

The Epidemiology Characteristics of Extra-pulmonary Tuberculosis in Taiwan, 1996-2003

Yu-Chen Hsu¹, Min-Hui Yang², Ying-Hwei Chen¹, Fung-Chang Sung²

1. The First Division, Centers for Disease Control, Department of Health, 2. Institute of Environmental Health, China Medical University College of Public Health

Abstract: from Chinese version, pp,447-447

Little about extra-pulmonary tuberculosis (EPTB) epidemiology has been made known to the public in Taiwan. The main objective of this study is to describe the epidemiological characteristics of the disease in Taiwan for the period from 1996 to 2003 using the health insurance data. Data from a nationally representative cohort consisting of 200,000 randomly selected individuals established in 2000 from the National Health Insurance Program was used. Data analyses used in this study included measuring annual incidence by sex, age, geographic area and population density-specific incidence rates based on a total of 168,977 persons insured in 1996. The hepatotoxicity prevalence associated with the tuberculosis treatment was measured.

During 1997 to 2003, the incidence of EPTB for males annually decreased from 33/100,000 to 20/100,000, and that for females decreased from 36 to 17 per 100,000. The risk of developing EPTB increased with age and was higher among the population in the eastern Taiwan than in other areas. The hepatotoxic effect was prevalent among EPTB patients and approximately 30% had been diagnosed with chronic liver injuries. The observed incidence of EPTB may have reached a plateau in Taiwan. The elderly were at much higher risk for the disease and the high prevalence of liver injury observed deserves further study. Intervention for TB prevention and control can focus to the elderly as well as Hepatitis B carriers and Hepatitis C infected patients.

Received: Aug 10, 2007; Accepted: Aug 13, 2007.

Correspondence author: Yu-Chen Hsu; Address: Address: No.6, Linshen S. Road, Taipei, Taiwan, R.O.C.

E-mail: yuchen@cdc.gov.tw

Introduction

Tuberculosis (TB) is an infectious disease caused by mycobacteria, mainly *Mycobacterium tuberculosis*. It has been present in humans since antiquity and become a major cause of death and disability in most parts of the world, especially in the developing countries [1,2]. The disease can affect multiple body systems. When the bacteria becomes active, about 75% of the cases are pulmonary TB and the remaining 25% are extra-pulmonary [1,2]. Although children and persons with immunodeficiencies, such as HIV infection, have a higher risk of extra-pulmonary TB, pulmonary disease remains the most common type of illness seen worldwide [2].

TB has probably killed 100 million people over the past 100 years, and been the world's second leading cause of death among the infectious diseases after HIV/AIDS [3]. According to the WHO estimate, there were 8.8 million new TB cases in 2005 throughout the world, of which 7.4 million (34% of the global incident cases) occurred in Asia and sub-Saharan Africa. However, the estimated incidence rate in sub-Saharan Africa is approximately twice that of the South-East Asia Region, at nearly 350 cases per 100,000 population [4,5]. It is estimated that a total of 1.6 million people died of TB, including 195,000 patients infected with HIV, in 2005, and both the highest number of deaths (544,000 cases) and the highest mortality per capita (74 cases per 100,000 population) are in the Africa Region [5]. Although global TB prevalence and death rates have possibly been declining for several years, the total number of new TB cases was still rising slowly due to the continuously growing case-load in African, Eastern Mediterranean and South-East Asia region [4].

In Taiwan, the TB mortality has gradually dropped from 294.44 per 100,000 population in 1947 to 4.3 per 100,000 population in 2005, making it the 13th leading cause of death in Taiwan [6]. There were 16,218 new TB cases reported in Taiwan with the incidence rate of 72.47 per 100,000 population. Further, people who aged 65 and above attributed to 51.04% of the new TB cases, and the incidence rate in the mountain areas (292.87 per 100,000 population) was 4.0 times higher than the overall incidence rate, 72.47 per 100,000 population [6]. Since TB has been at the highest incidence rate of any notifiable communicable diseases in Taiwan for years, Taiwan Centers for Disease Control (Taiwan CDC) has invested a considerable amount of effort in the fight against TB infection and multidrug-resistant (MDR) TB. However, compared to the other developed countries, TB control in Taiwan is still lagging behind. According to the Global Competitiveness Report 2006-2007[7], Taiwan ranks 60th on a worldwide scale in terms of effective TB control, which is below USA (3rd), Canada (5th), Australia (11th), UK (18th), Japan (45th) and Singapore (46th). In the US and Canada, the incidence rate for 2005 was 5 cases per 100,000 and the mortality rate was ≤ 1.0 per 100,000. The incidence rate in Australia, UK, Japan and Singapore was 6, 14, 28 and 29 cases per 100,000 respectively, while the mortality rate was

respectively ≤ 1 , 1, 4 and 3 cases per 100,000.

A pulmonary tuberculosis prevalence survey has been undertaken every 5 years in Taiwan since 1957 to evaluate epidemic trends. In addition, a computerized National TB Registration System has been developed to collect and analyze national TB surveillance data. However, little about the extra-pulmonary tuberculosis (EPTB) epidemiology has been reported in Taiwan and many other countries, because that it is difficult to estimate EPTB incidence except in countries where reliable national data is available [8]. In the United States, the proportion of EPTB among all TB cases had risen from 16% in 1991 to 20% in 2001 [9], in Hong Kong, about 22.3% of TB cases were diagnosed with EPTB patients in 1996 [10], and in Taiwan, approximately 14.45% of TB new cases were EPTB patients in 2001 [11].

Taiwan government has implemented a National Health Insurance (NHI) Program since March 1995, which also provides a reliable source of national data for epidemiological researches. In this study, we use health insurance data obtained from the NHI program to describe the epidemiological characteristics of the extra-pulmonary tuberculosis in Taiwan during the period between 1996 and 2003. In addition, we also extracted the overall TB incidence data in 1996-2003 obtained from the National Surveillance Network of Communicable Diseases (NSNOCD) for comparison with the trend of EPTB calculated using the data of the NHI cohort.

Methods

The annual overall TB incidence data used in this study was obtained from the National Surveillance Network of Communicable Diseases (NSNOCD), which is a user-friendly, web-based National TB Register established by the Taiwan CDC [12]. Basically, the National TB Register compiles detailed information about the TB cases in Taiwan, which is used to notify health authorities of new TB cases and aid health care professionals in determining the treatment to administer, tracking the patients and the close contacts, managing the patients, producing related statistics and epidemic report, making referrals, practicing quality management and supervising the directly observed treatment short-course (DOTS) activities [12]. The annual incidences of all TB from 1996 to 2003 were extracted for comparison with the EPTB incidences calculated from the cohort data.

A database that had been managed by the National Health Research Institute, nationally representative cohort consisting of 200,000 randomly selected individuals established in 2000 from the National Health Insurance (NHI) Program was used. More specifically, data analyses used in this study included measuring annual incidence by sex, age, geographic area and population density-specific incidence rates based on a total of 168,977 persons insured in 1996. The prevalence rates of liver injuries among the EPTB patients were also calculated by sex, age, geographic area and population density. In this study, all the data analyses were conducted by using SAS version 8.1 software program (SAS Institute, Inc. Cary, NC).

Results and Discussion

As shown in Figure 1, the incidence of TB in Taiwan obtained from the NSNOCD increased from 54 cases per 100,000 population in 1996 to 67 cases per 100,000 population in 2003, while the incidence of EPTB obtained from analyzing the NHI data decreased from 34 cases per 100,000 population in 1997 to 18 cases per 100,000 population in 2003 ($p=0.004$). The total TB incidence of 71 cases per 100,000 found in 1997 demonstrated an increase of 17 cases per 100,000 when compared to the incidence of TB in 1996. It is likely that this increase was a result of increase in the number of cases detection associated with the launch of the NHI program in 1996. We also consider that the EPTB incidence of 34 per 100,000 was a result of increased detection because the suspected patients had the access to medical care covered by the insurance. Therefore based on Figure 1, we can estimate that approximately 23.0% to 27.0% of TB cases are EPTB cases in Taiwan, which is similar to the ratio found in Hong-Kong in 1996 [10], but higher than the ratio reported by Taiwan CDC in 2001 [11]. The occurrence of under reporting is considered and need further investigations.

Table 1 illustrates the difference in EPTB incidence rates between males and females. During 1996 to 2003, the annual incidence of EPTB for males decreased from 33/100,000 to 20/100,000 ($p<0.0001$), and the incidence of EPTB for females annually decreased from 36 to 17 per 100,000 ($p<0.0001$). Comparing the rates in 1997 with the rates in the later years, we believe some cases in 1997 were in fact the prevalence cases from the earlier years. We thus believe that the average incidence rates among the population in Taiwan are about 20 per 100,000 in males and about 12-17 per 100,000 in females.

The risk of developing EPTB increased with age and was generally higher in males than in females among age groups (Table 2). The oldest population are approximately 10 times more likely to have EPTB. Geographic areas differences were also noted. Specifically, the risk of developing EPTB was higher in the population in eastern and southern Taiwan areas. With a rate of 68 per 100,000 person-years, the incidence was particularly high for females in eastern area. This incidence was 2 times higher than their counter part males, or more than 4 times higher than the incidence for females in central area. It is known that population living in rural eastern are prone to TB infection. But, it is not clear whether the observed gender difference in the eastern population is associated with the population characteristics. It is possible that there are more women than men in the elderly in the eastern rural villages.

Table 3 demonstrates that the hepatotoxic effect was prevalent among these EPTB patients and approximately 30% had been diagnosed with chronic liver injuries. Significant differences among different age groups were observed and the risk of EPTB patients developing chronic liver injuries increased with age. Although no significant differences were found among different geographic areas, a higher risk of developing chronic liver injuries was noted among EPTB patients in southern and eastern Taiwan when compared to other patients in other areas. The

prevalence was also higher in areas with lower population density. This may reflect that rural patients are at a higher risk of developing liver injuries. Among EPTB patients with co-morbidities, in fact, those with hepatitis B or C infection were at the highest risk of developing liver injury (odds ratio = 7.28, 95% confidence interval 2.61, 20.2) [13]. In general, the liver injury claim rates obtained from the NHI data are much higher than expected which deserves a more careful investigation. Moreover, since pyrazinamide is one of the primary drugs being used in treating tuberculosis, and some studies have illustrated that drug-induced liver injury can be fatal when treated with tuberculosis [14-15], further investigation for the liver injuries associated with the treatment is needed.

Conclusion

The decreasing trend observed in the incidence shows that the occurrence of EPTB has reached a constant plateau in Taiwan. The elderly were at much higher risk for the disease and the high prevalence of liver injury observed deserves further study. In Taiwan, there are approximately 2.5 million Hepatitis B carriers and 700,000 people infected with Hepatitis C [6]. According to the result showed in our study, approximately 30% of EPTB patients had been diagnosed with chronic liver injuries. Therefore, intervention for TB prevention and control focused to the elderly as well as Hepatitis B carriers and Hepatitis C infected patients is highly recommended.

Acknowledgements

This study was supported by the Executive Yuan Department of Health:
DOH95-TD-D-113-025

References

1. Wikipedia, The Free Encyclopedia. Tuberculosis. Available at:
<http://en.wikipedia.org/wiki/Tuberculosis>.
2. Heymann DL. Control of Communicable Diseases Manual. 18th ed. Washington DC: APHA 2004; 560-572.
3. Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. Lancet. 2003; 362: 887-899.
4. WHO. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report 2007. Geneva: World Health Organization (WHO/HTM/TB/2007.376).
5. WHO. Tuberculosis. Available at:
<http://www.who.int/mediacentre/factsheets/fs104/en>. July 2007.
6. Taiwan CDC. 2007 Annual Report. Taipei: Centers for Disease Control, Taiwan.
7. The Global Competitiveness Report 2006-2007. World Economic Forum, 26 September 2006.
8. David P. Extra-pulmonary tuberculosis. Available at:
<http://www.priory.com/cm01/extratb.htm>.

9. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, Cave MD, Bates JH. Identification of Risk Factors for Extrapulmonary. *CID*. 2004; 38: 199-205.
10. Noertjojo K, Tam CM, Chan SL, Chan-Yeung MMW. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. *Int J Tuberc Lung Dis*. 2002; 6: 879-886.
11. Taiwan CDC. Tuberculosis Annual Report 2001. Centers for Disease Control, Taiwan.
12. Chuang JH, Yang SL, Chiu CH, Kuo HS. Web-based Tools Help Fight TB in Taiwan. *Mednet*. 2006: 11th World Congress on Internet in Medicine. Available at: <http://www.mednetcongress.org/ocs/viewabstract.php?id=344>.
13. Yang, MH. Tuberculosis Epidemic Trend and the Prospective Study of Anti-TB Drugs-Induced Liver Injury in Taiwan. Master thesis, China Medical University Institute of Environmental Health. Taichung: China Medical University. 2007.
14. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuberc Lung Dis*. 1996; 77: 37-42.
15. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs*. 1982; 23: 56-74.

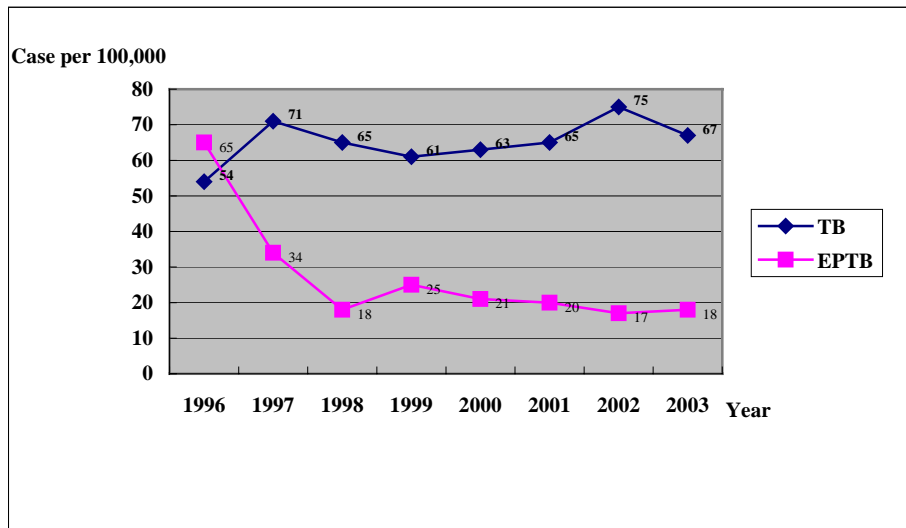


Figure 1. Comparison between annual incidences of tuberculosis in 1996-2003 from National Surveillance data (NSNOCD) and extra-pulmonary tuberculosis prevalence in 1996 and incidences in 1997-2003 measured from the National Health Insurance (NHI) cohort.

Table 1. Extra-pulmonary Tuberculosis Incidence Rate by Sex in 1996~2003

Year	Population	EPTB (Male)			EPTB (Female)			
		New Case	Case per 100,000	p value*	Population	New Case	Case per 100,000	p value*
1996	84792	51*	60*	<0.0001	84792	59*	70*	<0.0001
1997	82944	27	33		82944	30	36	
1998	82402	12	15		82402	17	21	
1999	81566	23	28		81566	17	21	
2000	80674	16	20		80674	18	22	
2001	80674	17	21		80674	16	20	
2002	79787	15	19		79787	12	15	
2003	78198	16	20		78198	13	17	

*prevalence

p value: for incidence 1997-2003

Table 2. Difference in Extra-pulmonary Tuberculosis Incidence by Age, Area and Population Density in 1996 and 2003

	Person-years in 1996~2003			EPTB New Cases			
	Male	Female		Male	Female	Ratio	
Age, years			n	Rate/100000	n	Rate/100000	
<30	319346	321722	43	13	49	15	0.87
30-39	116244	119946	32	28	25	21	1.33
40-49	89510	91874	26	29	43	47	0.62
50-59	51853	53834	20	39	18	33	1.18
60-69	45559	40155	24	53	21	52	1.02
70-79	23760	19826	25	105	18	91	1.15
>80	4746	5684	7	147	8	141	1.04
Area^a							
North	297107	310974	75	25	72	23	1.09
Central	149862	151608	40	27	25	16	1.69
South	163761	167160	56	34	72	43	0.79
East	15035	14813	5	33	10	68	0.49
Off-shore Island	3938	4014	0	0	1	25	
Population Density^b							
High	322528	341956	88	27	88	26	1.04
Middle	222415	222385	63	28	66	30	0.93
Low	84760	84228	25	29	26	31	0.94

a:

North Area: Keelung City, Taipei City, Taipei County, Taoyuan County, Hsinchu City, Hsinchu County, Yilan County

Central Area: Miaoli County, Taichung City, Taichung County, Changhwa County, Nantou County, Yunlin County

South Area: Chiayi City, Chiayi County, Tainan City, Tainan County, Kaohsiung City, Kaohsiung County, Pingtung County

East Area: Hualian County, Taitung County

Off-shore Island: Penghu County, Kinmen County, Lienchiang County

b:

High population density: Keelung City, Taipei City, Taipei County, Hsinchu City, Taichung City, Kaohsiung City, Tainan City, Chiayi City

Middle population density: Taoyuan County, Taichung County, Changhwa County, Yunlin County, Tainan County, Kaohsiung County, Pingtung County

Low population density: Hsinchu County, Yilan County, Miaoli County, Nantou County, Chiayi County, Hualian County, Taitung County, Off-shore Island

Table 3. Demographic Distribution of Extra-pulmonary Tuberculosis patients with Nonalcoholic Hepatitis in 1996 and 2003

	Liver Disease		Total	p value*
	No N=215 n (%)	Yes N=93 n (%)		
Sex				
Male	102 (68.9)	46 (31.1)	148	0.744
Female	113 (70.6)	47 (29.4)	160	
Age				0.004
<30	77 (86.5)	12 (13.5)	89	
30-39	34 (66.7)	17 (33.3)	51	
40-49	38 (62.3)	23 (37.7)	61	
50-59	16 (59.3)	11 (40.7)	27	
60-69	25 (69.4)	11 (30.6)	36	
70-79	18 (54.5)	15 (45.5)	33	
>80	7 (63.6)	4 (36.4)	11	
Area^a				0.282
North	97 (72.9)	36 (27.1)	133	
Central	41 (75.9)	13 (24.1)	54	
South	66 (62.8)	39 (37.2)	105	
East	8 (61.5)	5 (38.5)	13	
Off-shore Island	1 (100)	0 (0)	1	
Population Density^b				0.119
High	117 (73.1)	43 (26.9)	160	
Middle	71 (69.6)	31 (30.4)	102	
Low	25 (56.8)	19 (43.2)	44	

* chi-square test, fisher exact test

a:

North Area: Keelung City, Taipei City, Taipei County, Taoyuan County, Hsinchu City, Hsinchu County, Yilan County

Central Area: Miaoli County, Taichung City, Taichung County, Changhwa County, Nantou County, Yunlin County

South Area: Chiayi City, Chiayi County, Tainan City, Tainan County, Kaohsiung City, Kaohsiung County, Pingtung County

East Area: Hualian County, Taitung County

Off-shore Island: Penghu County, Kinmen County, Lienchiang County

b:

High population density: Keelung City, Taipei City, Taipei County, Hsinchu City, Taichung City, Kaohsiung City, Tainan City, Chiayi City

Middle population density: Taoyuan County, Taichung County, Changhwa County, Yunlin County, Tainan County, Kaohsiung County, Pingtung County

Low population density: Hsinchu County, Yilan County, Miaoli County, Nantou County, Chiayi County, Hualian County, Taitung County, Off-shore Island