

P-MS008

## RISK FACTORS FOR RECURRENCE OF PULMONARY TUBERCULOSIS IN NAN PROVINCE

Wisit Marin<sup>1,\*</sup>, Mathuros Tipayamongkholgul<sup>2</sup>, Petchawan Pungrassami<sup>3</sup>, Dusit Sujirarat<sup>2,#</sup>

<sup>1</sup>Graduate Program in Infectious Disease and Epidemiology, Department of Epidemiology, Faculty of Public Health, Mahidol University, Thailand

<sup>2</sup>Department of Epidemiology, Faculty of Public Health, Mahidol University, Thailand

<sup>3</sup>Bureau of Tuberculosis, Department of Disease Control, Ministry of Public Health, Thailand

\*e-mail: wisitmarin@hotmail.com, #e-mail: dusit.suj@mahidol.ac.th

### Abstract

**Background:** Recurrence of pulmonary tuberculosis can be both due to re-infection and relapse has been previously treated for TB disease. The recurrence of pulmonary tuberculosis remains unclear and has potential implications for public health. This study aims to estimate the incidence of, and investigate risk factors for, recurrent episodes of tuberculosis in Nan province.

**Method:** Episodes of recurrent cases of tuberculosis data using a TB clinic management program (TBCM) database, office of disease prevention and control, 10; Thailand, during January 2005 to December 2012. A new clinical and/or microbiological TB diagnosis in the cure or completion treatment patients was defined as a recurrent TB. To estimate the incidence and follow-up time, recurrence or censored was calculated. Poisson regression was used to determine risk factors, socio-demographic, history of tuberculosis treatment and comorbid condition factor, for recurrent pulmonary tuberculosis.

**Results:** Among the total 2011 cases report, 136 patients were resulting in recurrence of pulmonary tuberculosis (recurrence rate 20.37 per 1000 person-years of follow-up). The results of the present study indicate that older than 50 years old (IRR 1.43; 95% CI 1.01-2.05), BMI underweight (IRR 2.06; 95% CI 1.37 - 3.10), sputum smear positive at 2 months (IRR 1.92; 95% CI 1.22-3.03), abnormal chest radiography presented cavitation (IRR 1.91; 95% CI 1.07-3.42) and HIV-positive patients (IRR 3.30; 95% CI 2.19 - 4.98) were associated with recurrence of pulmonary tuberculosis at the multivariate level.

**Conclusion:** The older age at discharge, BMI underweight, sputum smear positive at 2 months, abnormal chest radiography presented cavitation and HIV-positive patients are strongly associated with recurrence of pulmonary tuberculosis. These factors should be considered when planning, surveillance, prevention and control TB program.

**Keywords:** pulmonary tuberculosis, recurrence, risk factors

### Introduction

Tuberculosis (TB) remains one of the most common infectious disease globally. According to World Health Organization (WHO) reported, there were an estimated 8.7 million new cases of TB and 1.4 million deaths. Since WHO launched a strategy and systemically monitoring TB in 1990, 51 million people were successfully treated for TB in the countries that adopted WHO strategy lead to 85% treatment success rate in 2010(1). However, rates of a subsequent episode after successful treatment of new pulmonary TB, or recurrence, have been reported 2.4% to 2.9% (2-4). Recurrent tuberculosis poses a particular challenge to public health systems since recurrent tuberculosis may result in multi-drug resistance (5-7).

Recurrent tuberculosis can be the result of a new infection (exogenous re-infection) or the reactivation of the tuberculosis strain responsible for the original episode of the disease (endogenous reactivation). The host factors including, adherence to treatment, the severity of the original episode,

the patient's immune status and the risk of re-infection can be influence of the recurrent tuberculosis (8). In the countries with low incidence of tuberculosis, recurrence TB can be due to relapse that occur within 3 months after treatment (9-11). In contrast , The country with a high incidence of tuberculosis found a high proportion of re-infection recurrence TB was higher because the risk of exposure was increased lead to re-infection recurrence TB within a half to one year(12-14). Especially, the effect of HIV infection was significantly associated risk factors for recurrent tuberculosis and significantly increased the effect of HIV infection (15-17).

Thailand is the endemic area of tuberculosis. According to World Health Organization (WHO) reported in 2010, WHO estimated that the prevalence and incidence rates of tuberculosis were 161 and 124 per 100000 population, respectively.(1) Incidence rates of tuberculosis through every region still high especially in the Northern part (18). Nan, a province of northern Thailand, is considerate to be a high incidence of 76 per 100000 population and the estimated death rate of tuberculosis 10.55 per 100000 population (19).

Therefore, tuberculosis affects the population health in Nan province.

The recurrence of pulmonary tuberculosis remains unclear and has potential implications for public health. Therefore, this study aims to estimate the incidence of, and investigate risk factors for, recurrent episodes of tuberculosis in Nan province. The study results will be used for planning, surveillance, prevention and control TB program.

## **Methodology**

### *Study sample and data collection*

The study sample was Nan patients aged 15 years or older who cure or complete treatment at the first episode. The study design was a retrospective cohort study, recurrent cases of tuberculosis data using a TB clinic management program (TBCM) database, office of disease prevention and control, 10; Thailand. The data set of TBCM includes socio-demographic, history of tuberculosis treatment and comorbid condition factors. Identification card number of TB patients in TBCM database was use identify re-notification among January 2005 to December 2012. To calculate the incidence of recurrent tuberculosis among all reported cases, follow-up time in days was calculated for all cases of discharge to re-notification or censure was identified.

The study, approved by the Ethical Review Committee for Human Research, Faculty of Public Health, Mahidol University.

### *Definitions*

A TB case was defined as a case with *Mycobacterium tuberculosis* complex identified from a clinical specimen and/or, culture, radiological evidence of mycobacterial disease a decision to treat with full course of antituberculosis therapy. Recurrence of pulmonary tuberculosis was defined as a new clinical and/or microbiological diagnosis of TB in any patient who had correctly completed treatment or cure for their first episode.

### *Statistical analysis*

Data were analyzed using STATA 12 software (STATA Corporation, College Station, TX, USA). In calculating density of recurrence incidence, the denominator was person-years of follow-up (PY). Poisson regression was used to calculate univariate and multivariate-adjusted recurrent TB incidence rate ratios for different variables from the expanded data set.

## **Results**

The study sample was predominantly status cure of TB treatment (50.67%), male (69.32%), the mean age was 51.17 years (S.D.16.83, Rang 16-97 years) and 91.05% remaining alive. The median body mass index was 17.99 kg/m<sup>2</sup> (IQR.16.85 kg/m<sup>2</sup> -20.07 kg/m<sup>2</sup>, Range 7.91 kg/m<sup>2</sup> - 40.82 kg/m<sup>2</sup>) and 57.83% were BIM underweight. The predominant type was pulmonary tuberculosis (73.62%), sputum smear-negative at 2 months were 65.84%, 30.28% abnormal chest radiograph presented non cavitation. Among the patients 71.46% were HIV negative (Table 1).

**Table 1** General characteristic of socio-demographic risk factors, historical of TB treatment and comorbid condition for the cohort of 2011 patients.

Characteristics	Number	Percent
<b>Total</b>	<b>2011</b>	<b>100.00</b>
<b>Status TB treatment</b>		
Cure	1,019	50.67
Complete treatment	992	49.33
<b>Socio-demographic risk factors</b>		
<b>Gender</b>		
male	1,394	69.32
female	617	30.68
<b>Status</b>		
death	180	8.98
live	1,831	91.05
<b>Age at discharge(years)</b>		
15-20	58	2.88
21-30	193	9.60
31-40	338	16.81
41-50	396	19.69
51-60	380	18.90
61-70	356	17.70
71-80	231	11.49
> 80	59	2.93
<b>BMI</b>		
Underweight (<18.5 kg/m <sup>2</sup> )	1,163	57.83
Normal (18.5-22.9 kg/m <sup>2</sup> )	632	31.43
Overweight (≥23 kg/m <sup>2</sup> )	216	10.74
<b>History of TB treatment</b>		
<b>Classified of TB</b>		
pulmonary tuberculosis	1,476	73.62
extrapulmonary tuberculosis	535	26.60
<b>Sputum status at 2 month</b>		
positive smear	154	7.66
negative smear	1,324	65.84
unknown	533	26.50
<b>Chest radiograph at discharge</b>		
cavity	62	3.08
non-cavity	609	30.28
unknown	1,340	66.63
<b>Comorbid conditions</b>		
<b>HIV status</b>		
HIV positive	248	12.33
HIV negative	1,437	71.46
unknown	362	16.21

Among the total 2011 cases report, 136 patients were resulting in recurrence of pulmonary tuberculosis. Five of 136 patients were second episodes. The median follow-up time was 1.19 years

(IQR 0.35-2.54). The majority of recurrence TB (44.11%) occurred within 1 years of follow-up (Table 2).

**Table 2** Time to recurrence TB by year since follow-up, Nan province 2005 – 2011.

Follow-up(years)	no of recurrence	% of total recurrence TB
0-1	60	44.11
1-2	31	22.79
2-3	18	13.23
3-4	10	7.35
4-5	10	7.35
> 5	7	5.14
<b>total</b>	<b>136</b>	<b>100.00</b>

Among the total 2011 cases report, 136 patients were resulting in recurrence of pulmonary tuberculosis (recurrence rate 20.37 per 1000 person-years of follow-up). The incidence of recurrence of pulmonary tuberculosis was observed male 21.73 per 1000 person-years of follow-up, older than 50 years old was 23.64 per 1000 person-years of follow-up, underweight patients was 26.30 per 1000 person-years of follow-up, extra-pulmonary tuberculosis 22.06 per 1000 person-years of follow-up, sputum smear positive at 2 month was 49.27 per 1000 person-years of follow-up, abnormal chest radiography presented cavitation 83.12 per 1000 person-years of follow-up and HIV-positive patient was 57.63 per 1000 person-years of follow-up (Table 3).

Factors independently associated risks of recurrence of pulmonary tuberculosis about each baseline group where previous status treatment, gender, age at discharge (older than 50 years old), BMI underweight, smear-positive, chest radiography presented cavitation and HIV-positive patients. In multivariate level, the results indicate that older than 50 years old (IRR 1.43; 95% CI 1.01-2.05), BMI underweight (IRR 2.06; 95% CI 1.37 - 3.10), sputum smear positive at 2 months (IRR 1.92; 95% CI 1.22-3.03), abnormal chest radiography presented cavitation (IRR 1.91; 95% CI 1.07-3.42) and HIV-positive patients (IRR 3.30 ; 95% CI 2.19 - 4.98) were associated with recurrence of pulmonary tuberculosis (Table 4).

### Discussion and Conclusion

There were an estimated 21 cases per 1000 person years of follow-up of recurrent tuberculosis in Nan province. This study also found that age at discharge (older than 50 years old), BMI underweight and HIV-positive patients were significantly associated with recurrence of pulmonary tuberculosis. A retrospective study in England and Wales show that the incidence rate of tuberculosis was 13 cases per 1000 000 population which a culture-confirmed pulmonary disease was 4 cases per 1000 person years of follow-up (15). In contrast, a prospective cohort studies and randomized clinical trials reviews found that a mean of recurrence rate was 18 episodes per 1000 person years of follow-up in low incidence countries and 79 episodes per 1000 person years in high incidence countries, respectively (20).

Anbesaw W, et al. (21) found that the age at discharge higher than 65 years old increase the risk of recurrent tuberculosis. In contrast to previous studies, the present study indicated that older age (> 50 years) increases the risk of recurrent tuberculosis. However, suggest that the risk of recurrent tuberculosis increases with age increase. Over 57.83% of tuberculosis cases reported in Nan province significantly associated with underweight which there was a 2.06 fold increase risk of recurrent TB than normal weight. According to Khan A, et al. (22) the person who underweight during the first 2 months of treatment may associate with an increased relapse risk. There Among persons underweight at diagnosis, weight during the first 2 mo of treatment is associated with an increased relapse.

**Table 3** The incidence density rate (IDR) of recurrence tuberculosis of socio-demographic, history of tuberculosis treatment and comorbid condition factors.

<b>Characteristics</b>	<b>Subjects</b>	<b>Number of recurrence TB</b>	<b>IDR per 1000 person-years</b>	<b>95% CI</b>
<b>All</b>	<b>2,011</b>	<b>136</b>	<b>20.37</b>	<b>18.34-22.40</b>
<b>Status TB treatment</b>				
cure	1,028	57	16.49	12.03-20.76
complete treatment	998	79	24.53	20.66-28.33
<b>Socio-demographic risk factors</b>				
<b>Gender</b>				
female	617	37	17.45	10.47-24.32
male	1,394	99	21.73	18.81-24.58
<b>Age at discharge(years)</b>				
15-51	985	61	17.41	13.19-21.60
≥ 51	1,026	75	23.64	19.63-27.56
<b>BMI</b>				
Normal weight (18.5-22.9 kg/m <sup>2</sup> )	632	26	12.74	4.25-21.14
Underweight (<18.5kg/m <sup>2</sup> )	1,163	105	26.30	20.76-26.43
Overweight (≥23 kg/m <sup>2</sup> )	216	5	7.78	2.65-8.19
<b>History of TB treatment</b>				
<b>Classified of TB</b>				
pulmonary tuberculosis	1,476	37	19.80	14.22-29.77
extrapulmonary tuberculosis	535	99	22.06	17.04-22.55
<b>Sputum status at 2 month</b>				
negative smear	1,857	113	18.22	15.88-20.51
positive smear	154	23	49.27	30.76-67.63
<b>Chest radiograph at discharge</b>				
non-cavity	1,949	120	18.53	16.29-20.70
cavity	62	16	83.12	49.28-116.91
<b>Comorbid condition</b>				
<b>HIV status</b>				
HIV negative	1,799	92	15.58	12.86-18.13
HIV positive	248	44	57.63	47.22-67.97

**Table 4** The incidence density rate ratio(IRR) of recurrence tuberculosis by univariate and multivariate-adjusted incidence rate ratios for recurrence of pulmonary tuberculosis

Characteristics	Univariate Analysis			Multivariate Analysis		
	IRR	95% CI	p-value	IRR	95% CI	p-value
<b>Status TB treatment</b>						
cure	1.00			1.00		
complete treatment	1.48	1.04-2.12	0.021	1.38	0.98-1.94	0.064
<b>Socio-demographic risk factors</b>						
<b>Gender</b>						
female	1.00			1.00		
male	1.24	0.84-1.86	0.254	1.22	0.83-1.75	0.291
<b>Age at discharge(years)</b>						
15-51	1.00			1.00		
≥ 51	1.35	0.95-1.93	0.076	1.43	1.01-2.05	<b>0.049</b>
<b>BMI</b>						
Normal weight	1.00			1.00		
Underweight	2.06	1.34-3.17	0.001	2.06	1.37-3.10	<b>0.001</b>
Overweight	0.60	0.23-1.58	0.311	0.59	0.22-1.54	0.287
<b>History of TB treatment</b>						
<b>Classified of TB</b>						
pulmonary tuberculosis	1.00			1.00		
extrapulmonary tuberculosis	1.11	0.74-1.64	0.570	1.04	0.71-1.53	0.814
<b>Sputum status at 2 month</b>						
negative smear	1.00			1.00		
positive smear	2.70	1.64-4.26	< 0.001	1.92	1.22-3.03	<b>0.005</b>
<b>Chest radiograph at discharge</b>						
non-cavity	1.00			1.00		
cavity	4.48	2.48-7.58	< 0.001	1.91	1.07-3.42	<b>0.028</b>
<b>Comorbid condition</b>						
<b>HIV status</b>						
HIV negative	1.00			1.00		
HIV positive	3.69	2.52-5.35	< 0.001	3.30	2.19-4.98	< <b>0.001</b>

According to the WHO treatment of tuberculosis guidelines, sputum must be examined at the end the two-month initial phase of treatment. If the result is positive, to continue the initial phase for an extra month before proceeding with the standard four or six month continuation phase (23). However, the present study found the association between the positive sputum smear at two months may increase the risk of recurrent tuberculosis, with 1.92 fold when compare with a negative smear. Therefore, the detection of positive sputum smears still important for monitoring tuberculosis treatment. The chest radiography in the end of tuberculosis chemotherapy patient that present residual scarring was associated with recurrent tuberculosis. The previous study found the factor that induced the residual cavitation in chest radiography at the end of chemotherapy (16, 17, 24). According to Mallory KF, et al. (16) the patients who post-tuberculosis scarring on three or more zones were 4.0 fold increase risk of recurrence TB than one or two scarring lung zones. HIV-infected patients significantly associated with recurrent tuberculosis; with 3.3 fold of the risk. A Previous study has shown that HIV infection increased the risk for recurrent tuberculosis (15-17) The disadvantage of

cohort studies is the inadequacy of CD4 cell count data, according to HIV patients, a low CD4 cell count is also associated with recurrent tuberculosis. (17, 25, 26).

The limitation of our study is TB in HIV positive patients may overestimate because the limitation of data access and permission on the data is required. The study also follow-up the study sample that register to treat the disease in another province in Northern region, but some case may be lost because a patient may treated in the hospital outside the Northern region.

In the future study, the interventions to decrease the risk of recurrent tuberculosis in an underweight patient should be investigated. The CD4 cell count that may affect to the recurrent tuberculosis should be determined. The sputum smear at 2 month and chest radiograph at the completion treatment was an important indicator for tuberculosis surveillance. The older age at discharge, BMI underweight, sputum smear positive at 2 months, abnormal chest radiography presented cavitation and HIV-positive patients are strongly associated with recurrence of pulmonary tuberculosis. These factors should be considered when planning, surveillance, prevention and control TB program.

### Acknowledgements

This study was supported by Department of Epidemiology Faculty of Public Health Mahidol University.

### References

1. WHO. Global Tuberculosis Report 2012. Geneva: WHO, 2012.
2. Kritski AL, Rodrigues de Jesus LS, Andrade MK, et al. Retreatment tuberculosis cases. Factors associated with drug resistance and adverse outcomes. *Chest*. 1997;111(5):1162-7.
3. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *The New England journal of medicine*. 1994;330(17):1179-84.
4. Bechan S, Connolly C, Short GM, et al. Directly observed therapy for tuberculosis given twice weekly in the workplace in urban South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1997;91(6):704-7.
5. El Sahly HM, Wright JA, Soini H, et al. Recurrent tuberculosis in Houston, Texas: a population-based study. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2004;8(3):333-40.
6. Centers for Disease C. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons--Florida and New York, 1988-1991. *MMWR Morbidity and mortality weekly report*. 1991;40(34):585-91.
7. La Raja M, Screm C, Talmassons G, et al. Antituberculosis drug-resistance surveillance as a tool for tuberculosis control programmes: a retrospective study. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo*. 1997;52(5):450-4.
8. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *American journal of respiratory and critical care medicine*. 2004;170(12):1360-6.
9. Sahadevan R, Narayanan S, Paramasivan CN, et al. Restriction fragment length polymorphism typing of clinical isolates of *Mycobacterium tuberculosis* from patients with pulmonary tuberculosis in Madras, India, by use of direct-repeat probe. *Journal of clinical microbiology*. 1995;33(11):3037-9.
10. Cacho J, Perez Meixeira A, et al. Recurrent tuberculosis from 1992 to 2004 in a metropolitan area. *The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology*. 2007;30(2):333-7.



11. Bandera A, Gori A, Catozzi L, et al. Molecular epidemiology study of exogenous reinfection in an area with a low incidence of tuberculosis. *Journal of clinical microbiology*. 2001;39(6):2213-8.
12. Das S, Paramasivan CN, Lowrie DB, et al. IS6110 restriction fragment length polymorphism typing of clinical isolates of *Mycobacterium tuberculosis* from patients with pulmonary tuberculosis in Madras, south India. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 1995;76(6):550-4.
13. Van Rie A, Warren R, Richardson M, et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *The New England journal of medicine*. 1999;341(16):1174-9.
14. Das S, Chan SL, Allen BW, et al. Application of DNA fingerprinting with IS986 to sequential mycobacterial isolates obtained from pulmonary tuberculosis patients in Hong Kong before, during and after short-course chemotherapy. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 1993;74(1):47-51.
15. Crofts JP, Andrews NJ, Barker RD, et al. Risk factors for recurrent tuberculosis in England and Wales, 1998-2005. *Thorax*. 2010;65(4):310-4.
16. Mallory KF, Churchyard GJ, Kleinschmidt I, et al. The impact of HIV infection on recurrence of tuberculosis in South African gold miners. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2000;4(5):455-62.
17. Sonnenberg P, Murray J, Glynn JR, et al. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. 2001;358(9294):1687-93.
18. Bureau of Epidemiology. Annual Epidemiological Surveillance Report 2011. Nonthaburi Thailand: Ministry of Public Health, 2011.
19. Phokaew P. TB situation in the northern of Thailand 2010. *Thai journal of Tuberculosis Chest Disease and Critical Care*. 2011;3:134-45.
20. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease*. 2007;11(8):828-37.
21. Selassie AW, Pozsik C, Wilson D, Ferguson PL. Why pulmonary tuberculosis recurs: a population-based epidemiological study. *Annals of epidemiology*. 2005;15(7):519-25.
22. Khan A, Sterling TR, Reves R, et al. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *American journal of respiratory and critical care medicine*. 2006;174(3):344-8.
23. WHO. Treatment of tuberculosis: guidelines – 4th ed. Geneva: WHO; 2010.
24. Oyama T. Factors influencing relapse in pulmonary tuberculosis; a statistical analysis of 1,259 patients followed from eleven months to six years after discharge. *American review of tuberculosis*. 1955;72(5):613-32.
25. Pulido F, Pena JM, Rubio R, Moreno S, Gonzalez J, Guijarro C, et al. Relapse of tuberculosis after treatment in human immunodeficiency virus-infected patients. *Archives of internal medicine*. 1997;157(2):227-32.
26. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Tuberculosis Trials Consortium. Lancet*. 1999;353(9167):1843-7.