were relatively severe; 1/2 of the patients had co-morbid diseases and 1/4 had extrapulmonary TB. Despite the low amount of HIV testing (28% of patients with unknown HIV status, at least 1/5 of our patients were found to have HIV/AIDS.

A high prevalence of drug-resistant *M. tuberculosis* has been reported from many regions of Thailand (Pablos-Mendez *et al*, 1998; Riantawan *et al*, 1998; Payanandana *et al*, 2000). In this study, sputum culture and drug susceptibility testing for *Mycobacteria* were obtained in only 38.1% of all the patients, and the yield of the cultures was low. Of the 5 cases that were identified to have drug resistance, 4 cases had acquired resistance and the overall drug resistant rate among the culture positive cases was 13.9%. These results suggest that sputum culture and drug susceptibility testing for *Mycobacteria* can be limited to patients with a prior history of treatment for TB. Our data also suggests that the drug susceptibility profile of *M. tuberculosis* should be monitored at regular intervals because the proportion of patients with treatment interruption was high (30.5%) and this can favor the development of further drug-resistant *M. tuberculosis*.

The success rates of treatment in our study were low (30.5% of all patients and 45.1% of patients with known treatment outcomes) and is less than the 60% success rate reported by the Thai National Tuberculosis Control Program (Payanandana *et al*, 1995). In our study, drug resistance was associated with only 2 cases of treatment failure. In univariate analysis, we found that residence outside Khon Kaen Province, male gender, older age, HIV co-infection, and care by a non-pulmonary physician were associated with treatment interruption; however only 2 factors which, male gender and care by a non-pulmonary physician, were independently related to treatment interruption. This is in agreement with previous studies suggesting that multiple factors are involved in the success of TB treatment, and that developing a TB control strategy providing care at the community level can promote more successful treatment. In our study, patients who received TB treatment from a non-pulmonary physician were 3.8 times more likely to interrupt treatment, compared to those who received care from a pulmonary physician. The TB clinic at Srinagarind Hospital provides health education on TB and emphasizes the importance of treatment compliance and completion at every clinic visit. Patients who are registered at the TB clinic receive anti-tuberculous drug treatment without cost as a part of the Thai National Tuberculosis Control Program. If a patient is lost to follow-up, clinic personnel attempt to contact them to return for care. This suggests that the support and coordination of care provided by the 'Tuberculosis Clinic' in the pulmonary out-patient clinic is important to the success of the treatment. Therefore, each health care center should attempt to create such a supportive TB clinic system to provide health services for these patients.

Regarding treatment failure and death, our study found that older age, prior history of TB treatment, and HIV co-infection were independently associated with these grave outcomes. The elderly patients in our study were also uneducated and lived in poverty, which further complicated their ability to complete treatment. Previously receiving TB treatment carried a risk of developing drug-resistant *M. tuberculosis*, which was related to treatment failure and death. Co-infection with TB and HIV is also associated with poor TB treatment outcomes (Pablos-Mendez *et al*, 1997; Tansuphasawadikul *et al*, 1998). The majority of our HIV-infected patients had advanced HIV disease and were not treated effectively for their HIV infection, therefore, they were also at risk of contracting other opportunistic infections related to death as an outcome.

The main limitations of our study were selection bias and the bias potentially induced through missing data, as well as the variety of approaches to management by the treating phy-

sicians. Nevertheless, our study reveals that TB is still a major public health problem in Thailand. The results of the present study indicate a need for a coordinated tuberculosis control program which should include active case surveillance, effective care and treatment, and directly observed therapy. Attention should be focused on patients who present with factors identified as high-risk for treatment interruption or poor treatment outcomes. Physicians should be encouraged to assess HIV risk factors in patients who present with TB and to offer HIV testing to all TB patients, as well as to monitor treatment responses.

ACKNOWLEDGEMENTS

We would like to thank the staff of the registration unit and the microbiology laboratory, Srinagarind Hospital for their excellent cooperation. We are grateful for the guidance and support provided by Dr Anthony L Schlaff and Elena Naumova, Department of Family Medicine and Community Health, Tufts University School of Medicine. This study was supported by the AIDS International Research and Training Program of the Fogarty International Center of the National Institutes of Health, USA (#7D43TW00237).

REFERENCES

Accorsi S, Fabiani M, Lukwiya M, *et al*. Impact of insecurity, the AIDS epidemic, and poverty on population health: disease patterns and trends in Northern Uganda. *Am J Trop Med Hyg* 2001; 64: 214-21.

Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *J Am Med Assoc* 1999; 282: 677-86.

Nunn P. Proceedings of a Nobel Symposium on Tuberculosis. The global control of tuberculosis: what are the prospects? *Scand J Infect Dis* 2001; 33: 329–32.

Pablos-Mendez A, Knirsch CA, Barr RG, Lerner BH, Frieden TR. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. *Am J Med* 1997; 102: 164-70.

Pablos-Mendez A, Raviglione MC, Laszlo A, *et al*. Global surveillance for antituberculosis-drug resistance, 1994-1997. *N Engl J Med* 1998; 338: 1641-9.

Payanandana V, Kladphuang B, Talkitkul N, Tornee S. Information in preparation for an external review of the National Tuberculosis Programme, Bangkok: Ministry of Public Health, 1995.

Payanandana V, Rienthong D, Rienthong S, Ratanavichit L, Kim SJ, Sawert H. Surveillance for antituberculosis drug resistance in Thailand: results from a national survey. *Thai J Tuberc Chest Dis* 2000; 21: 1-8.

Riantawan P, Punnotok J, Chaisuksuwan R, Pransujarit V. Resistance of *Mycobacterium tuberculosis* to antituberculosis drugs in the Central Region of Thailand, 1996. *Int J Tuberc Lung Dis* 1998; 2: 616-20.

Tansuphasawadikul S, Poprawski DM, Pitisuttithum P, Phonrat B. Nonadherence in tuberculosis treatment among HIV patients attending Bamrasnaradura Hospital, Nonthaburi. *J Med Assoc Thai* 1998; 81: 964-9.

Tekkel M, Rahu M, Loit HM, Baburin A. Risk factors for pulmonary tuberculosis in Estonia. *Int J Tuberc Lung Dis* 2002; 6: 887-94.

World Health Organization. Global tuberculosis control: WHO report, 2002. Geneva: World Health Organization, 2002.

World Health Organization. Treatment of tuberculosis: Guidelines for national programmes. 2nd ed. Geneva: World Health Organization, 1997.