PREDICTING THE FUTURE TREND OF DRUG-RESISTANT TUBERCULOSIS IN THAILAND: ASSESSING THE IMPACT OF CONTROL STRATEGIES

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Abstract. The purposes of this study are to predict the future trend of drug-sensitive and resistant tuberculosis (TB) in Thailand, and to assess the impact of different control strategies on the generation of drug resistant TB, through the use of mathematical analysis. We assume that the present status of TB and the emergence of drug-resistant TB in Thailand are the consequence of past epidemics. Control strategies in the model are defined by specifying the value of the effective treatment rate (baseline value = 0.74) and the relative treatment efficacy (baseline value = 0.84). It is predicted that the total number of new TB cases would continue to decrease at the current level of intervention. Although a dramatic decline in the incidence rate of drug-sensitive cases is expected, drug-resistant cases are predicted to increase gradually, so that more than half of the TB strains would not be drug-sensitive after 2020. The prediction is not greatly altered by improving the interventions. They could, however, delay the emergence of drug-resistant strains for a few years. Our study demonstrates it would be impossible to avoid the continued emergence of drug-resistant TB in the future. It is pointed out that there are urgent needs to ensure adequate supervision and monitoring, to insure treatment of 100% of the targeted population with Directly Observed Therapy.

INTRODUCTION

Thailand is one of the 22 countries having 80% of the estimated cases of tuberculosis (TB) in the world (WHO, 2000) and one of the 10 countries having the highest prevalence of primary multidrug resistance (WHO/IUATLD, 1997). Although the National Tuberculosis Control Program (NTP) in Thailand was established in 1966 and short course chemotherapy has been used since 1985, the epidemiologic situation seems to have improved only slowly. A team of international and national experts conducted an external program review in 1995 and later in 1999 to improve the national control of TB and found low cure rates (17-68%) (Ministry of Public Health and WHO, 1995). Following the WHO recommendations for strengthening NTP, Thai NTP has adopted the Directly Observed Treatment, Short Course (DOTS) strategy since 1996 as a core strategy to assure quality of care, secure maximum cure rates and to prevent multidrug resistance. Nationwide DOTS expansion was expected to be complete by the year 2001. However, the rapid expansion of DOTS, led initially to difficulties in monitoring the progress of DOTS expansion; this being due to inadequate understanding by health workers and the lack of quality supervision (Ministry of Public Health, 1999). As a result, it could not reach the 100% target as originally planned. More than one-third of the patients took their medicine alone, even if the district health officers provided them with DOTS (Pungrassami and Chongsuvivatwong, 2002).

The rapid emergence of drug resistance, particularly multidrug resistant tuberculosis (MDR-TB) has become a major threat to TB control, even in countries with an effective NTP. Results from the first drug resistance surveillance in Thailand, reflected the deficiencies of the previous control strategy, which had not used the newly revised DOTS. Twenty-five percent primary resistance to one or more drugs together with 2.02% of MDR-

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TB, are warning signs for the future TB situation of the country (Payanandana *et al*, 1999). Medical errors in the prescribing of chemotherapy and unreliable drug supplies must be corrected.

Many mathematical biologists have challenged the current models for describing the possible mechanisms for survival and spread of naturally resistant strains of TB, as well as for the generation of antibiotic-resistant strains of TB (Blower *et al*, 1996; Brewer *et al*, 1996; Castillo-Chavez and Feng, 1997; Feng *et al*, 2000; 2002). Models may be conceptualized as thought experiments, and are extremely useful tools when physical experiments are impossible to perform due to time, monetary, practical, or ethical constraints (Blower and Medley, 1992). They may also help us to realize which factors are the most important determinants of the development, and therefore which factors should be studied more closely and measured more precisely. The purposes of this study are to predict the future trend of drug-sensitive and resistant TB in Thailand, as well as to assess the impact of different control strategies on the generation of drug resistant TB, within a mathematical framework.

MATERIALS AND METHODS

The analysis presented in this paper is based on a deterministic mathematical model predicting the epidemiological outcome of any specified control strategy, while simultaneously evaluating the effect of an inappropriate strategy on drug resistant TB. The model is defined as a set of ordinal differential equations based upon specific biological and interventional assumptions about the transmission dynamics of TB. A brief description of the model is provided in Table 1. Detailed analysis is beyond the scope of this paper, but can be found elsewhere (Blower *et al*, 1996; Blower and Gerberding, 1998). Briefly, the model divides the total population into susceptible individuals, latently infected and considers cases for both drug-sensitive and resistant TB. A description of the principal parameters in the model and of their assigned value is presented below.

First, TB epidemics rise and fall over a period of many decades or even hundreds of years (Porco and Blower, 1998). Hence we assume the present status of TB and the emergence of drug resistant TB in Thailand is a consequence of past epidemics occurring before 1950 (Sunakorn, 1969). The model's parameters are described in Table 2. Assuming the biological variables do not differ for different geographical regions, we have used the parameter values given in a previous

Table 1
Brief description of the model.

The model is a modification of the SEIR model, which separates the population into classes of people who are susceptible (S), exposed (E), infectious (I), diagnosed (J), and recovered (R). Except susceptible individuals, we need to separate *E*, *I* and *R* into two different subclasses: drug-sensitive and resistant tuberculosis. A tuberculosis infection among the susceptible population (S) begins with a non-infectious incubation period (E), which constitutes the latency period. It is followed by symptoms and/or the infectious (I) stage. Among the exposed population, fraction p will develop tuberculosis within 5 years of exposure, while rest [fraction, $(1-p)$] will or will not develop tuberculosis after 5 years. We assumed the transmission coefficient for drug-resistant tuberculosis would be a times higher (or lower) than β_s. Drug-sensitive cases would be effectively treated at a per capita rate of ϕ, and acquired drug-resistance would arise at a probability of r. On the other hand, drug-resistant tuberculosis patients would be cured at a rate equal to $\delta\phi$. This process can be described by:

$$\frac{dS}{dt} = \prod - \beta_s S (I = I_R) - \mu S$$

$$\frac{dE}{dt} = (1 - p)\,\beta_s SI - (\nu + \sigma + \mu)\,E$$

$$\frac{dE_R}{dt} = (1 - p)\,\alpha\beta_s SI_R - (\nu + \mu)\,E_R$$

$$\frac{dI}{dt} = \nu E + p\beta_s SI + \eta R - (\phi + \mu + \mu_t)\,I$$

$$\frac{dI_R}{dt} = \nu E_R + p\alpha\beta_s SI_R + \eta R_R + r\phi I - (\delta\phi + \mu + \mu_t)\,I_R$$

$$\frac{dR}{dt} = (1 - r)\,\phi I - (\eta + \mu)\,R$$

$$\frac{dR_R}{dt} = \delta\phi I_R - (\eta + \mu)\,R_R$$

Table 2
Parameters for transmission dynamics of tuberculosis in Thailand. Population census has been fitted by finding a least sum of squares.

Parameters	Description	Baseline values	Intervention analysis
Π	Rate of arrival of new susceptibles	70,000 ~ 115,000 (according to population growth and initial time period)	
β_s	Transmission coefficient	0.000005714	
α	Relative transmissibility	0.80	
$1/\mu$	Average life expectancy	0.014285714	
p	Proportion of new infections that develop disease within 1 year	0.05	
v	Progression rate to disease	0.00256	
σ	Per capita rate of effective chemoprophylaxis	0.10	
ϕ	Per capita treatment rate	0.74	0.59 (20% below) and 0.89 (20% above) coverage
μ_t	Mortality rate due to tuberculosis	0.06 ~ 0.85 (according to initial time period)	
δ	Relative treatment efficacy	0.84	0.88 (5% better efficacy)
r	Probability of drug resistance emerging during treatment	0.10	
η	Rate of relapse to active tuberculosis	0.02	
t	Initial time period	Before 1950 (described in text)	

study (Blower and Gerberding, 1998) for those parameters whose values are unavailable from Thailand's epidemiological records. For specified TB control strategies, the control strategy in the model was defined by specifying the value of the effective treatment rate, the relative treatment efficacy, and the probability of drug resistance emerging during treatment. As for the per capita treatment rate, it was roughly estimated at 74% as a present baseline value on the assumption that NTP strategy had fulfilled the targeted goals of DOTS coverage so far (Ministry of Public Health, 2001). According to the report on NTP achievements by the Ministry of Public Health (1999), 84% of the relative treatment efficacy was defined as a baseline value. Since it does not affect the basic reproductive rate both for drug-sensitive and resistant TB, and was unavailable from any epidemiological records, we analyzed the model using a fixed value of 0.10 probability of drug resistance emerging during treatment, as was done by Blower and Gerberding (1998). The initial demographic values in the model were those characteristics of the Thai population in defined years of first epidemic and were obtained from the Ministry of Public Health (1995). Reasonably estimated data are available for the TB incidence of new smear positive patients over time in Thailand (Ministry of Public Health, 1999). We estimated the TB incidence in Thailand as a whole from the available data and fitted those over time by repeating simulations. We carried out the simulations more than 10,000 times in order to obtain the suitable values. Finally, we measured the impact of the interventions below and above present levels of coverage in per capita treatment rates as well as relative treatment efficacy.

In this study, drug resistant *Mycobacterium tuberculosis*, which is resistant to rifampicin, was studied. So far no study has investigated the transmission dynamics of MDR-TB using deterministic models, we have chosen to model the resistance against one drug. It is reasonable to use rifampicin as the drug that the TB is resistant to

since it had not been commonly used as chemoprophylaxis, as has isoniazid. Furthermore, we have the data needed to fit the recent trends of resistance (Punnotok *et al*, 1985; Sriyabhaya *et al*, 1993; Riantawan *et al*, 1998). The model has been programed by ourselves using Turbo Pascal Version 1.5 (Borland International Inc, Scotts Valley, CA, USA) working on the Microsoft Windows™ platform. All data from the program were analyzed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The trend of TB incidence rates until now in Thailand fitted very well with the models, both for drug-sensitive and resistant TB. It was affected by 'fast' the subepidemics of primary progressive TB and the 'slow' epidemics of endogenous reactivation in the past. The results of the analyses are shown in the figure up to 2030. It is unrealistic to estimate for longer time periods since one would not expect health policies and control strategies to remain static over longer periods.

Fig 1a shows the model generated incidence rates for both drug-sensitive and drug-resistant cases, after effective DOTS has gradually started to cover. The incidence rates for both drug-sensitive and resistant TB in 2010 are estimated to be 22.8 and 8.6 per 100,000, respectively. The total incidence rate was expected to decline to 31.4 per 100,000 in 2010. Over time, a rapid decline in the incidence rate of drug-sensitive cases is seen. On the other hand, the incidence rate of drug-resistant cases increases gradually. It is estimated that a 41.0% increase could be seen by the year 2020 in the incidence rate of drug-resistant cases (10.9 per 100,000). Fig 1b shows the contribution of drug resistance to the number of new cases that require treatment. Even though the total number of new TB cases was estimated to decrease, the proportion of drug-resistant strains among new cases was observed to increase sharply. Without any significant changes in control strategy, less than half of the new TB cases could be drug-sensitive after 2020.

Fig 2a shows the incidence rates for both drug-sensitive and resistant cases arising from different treatment rates. Fig 2b shows the relative contribution of drug resistance in the same way. As a whole, the per capita treatment rate seems to not affect the trend; *ie* both sharp decline in drug-sensitive cases and gradual increase in drug-resistant cases. However, a 20% increase

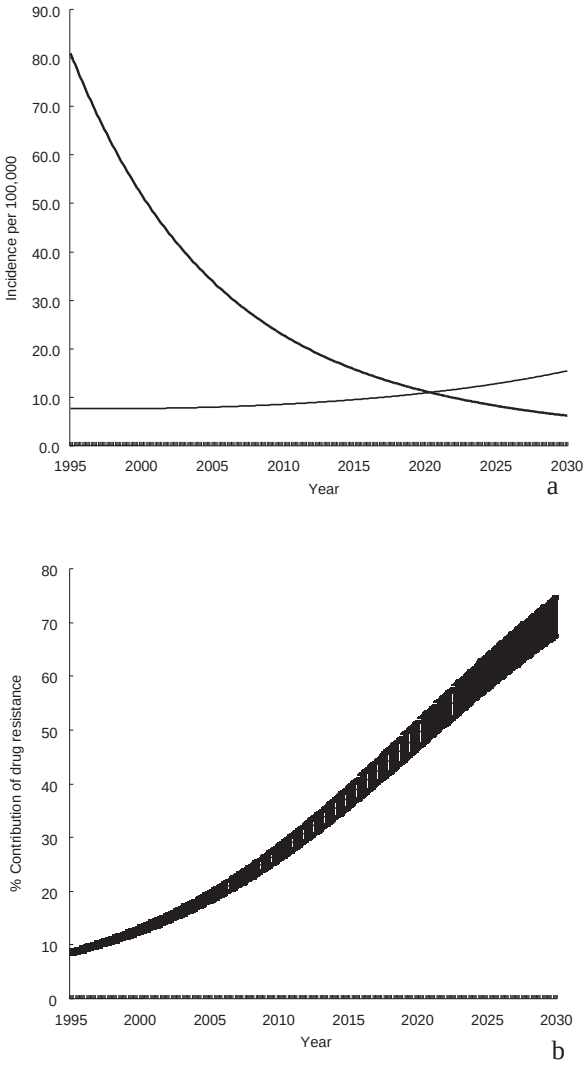
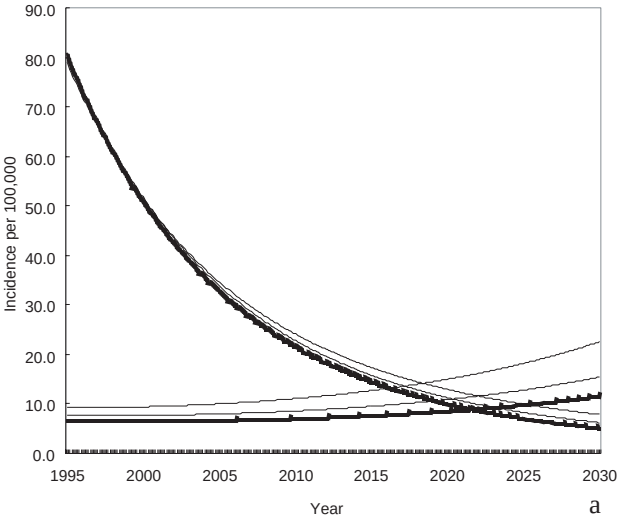


Fig 1–a) Projected TB incidence with the current levels of intervention. The incidence rate of drug resistance is composed of primary plus acquired drug resistance. b) Data shown in (a) is used, but the data are replotted in order to show the relative contribution of drug resistance to the number of new TB cases (with 95% confidence limits). The y-axis is the incidence of drug-resistant cases divided by the incidence of drug-resistant plus drug-sensitive cases.



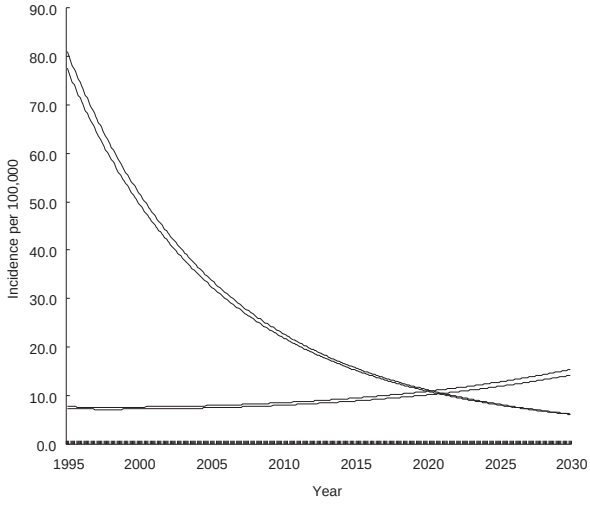


Fig 3–Projected changes in TB incidence in Thailand 5% under improved relative treatment efficacy (thick line). Thin line denotes the baseline value.

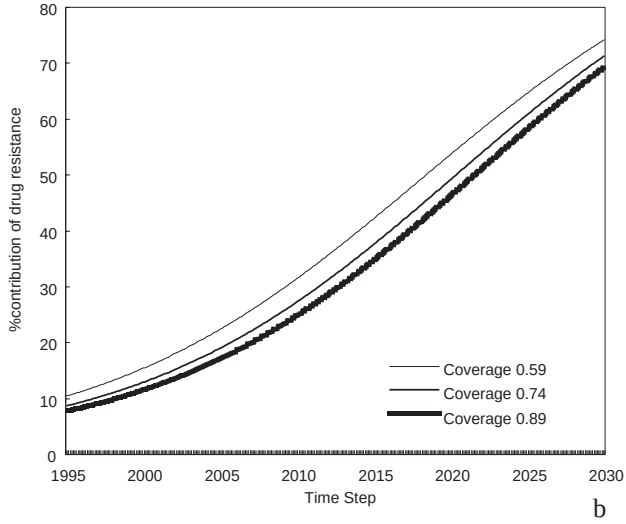


Fig 2–a) Three possible trajectories expressed as drug-sensitive and resistant TB incidence. b) The relative contribution of drug resistance in three possible trajectories under different effective treatment rates of 80%, 100% or 120% of its current value.

in treatment rate shows a more rapid decline in the incidence rate of drug-sensitive cases and a more gradual increase in drug-resistant cases. It delays the time, to the point in which less than half of the new TB cases are drug-sensitive, by 1.6 years. A completely adverse trend was observed at a 20% decrease in the per capita treatment rate. The impact of a 5% increase in relative treatment efficacy is shown in Fig 3. No significant difference was observed for better treatment efficacy.

DISCUSSION

Three important conclusions can be drawn from our analyses on assessing the impact of intervention on the TB trend in Thailand. First, Thailand's present endemic state of tuberculosis, being the result of past epidemics occurring decades ago, places Thailand in the third phase in the sequence of the emergence of drug resistance. Second, the total number of new TB cases will continue to decrease with the current level of intervention. A dramatic decline in the incidence rate of drug-sensitive cases is expected. Finally, the incidence rate of drug-resistant cases is estimated to increase gradually. More than half of the TB strains could be drug-resistant by 2020. The prediction is not greatly affected by improved interventions though they could delay the emergence of drug resistance for a few years.

Over the long time period, three phases occur in the emergence of drug resistance: the contribution of drug resistance will lead to a sharp increase in the number of new cases that require treatment, the number will then decrease, and finally the number will gradually increase again

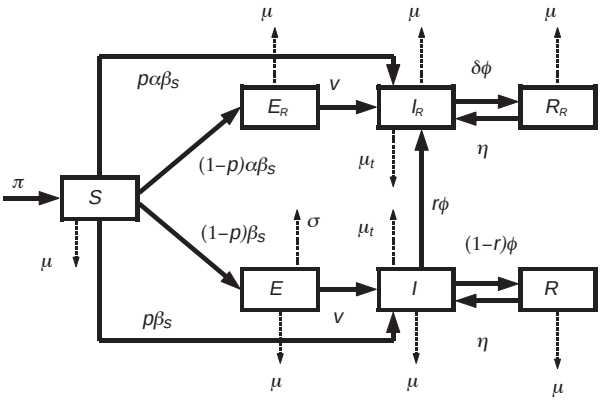


Fig 4–The transmission dynamics of drug-sensitive and resistant TB. Here: S represents the number of population susceptible; E and E_R the number of latent drug-sensitive and resistant tuberculosis, respectively; I and I_R the number of infectious drug-sensitive and resistant tuberculosis, respectively; R and R_R the number of recovered drug-sensitive and resistant tuberculosis, respectively.

(Blower and Gerberding, 1998). This qualitative pattern is due to the changing dynamics between drug-sensitive and drug-resistant TB that are produced by the control strategy. In Thailand, the third phase is occurring, since the control strategy is still effective in decreasing the incidence of drug-sensitive cases but is less effective in decreasing the incidence of drug-resistant cases. Therefore, the proportion of drug-resistant strains among new cases is predicted to increase sharply over the next few decades.

TB had decreased significantly in the past 30 to 40 years because of the initiation, expansion and integration of the TB control program in Thailand. Achievement in the control of TB was due to economic development (especially between 1967 and 1995), and the improvement in living standards, leading to a decrease in poverty (Ministry of Public Health and WHO, 2001). From our study, the trend of decline in incidence should continue even though TB control is currently affected by drastic economic changes, the human immunodeficiency virus (HIV) epidemic and an increase in mobile populations. NTP coverage is quite extensive compared to other developing countries. The WHO predicts, on the basis of TB and HIV epidemiology, that after covering the whole country with the newly revised control strategy in the year 2001, the trend of TB burden in this country could start to decline (Ministry of Public Health, 1999).

The DOTS strategy has been recommended for all patients with TB because of the expected difficulties in predicting whether a given patient will adhere to treatment (WHO, 1999). It should be stressed that our study demonstrates expanding DOTS, and improving effective treatment rates, would delay the emergence of drug resistant strains. Kasetjaroen *et al* (1995) performed a study to evaluate the output of DOTS and confirmed the importance of DOTS in MDR-TB treatment. Most TB experts are now following WHO guidelines (1993) and have been able to achieve better sputum conversion rates (Payanandana *et al*, 1993). This may be the reason why our studied values of improved relative treatment efficacy did not have much effect on the incidence. The major problem for DOTS expansion in Thailand is quality assurance. In particular, urban TB programs needs more attention, efforts, and advocacy (Ministry of Public Health, 2001). The quality of DOTS needs to be improved and regularly evaluated. There is an urgent need to ensure adequate supervision and monitoring. These are the keys to the integrity and effectiveness of the control program, needed to provide treatment for 100% of the targeted population with DOTS.

Our study demonstrates that it is impossible to avoid the continued emergence of drug-resistant TB in the future. One should not expect the incidence of drug-resistant strains to remain stable even though the second National Surveillance by Ministry of Public Health (2001) was more or less the same as the first. Optimal treatment based on the guidelines should be strictly followed (Maranetra, 1996). Otherwise, it will become necessary to revise treatment guidelines drastically in Thailand. Good organization of ambulatory TB management combined with DOTS will help to reduce the incidence of drug-resistant TB.

Our study has limitations. First, as described above, so far it is impossible to predict the development of MDR-TB. The trend of drug-resistant TB in this study is limited to the TB resistant to rifampicin. Second, the HIV epidemic in 1990s

was not taken into consideration in our model. It has not been possible to model the impact of the HIV epidemic on the TB epidemic. We tried to fit the estimated incidence of TB to the real data as best we could. Finally, one of the basic assumptions of this model has been criticized as being unrealistic (Giesecke, 2002): *ie* every person in the population will meet every other person with equal probability. Further research on the mathematical modelling of TB in Thailand is necessary. This includes understanding and predicting the impact of HIV/AIDS. It is hoped that MDR-TB modelling, that does not need many epidemiological records, will be developed in the future.

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REFERRENCES

Blower SM, Gerberding JL. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. *J Mol Med* 1998; 76: 624-36.

Blower SM, Medley GF. Epidemiology, HIV and drugs: mathematical models and data. *Br J Addiction* 1992; 87: 31-9.

Blower SM, Small PM, Hopewell PC. Control strategies for tuberculosis epidemics: new models for old problems. *Science* 1996; 273: 497-500.

Brewer TF, Heymann SJ, Colditz GA, *et al*. Evaluation of tuberculosis control policies using computer simulation. *J Am Med Assoc* 1996; 276: 1898-903.

Castillo-Chavez C, Feng Z. To treat or not to treat: the case of tuberculosis. *J Math Biol* 1997; 35: 629-59.

Feng Z, Castillo-Chavez C, Capurro A. A model for TB with exogenous reinfection. *Theor Popul Biol* 2000; 57: 235-47.

Feng Z, Ianneli M, Milner FA. A two-strain tuberculosis model with age of infection. *SIAM J Appl Math* 2002; 62; 1634-56.

Giesecke J. Modern infectious disease epidemiology. 2nd ed. London: Arnold, 2002.

Kasetjaroen Y, Pungrassami P, Maneesang P, Hanapark P, Tunsawai V, Tonhaem D. Directly observed therapy (DOT) of pulmonary tuberculosis – role of family members. *Thai J Tuberc Chest Dis* 1995; 16: 237-49.

Maranetra KN. Treatment of multidrug-resistant tuberculosis in Thailand. *Chemotherapy* 1996; 42: s10-s15.

Ministry of Public Health. Battle against TB. National Tuberculosis Programme, Thailand 1999. Bangkok: Ministry of Public Health, 1999.

Ministry of Public Health. Current TB status in Thailand; activities and achievements. Bangkok: Ministry of Public Health, 2001.

Ministry of Public Health, Thailand. Information in preparation for an external review of the National Tuberculosis Programme, Thailand 1995. Bangkok: Ministry of Public Health. 1995.

Ministry of Public Health and WHO. National Recommendations guideline: the integrated HIV-TB care strategies for the control and prevention of tuberculosis in Thailand. Bangkok: Ministry of Public Health, 2001.

Ministry of Public Health and WHO. The External Review of the National Tuberculosis Programme, Thailand, 18-29 June 1995. Geneva: World Health Organization, 1995.

Payanandana V, Bamruntrakul T, Kannjanart S, Sriyabhaya N. Efficacy of regimens for retreatment of tuberculosis: treatment evaluation and research studies (1983-1986). Report on an international evaluation of the National Tuberculosis Programme, Thailand. Bangkok: Ministry of Public Health, 1993.

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* 1999; 21: 1-8.

Porco TC, Blower SM. Quantifying the intrinsic transmission dynamics of tuberculosis epidemics. *Theor Popul Biol* 1998; 54: 117-32.

Pungrassami P, Chongsuvivatwong. Are health personnel the best choice for directly observed treatment

in southern Thailand? A comparison of treatment outcomes among different types of observers. *Trans R Soc Trop Med Hyg* 2002; 96: 695-9.

Punnotok J, Fuangtong P, Wongsangiem M. Primary drug resistance in newly diagnosed untreated tuberculosis in Central Chest Hospital 1979-1981. *Thai J Tuberc Chest Dis* 1985; 2: 69-77.

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.

Sriyabhaya N, Payanandana V, Bamrungtrakul T, Konjanart S. Status of tuberculosis control in Thailand. *Southeast Asian J Trop Med Public Health* 1993; 24: 410-9.

Sunakorn B. The epidemiology of tuberculosis in Thailand. *J Med Assoc Thai* 1969; 52: 127-62.

WHO. Global tuberculosis control. WHO Report 2000. Geneva: World Health Organization. *WHO/CDS/TB/2000.275*, 2000.

WHO. Treatment of tuberculosis. Guidelines for national programmes. Geneva: World Health Organization, 1993.

WHO. What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS. Geneva: World Health Organization. *WHO/CDS/TB/99.270*, 1999.

WHO/IUATLD. Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994-1997. Anti-tuberculosis Drug Resistance in the World. Geneva: World Health Organization, *WHO/TB/97.229*, 1997.