Integration of tuberculosis services in Taiwan, 2001: challenges and opportunities

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Thesis for the degree of Doctor Philosophiae (Dr Philos)
at the University of Bergen

2012

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Acknowledgements

In February 2010 when I visited the Center for International Health (CIH), University of Bergen, Norway, to teach in a course entitled "International course in global tuberculosis epidemiology and intervention" for master and doctoral students of European Universities, Professor Sven Gudmund **Hinderaker** encouraged me to prepare a thesis for the degree of Doctor Philosophiae at the University of Bergen. I first met Professor Hinderaker in 2001 in a tuberculosis program review in Arkhangelsk, Russia. Thereafter, we worked closely for the Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB (FIDELIS) which was funded by the Canadian International Development Agency (CIDA) and managed by the International Union Against Tuberculosis and Lung Disease (The Union). Professor Odd **Mørkve**, who was one of the coordinators of the course in Bergen, also encouraged me to prepare the thesis. After discussion with Professor Hinderaker and Professor Mørkve for a few days, I consulted Professor Rune **Nilsen**, Director of CIH, who provided useful information and helpful advice. I decided to move this project forward. Over the period 2010-2012, Professor Hinderaker and Professor Mørkve have been excellent advisers who constantly offered support through emails and in face-to-face discussion; they reviewed my thesis and provided valuable comments on several occasions, without which this thesis will never be completed.

This endeavor gained immediate support of Dr. Nils **Billo**, Executive Director of The Union, and Professor Donald A **Enarson,** senior adviser of The Union. Dr Billo entrusted me to lead the Department of Lung Health and NCDs of The Union, supported me to carry out new initiatives in resource limited settings, and encouraged me to conduct research and to participate in academic activities. Professor Enarson

enrolled me in a research course in 1999, trained me for national tuberculosis program review, recruited me to work with The Union, and provided great mentorship in my international career. He has been a co-author of the majority of my scientific publications and as he always did, provided helpful advice on this thesis. Without their offer and encouragement, I would not have the opportunity to be deeply involved in international health.

Before I joined The Union, I had several years of clinical training in Internal Medicine, Respiratory Medicine and Critical Care in Taipei, started in 1991, and was heavily involved in the tuberculosis program in Taiwan. During that period, Dr. **Lin** Tao-Ping, Professor **Luh** Kwen-Tay, and Dr. **Suo** Jen played important roles in the development of my professional life. Dr Lin was the head of Chronic Disease Control Bureau where I developed my commitment to the fight against tuberculosis. In the Bureau authority and experience were respected but scientific evidence got priority and critical thinking was encouraged. Prof Luh was a respected specialist and has been my role model in respiratory medicine. Dr. Suo was highly committed to the fight against tuberculosis; he was a man of the field who enjoyed public health action. They were co-authors of my several publications and all reviewed my thesis and provided helpful comments.

Since I joined The Union in 2003, I have not been directly involved in the tuberculosis program of Taiwan. I appreciated that several colleagues of Centers of Disease Control, Department of Health, Republic of China, and Department of Disease Control and Prevention, Taipei City Government, accepted my request to update my knowledge on recent progress of tuberculosis services in Taiwan. They were (by alphabet order of family name) Dr. **Chan** Pei-Chun**,** Ms. **Hsu** Yu-Ling, Prof.

Jou Ruwen**,** Dr. Steve H-S **Kuo**, Dr. **Lei** Yung-Chao, Dr. **Lo** Hsiu-Yun, Ms. **Shih** Hsiu-Chen, Ms. **Wang** Kwei-Feng**,** Dr. **Yang** Chin-Hui**,** and Mr. **Yang** Shiang-Lin.

I wish to thank all my friends and colleagues who have worked with me in strengthening tuberculosis services and promoting lung health. I would not be able to list everyone except those who worked with me in preparing original articles which are included in this thesis. They were (by alphabet order of family name) Prof **Bai** Kuan-Jen, Dr. David **Dawson,** Dr. **Kam** Kai-Man, Dr. **Kim** Sang-Jae**,** Prof **Lee** Chun-Nin, Dr. **Lee** Jen-Jyh, Prof Hans L **Rieder,** Dr. **Wu** Yi-Chun, Mr. **Yang** Shiang-Lin, and Prof **Yu** Ming-Chih.

Special thanks go to my parents who brought me into this world and raised me in a tolerant manner; they emphasized knowledge and education, respected independence and supported adventure. I am particularly grateful for having my wife, Sung-Hui, as my lifetime partner. She is a highly qualified clinician practicing in a teaching hospital and doing scientific research. While she has a busy professional life, she did a great job in raising our children, Chi-Hung and Chi-Jung, when most of the time I was away from home on duty travel. She encouraged me with lovely smiles and never complained about my absence, which formed a solid base of my international participation through The Union.

Chiang Chen-Yuan
2012 March 11, Taipei

Abbreviations

adjHR	Adjusted hazard ratio
AFB	Acid fast bacilli
AIDS	Acquired immunodeficiency syndrome
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control
CDCB	Chronic Disease Control Bureau
CI	Confidence interval
CXR	Chest radiograph
DOT	Directly observed therapy
DOTS	Directly-observed treatment short-course
E	Ethambutol
EQA	External Quality Assessment
FDC	Fixed-dose combination
H	Isoniazid
HIV	Human immunodeficiency virus
ISTC	International Standards for Tuberculosis Care
IUAT	International Union Against Tuberculosis
MDR-TB	Multidrug-resistant tuberculosis
Mg	Milligram
NF	Notification-fee
NHI	National Health Insurance
NNNR	No-notification-no-reimbursement
NRL	National reference laboratory
NTM	Non-tuberculosis mycobacteria

NTP	National tuberculosis program
PAS	Para-aminosalicylic acid
PRC	People’s Republic of China
R	Rifampicin
ROC	Republic of China
Rrr	Relative risk ratio
S	Streptomycin
T	Thiacetazone
The Union	International Union Against Tuberculosis and Lung Disease (IUATLD)
TPTCB	Taiwan Provincial Tuberculosis Control Bureau
TU	Tuberculin unit
UNICEF	United Nations Children's Fund
WHO	World Health Organization
Z	Pyrazinamide

List of original articles

1) **Chiang C-Y**, Rieder HL, Kim SJ, Kam KM, Dawson D, Lin T-P, et al. Quality of sputum smear microscopy in Taiwan. J Formos Med Assoc 2005;104:502-6.
2) **Chiang C-Y**, Lee J-J, Yu M-C, Lin T-P, Luh K-T. Tuberculosis-related deaths without treatment. Int J Tuberc Lung Dis 2009;13:1563-5.
3) **Chiang C-Y**, Enarson DA, Bai K-J, Suo J, Wu Y-C, Lin T-P, et al. Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion. Int J Tuberc Lung Dis 2008;12:441-6.
4) **Chiang C-Y**, Bai K-J, Lee C-N, Enarson DA, Suo J, Luh K-T. Inconsistent dosing of anti-tuberculosis drugs in Taipei. Int J Tuberc Lung Dis 2010;14:878-883.
5) **Chiang C-Y**, Lee J-J, Yu M-C, Enarson DA, Lin T-P, Luh K-T. Tuberculosis outcomes in Taipei: factors associated with treatment interruption for 2 months and death. Int J Tuberc Lung Dis 2009;13:105-11.
6) **Chiang C-Y**, Luh K-T, Enarson DA, Yang S-L, Wu Y-C, Lin T-P. Accuracy of classification of notified tuberculosis cases in Taiwan. Int J Tuberc Lung Dis 2007;11:876-81.

Summary

Tuberculosis has been an endemic disease in Taiwan for decades. After the Second World War, a vertical tuberculosis program was established. Tuberculosis services in Taiwan from 1950s -1990s partly reflected the evolution of international tuberculosis control policy but had its unique development, challenges and achievements. Tuberculosis mortality and prevalence declined substantially from 1950s -1990s in Taiwan. However, it became increasingly difficult to provide tuberculosis services through a vertical program after implementing the national health insurance program in 1995. The government of Taiwan dismantled the vertical tuberculosis program in 2001 and integrated tuberculosis services into the general health care system, which presented an opportunity for strengthening tuberculosis services but also implied threats of disintegration. Constraints needed to be identified and addressed to ensure efficiency and effectiveness of this fully integrated approach. This thesis reports on a series of studies of the operation of the services and demonstrates that (1) the quality of smear microscopy in a few laboratories in 2004 was not satisfactory; (2) tuberculosis-related death without treatment in Taipei in 2003 was substantial; (3) a high proportion of tuberculosis patients were treated with anti-tuberculosis drugs on the basis of radiographic findings in Taipei in 2003 and subsequently were advised to stop anti-tuberculosis treatment before completion; (4) prescribing practices for anti-tuberculosis drugs in the treatment of tuberculosis in Taipei in 2003 was substandard; (5) treatment interruption for 2 consecutive months and sputum positive at 5 months or later was largely under-detected; and (6) there was substantial misclassification of notified tuberculosis cases in Taipei in 2003. Findings of these studies resulted in corrective actions and policy changes undertaken by health authorities to strengthen tuberculosis services in Taiwan.

1. Introduction

1.1 Mycobacterium tuberculosis and tuberculosis disease

The agent causing tuberculosis in humans is mainly *Mycobacterium tuberculosis (M. tuberculosis).* Tuberculosis is thought to have 2 distinct stages, namely latent infection with *M. tuberculosis* and active tuberculosis disease. Persons who are exposed to infectious tuberculosis patients are at risk of infection with *M. tuberculosis*. The probability of infection, given exposure, is determined by the infectiousness of the source case, the characteristics of the environment in which exposure takes place, the duration of exposure, and probably also the virulence of the tubercle bacilli.[1] Once infected, the risk of progression to active tuberculosis disease is largely determined by the ability of the immune system to contain or eliminate tubercle bacilli. The risk is highest within the first year after acquiring infection. Children under 5 years of age have a higher risk of progression because of immaturity of the immune system.[2] Human immunodeficiency virus infection is a strong risk factor in reactivating latent infection and rapid progression of recent infection.[3] There is no permanent protective immunity against re-infection.[4] Given exposure, persons who have been previously infected with tuberculosis are still at risk of re-infection.

1.2 Treatment of tuberculosis

There was no specific treatment of tuberculosis till the 1940s when streptomycin[5] and para-aminosalicylic acid[6, 7] were introduced. It was soon realized that treatment of tuberculosis using a single drug results in decline of drug susceptible bacilli and predominant replication of drug-resistant mutants, and that multiple drugs should be

used simultaneously to avoid the emergence of drug-resistant tuberculosis.[8] In the 1950s, some experts believed that tuberculosis could only be suppressed for a period of time but was not curable. Crofton demonstrated that adequate treatment of tuberculosis resulted in a dramatic fall in deaths from tuberculosis and had an impact on the number of new cases of tuberculosis in Edinburgh; he argued that it is possible to aim at 100% success in the treatment of pulmonary tuberculosis.[9, 10] Subsequently, several clinical trials were conducted,[11] eventually demonstrating that rifampicin-based short-course chemotherapy is highly efficacious with a high cure rate and low relapse rate, and this formed the basis of modern tuberculosis control. Unfortunately, drug-resistant tuberculosis may emerge during anti-tuberculosis treatment. Factors associated with drug-resistant tuberculosis include inadequate regimens, inconsistent dosing, poor quality of drugs, and poor adherence to treatment.[12] Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis caused by *M. tuberculosis* that is resistant to at least isoniazid and rifampicin, is difficult and expensive to treat and poses huge challenges to tuberculosis services.[13,14]

1.3 Principles of tuberculosis service

Tuberculosis services aim at reducing the transmission of tuberculosis in a community. Smear-positive cases have been shown to be the most powerful source of transmission.[15] Interventions for tuberculosis control and elimination include chemotherapy of tuberculosis, vaccination with Bacille Calmette-Guérin (BCG), and preventive therapy,[16] as well as addressing social determinants and managing risk factors.[17] Vaccination against tuberculosis using BCG has been recommended by United Nations Children's Fund (UNICEF) and World Health Organization (WHO) since

the 1940s; at that time, it was the most feasible intervention that could be implemented on a large scale. The International Tuberculosis Campaign that started in the war-torn areas of Europe administered BCG to 14 million persons.[18, 19] However, the efficacy of BCG in preventing tuberculosis varied across settings.[20] BCG vaccination might reduce the risk of severe tuberculosis (tuberculosis meningitis and miliary tuberculosis) in children[21] but has limited impact on the transmission of tuberculosis, especially if the risk of infection is high.[22]

Preventive chemotherapy is efficacious in reducing the risk of tuberculosis[23] and has been used extensively in the United States[24] and several developed countries. However, it is difficult to ensure adherence to preventive chemotherapy.[25] Further, persons who complete a course of preventive chemotherapy are still at risk of re-infection.[26] Therefore, preventive chemotherapy has not yet been widely applied for tuberculosis control in developing countries, including most settings with a high prevalence of HIV infection.[27] Addressing social determinants (such as poverty), improving access to care of vulnerable groups and marginalized populations,[28] reducing the prevalence of risk factors (such as reducing the prevalence of smoking through implementing Framework Convention of Tobacco Control)[29] and reducing the impact of risk factors on the development of tuberculosis (such as reducing the risk of tuberculosis among the HIV-infected by anti-retroviral therapy)[30] may contribute to tuberculosis control.

The tools that are most commonly used in the diagnosis of tuberculosis are chest radiography and sputum bacteriological examination.[31] Under-reading and over-reading have been concerns in the use of the chest radiograph. An international study on the classification of chest radiograph readings demonstrated a high degree

of disagreement on reading chest radiographs among 90 experts.[32] Thereafter, it was commonly agreed that the chest radiograph cannot be used alone in the diagnosis of pulmonary tuberculosis. Studies of indiscriminate mass radiography, which was applied for tuberculosis case-finding in the 1950s-1960s, also contributed to a shift of focus from chest radiography to the mycobacteriology laboratory in tuberculosis services. The rationale for mass radiography was to detect tuberculosis cases at an early stage before progressing to becoming smear-positive by periodic screening repeated at short intervals.[33] However, mass radiography identified only a small proportion of smear-positive incident cases. The majority of smear-positive cases were diagnosed among symptomatic patients who presented themselves to health care services.[34] Further, the proportion of smear-positive cases in a population remained relatively unchanged after repeated screening.[33] Therefore, indiscriminate mass radiography was replaced by other approaches.[35]

In the 1970s, Grzybowski and Enarson[36] investigated the fate of tuberculosis cases in different programs and reported that inadequate treatment failing to achieve a high proportion of treatment success prolonged the duration of infectiousness of tuberculosis patients, which may potentially make the epidemic of tuberculosis even worse than with no treatment. This finding triggered the development of International Union Against Tuberculosis (IUAT) model program, which aimed, as a first priority, at achieving a high cure rate. The current basis of tuberculosis control is to efficiently detect infectious tuberculosis cases, especially smear-positive cases, and render them non-infectious by effective anti-tuberculosis treatment. The objective is to create an “infection-free” generation that will eventually lead to the elimination of tuberculosis.[37]

1.4 Evolution of global policies for tuberculosis control

Policies for global tuberculosis control have evolved in recent decades.[38-40] The first World Health Assembly in 1948 recommended that governments take preventive, curative, legislative, and social measures for tuberculosis control. Services of diagnosis and treatment of tuberculosis were mainly provided through a vertical approach characterized by a central tuberculosis unit that directly operated several specialized hospitals and tuberculosis clinics, and a specialized program operated through its own officers for training, supervision, logistics, and offered its own laboratory services.[39] In 1964, the principles of modern tuberculosis control were formulated in a WHO Expert Committee of Tuberculosis Eighth Report,[41] in which development and implementation of the national tuberculosis program (NTP) comprising case-finding and treatment, with particular emphasis on smear-positive cases, and mass BCG vaccination, were recommended. Thereafter, integration of service delivery took place, in which the delivery of case management activities was operated through the general health services, but the specialized approach was kept intact for the managerial functions; tuberculosis control experts continued to be responsible for training, supervision, logistics, health education, and evaluation. The recommendation for the implementation of NTP was re-iterated and expanded 10 years later in WHO Expert Committee of Tuberculosis Ninth Report.[35] In 1978, a conference on Primary Health Care as the framework of health development was held in Alma Alta, in which equity, community participation, health promotion, inter-sectoral collaboration, and appropriate use of resources were highly promoted under the slogan "Health for all by the year 2000".[42, 43] Consequently, further steps in integration of managerial functions of tuberculosis and other programs were undertaken, driven by general public-health experts and primary health care

promoters. Unfortunately, the quality of tuberculosis case-finding and treatment deteriorated, partly because general health experts without proper training were unable to provide adequate supervision and training for tuberculosis control. During that period, Styblo, inspired by the report that poor treatment is worse than no treatment,[36, 44] pilot tested the IUAT collaborative program in Tanzania and several other developing countries, aiming to achieve a high cure rate and to avoid creating chronic tuberculosis cases harboring drug-resistant tuberculosis.[45, 46] The approach taken by Styblo underscoring the importance of ensuring a high cure rate was a paradigm shift, departing from previous approach that emphasized tuberculosis case finding. In the 1990s, the innovative approaches of the IUAT collaborative program[47] was ranked as one of the most cost-effective public health intervention in developing countries by the World Bank .[48, 49] WHO re-focused on tuberculosis, adopted IUAT collaborative model program as a new framework of a global tuberculosis control strategy, and re-directed global tuberculosis control policy back to a specialized managerial approach, in which specialized managerial functions at central, regional, and district levels was re-established but the principles of integration of service delivery into the primary health care infrastructure were maintained.[50-52] In 1993, tuberculosis was declared a global emergency and in 1994, a new framework for tuberculosis control was published,[50] which kick-started a new era of global tuberculosis control. Most countries re-structured national tuberculosis programs to implement the 'directly-observed treatment short-course' (nicknamed "DOTS" by WHO) strategy. [53-64] Targets were set to detect 70% of existing cases and to achieve 85% successful treatment, and subsequently were expanded with an aim to half mortality and prevalence of tuberculosis as well as to reverse the incidence of tuberculosis by 2015 as compared with that in 1990 as baseline. Global tuberculosis reports have been published annually to keep track of progress in global tuberculosis

control. A Stop Tuberculosis Partnership was established. A global plan to stop tuberculosis was developed. New funding mechanisms, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, were born. In 2006, the Stop Tuberculosis Strategy was launched, expanding on the former DOTS strategy.[65]

1.5 Taiwan: land and people

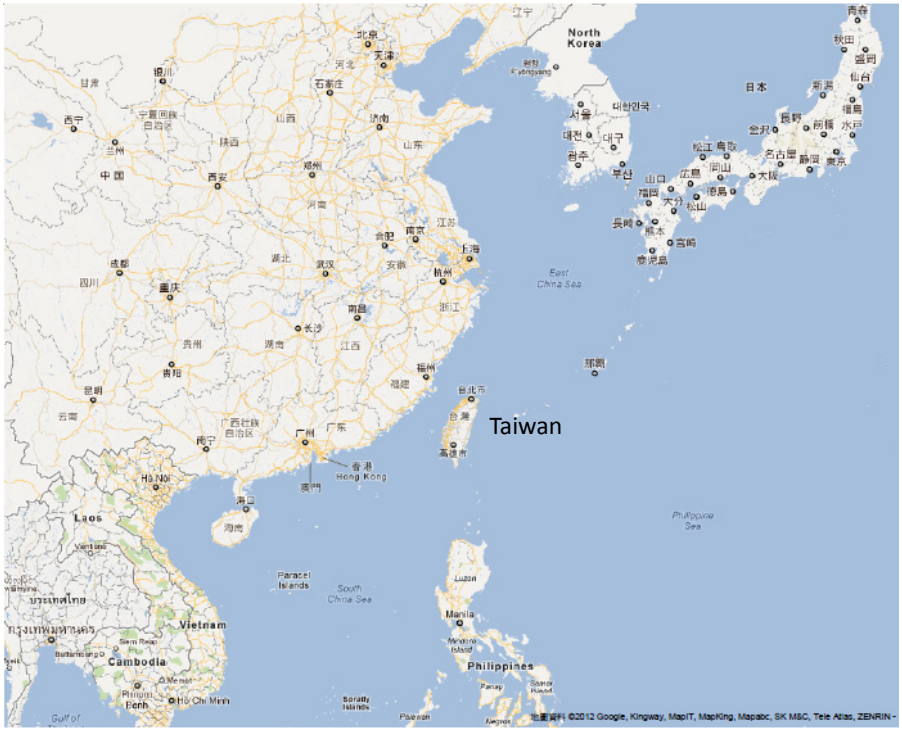

Figure 1. Map of Taiwan and Asia Pacific. (Source: Google map http://maps.google.com/maps?hl=zh-TW&q=taiwan%20map%20in%20english&bav=on.2,or.r_gc.r_pw.,cf.osb&biw=1680&bih=920&wrapid=tlif133144224921811&um=1&ie=UTF-8&sa=N&tab=wl)

Taiwan is an island of East Asia located in the western Pacific Ocean off the southeastern coast of China. It has a land mass of 36,000 square kilometers. The majority of inhabitants are Han people from the mainland of China and a minority

are aboriginal (Austronesian) people (about 2%). Taiwan was ceded to Japan in the Treaty of Shimonoseki after the First Sino-Japanese War in 1895, and was colonized by Japan till the end of the Second World War (1945). In 1945, a civil war broke out in China. In 1949, the government of the Republic of China (ROC), defeated by the communists, moved to Taiwan; on the mainland, the People's Republic of China (PRC) was established by the victorious communists. In 1950s-1960s, ROC (Taiwan) was the representative entity of China in the United Nations. In 1971, PRC (mainland China) replaced ROC (Taiwan) as the representative entity of China to the United Nations and all organizations related to the United Nations, including WHO.[66] Thereafter, Taiwan has been isolated from the international community and has had very limited opportunity to participate in meetings of WHO and other international activities.

1.6 Structure of tuberculosis services in Taiwan, 1950- 2000

In the era of Japan's colonial occupation, there were Sungshan Sanatorium in northern Taiwan and Chingfeng Sanatorium in southern Taiwan.[67] After the Second World War, the tuberculosis program was established step by step, beginning with the establishment of Taipei Tuberculosis Control Center (the former Sungshan Sanatorium) on 1 May 1950; subsequently, Chiayi Tuberculosis Control Center was established in 1951 (the former Nanjing Tuberculosis Control center in China was moved to Chiayi in 1949), Tainan Tuberculosis Control Center (the former Chingfeng Sanatorium) in 1952, and Taichung Tuberculosis Control Center in 1960. These four centers formed the backbone of a vertical tuberculosis program over the period 1950-2000 in Taiwan. The first local Anti-Tuberculosis Association was initiated in 1951 in Chiayi.[67] To strengthen tuberculosis services at district (county/city) level, the first district tuberculosis dispensary was set up in 1955; by 1964, a district

tuberculosis dispensary has been established in each of the 22 districts (county/city) in Taiwan. In 1965, tuberculosis control was listed as the top priority of public health (through an official statement of the President of ROC). Consequently, in 1967, the four tuberculosis centers were re-structured as Taiwan Provincial Tuberculosis Control Bureau (TPTCB) and its three regional branches in Taichung, Chiayi and Tainan. A demonstration center was established within TPTCB to guide the policy in the diagnosis and treatment of tuberculosis. The district tuberculosis dispensary was supported by a health station at each township and village.[67] In addition, there were 2 metropolitan centers, Taipei City and Kaohsiung City, being established at a later point in time, in which tuberculosis services were managed by Taipei Municipal Chronic Disease Hospital and Kaohsiung Chronic Disease Control Center, respectively. The Bureau, 3 regional branches and 2 metropolitan centers formed the structure in which tuberculosis services were provided to inhabitants of Taiwan till 2000 (Figure 2).

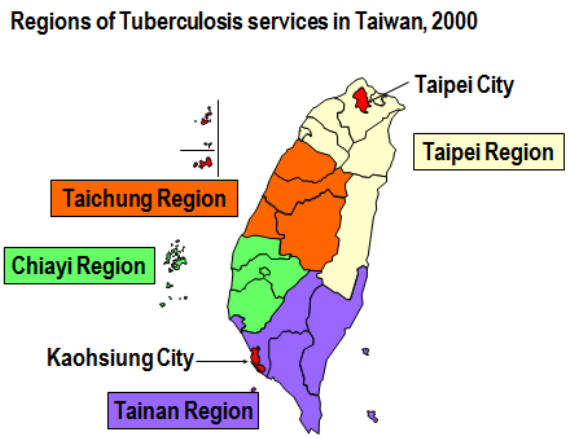

Figure 2. Regions of tuberculosis services in Taiwan, 2000

1.7 Burden of tuberculosis in Taiwan

Tuberculosis was an endemic disease in the 1950s in Taiwan. In 1951-1952, a large scale tuberculin survey was conducted, in which 5 TU purified protein derivative RT-22 tuberculin was used and a positive cut-off was defined as an induration of 5 mm or greater. The proportion of children 5 years old with a positive reaction was 15.4%, and that at 10, 15 and 20 years old were 28.1%, 50.7% and 74.8%. (Figure 3).[67]

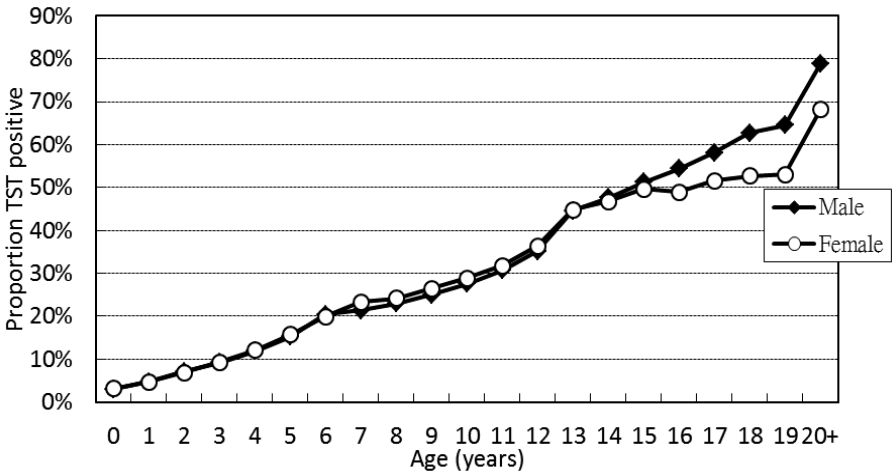

Figure 3. Tuberculin survey in Taiwan, 1951-1952: proportion with a positive tuberculin skin test (TST), by age and sex

Thereafter, the tuberculin skin test was done among students of the first grade of primary school if they had no BCG scar, which provided data on annual risk of infection for decades (Figure 2).[68] However, BCG was introduced in Taiwan in 1950. As the proportion of students of the first grade of primary school without a BCG scar decreased from 37% in 1972, to 21.9% in 1980, 6.2% in 1990 and 2.5% in 2000, data obtained from this subset of students may not be representative. Before the

establishment of a proper surveillance system, tuberculosis mortality and prevalence surveys provided a better insight on the trend of tuberculosis in Taiwan.

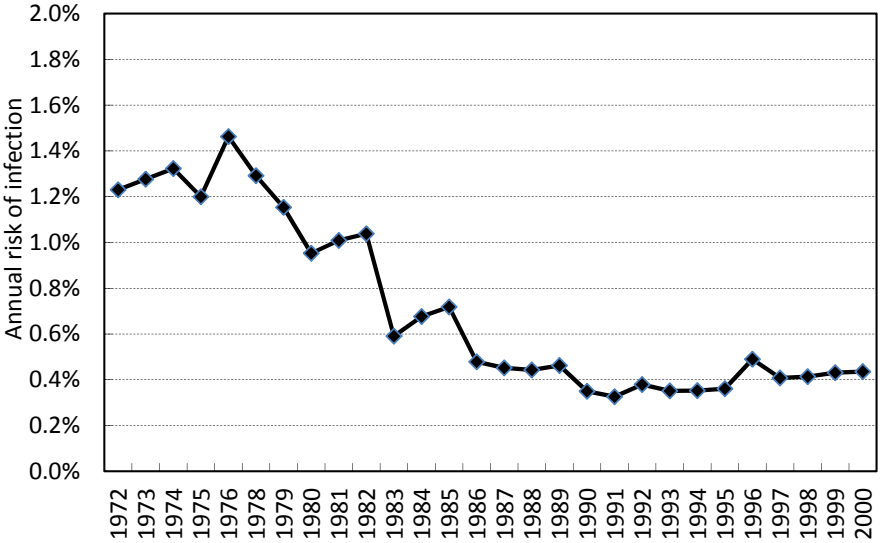

Figure 3. Estimated Annual risk of infection (ARI), Taiwan, 1972-2000

Note: ARI=1-(1-P)$^{1/n}$, where p is prevalence of tuberculous infection among children 6 years old determined by 1 Tuberculin Unit (RT23) and n is age. Data of 1982, and 1992-1995 were missing and were imputed using a moving average of the previous three years

1.8 Mortality of tuberculosis in Taiwan

Taiwan established a vital registration system after the Second World War.[69, 70] In 1947, the number of persons who died of tuberculosis was as high as 18,533 persons with a tuberculosis mortality rate of 294.4 per 100 000 population (figure 4);[67, 71] tuberculosis accounted for 16.2% of all deaths in Taiwan. Tuberculosis mortality decreased substantially to 91.6 per 100 000 population in 1952 (accounting for 9.6% of total deaths and ranked 3rd among the leading causes of death), and further went

down to 45.7 per 100 000 population in 1960 (5th leading cause of death), 28.4 per 100 000 population in 1970 (6th leading cause of death), 14.1 per 100 000 population in 1980 (9th leading cause of death), 10.7 per 100 000 population in 1985 (first time not on the list of top ten leading cause of death in Taiwan), 9.6 per 100 000 in 1990 (11th leading cause of death), 6.9 per 100 000 population in 2000 (11th leading cause of death), and 3.2 per 100 000 in 2009.[69, 70]

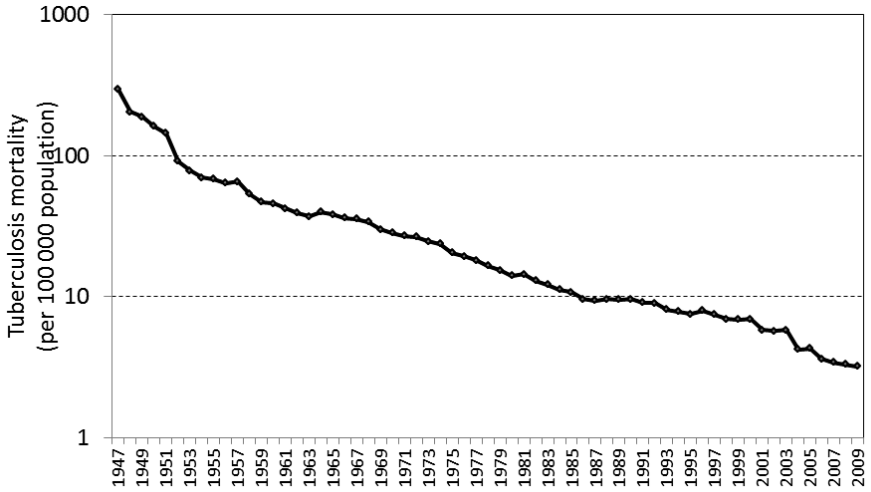

Figure 4. Tuberculosis Mortality in Taiwan, 1947 – 2009

Tuberculosis mortality among males has been consistently higher than that among females in Taiwan. The male to female tuberculosis mortality ratio was 1.6 in 1952, 2.5 in 1976, and 3.6 in 2000.[68] There was a shift of tuberculosis deaths from the youth to the elderly over time (Figure 5). In 1952, a total of 7,262 persons died of tuberculosis among whom 31.3% were aged 0-24 years and 9.9% aged 65 years or more; in 1976, 3,155 died of tuberculosis among whom 4.7% were aged 0-24 years and 39.4% aged 65 years or more; in 2000, 1,534 died of tuberculosis among whom 0.5% were aged 0-24 years and 78.0% aged 65 years or more.

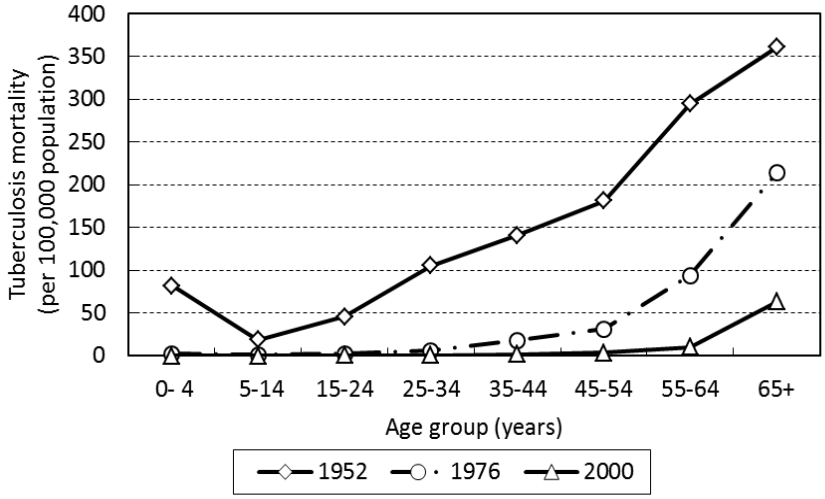

Figure 5. Tuberculosis Mortality, Taiwan, 1952, 1976 ,2000, by age group

1.9 Prevalence of tuberculosis in Taiwan

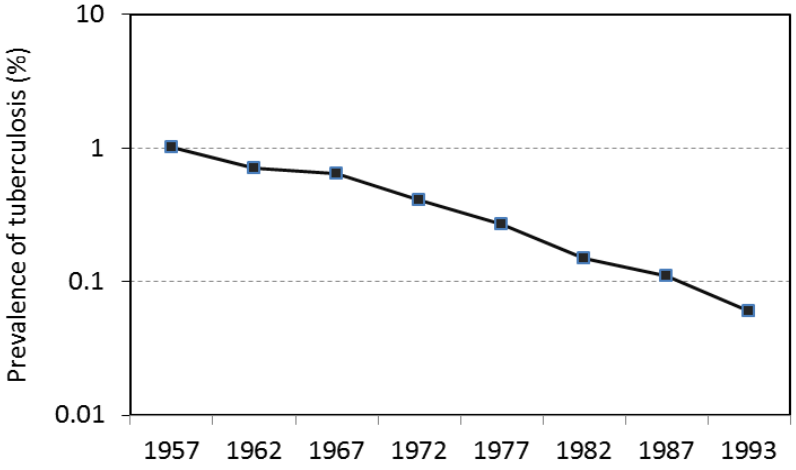

Figure 6. Prevalence of bacteriologically-confirmed pulmonary tuberculosis, Taiwan, 1957-1993

Tuberculosis prevalence surveys have been conducted eight times in Taiwan. The first prevalence survey was conducted in 1957 and the prevalence of bacteriologically-confirmed pulmonary tuberculosis was 1.02%, which decreased to 0.70% in 1962,

0.64% in 1967, 0.41% in 1972, 0.27% in 1977, 0.15% in 1982, 0.11%, and 0.06% in 1993. (Figure 6)[72-79]

1.10 BCG vaccination in Taiwan

BCG vaccination was introduced in 1950.[67] A laboratory was established in 1952 to produce BCG locally and the quality of the BCG laboratory was accredited by WHO in March 1953. The BCG strain used in the earlier period was Pasteur 1173 P2, which was changed to Tokyo 172 in 1976. In the beginning, the target population for BCG vaccination was school children, followed by preschool children, and subsequently expanded to infants and the newborn. Between 1950-1975, a total of 15,623,660 children were vaccinated with BCG, of whom 52.7% were school children, 24.0% preschool children, 21.1% infants and 2.2% newborn.[67] In the 1990s, the BCG coverage rate for infants was 95%. The BCG vaccination program continues up to the present time, but re-vaccination of children at 12 years-old was discontinued in July 1997.[79]

1.11 Case-finding of tuberculosis in Taiwan

The tools used for examination were bacteriological examinations (sputum smear, sputum culture, and laryngeal swab culture) and chest radiography. In 1955, a central mycobacteriology laboratory was set up at Taipei Tuberculosis Control Center. Subsequently, a mycobacteriology laboratory was established at each tuberculosis control center and district Tuberculosis dispensary.[67] In 1966, 200 tuberculosis workers (expanded to 313 in 1968) were hired and each was assigned to one township/village health station to carry out activities of tuberculosis control, including identification of individuals with suspected tuberculosis in the community

by household visits and sputum smear examination.

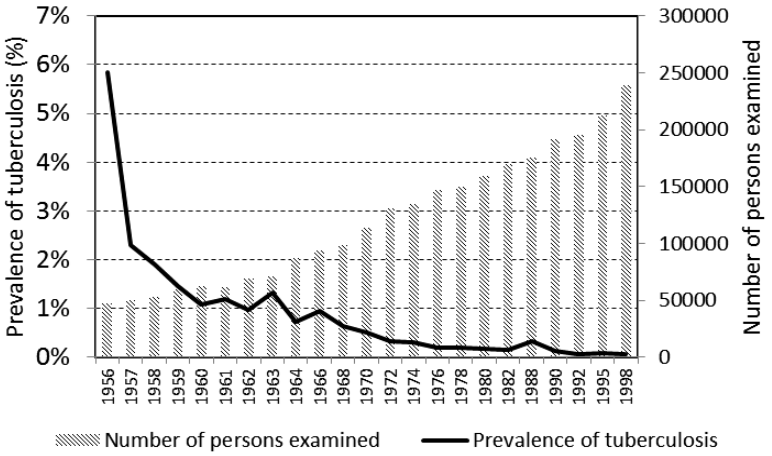

Figure 8. Radiographic screening and prevalence of tuberculosis among teachers, Taiwan, 1956 - 1998

The first mobile radiography unit was procured in 1949; the second unit was donated by UNICEF in 1952, and another 3 units by Mutual Security Agency USA in 1953.[67] Thereafter, mobile radiographic screening has been widely used in case-finding of tuberculosis through different screening programs, such as township/village comprehensive program, community mass radiographic screening , target group examination (teachers (Figure 8)[80], institutes, prisons, work places, military conscripts, etc), and special projects in aboriginal areas.[81] In the township/village comprehensive program, children under 5 years of age were given BCG vaccination and those aged 20 years or older had both symptom screening and radiographic screening. Such a comprehensive program was mainly conducted in high tuberculosis prevalence areas. Screening among teachers was conducted annually from 1956 and every 2-3 years from 1966 till the 1990s. Community mobile screening continued up to the 1990s, and gradually shifted to high risk group screening (prison and long term

care facility).[82]

1.12 Registration and treatment of tuberculosis in Taiwan

Registration and treatment of tuberculosis started in 1957.[82] Initially, only bacteriologically-confirmed cases were registered and treated with anti-tuberculosis drugs; thereafter, it was expanded to include cavitary pulmonary tuberculosis in 1969, cases with extensive parenchymal involvement in 1974, pleural tuberculosis cases in 1978, pathologically-confirmed extra-pulmonary tuberculosis cases in 1981, moderately advanced pulmonary tuberculosis cases in high incidence areas in 1984, and minimal pulmonary tuberculosis cases in aboriginal areas in 1988.[82] Isoniazid (H) alone was used for anti-tuberculosis treatment in 1957. Streptomycin (S) and PAS were introduced in 1958; the regimens commonly used were the combination of H and S, or of H and PAS. In 1967, thiacetazone(T) was introduced to replace PAS. In 1974, the standard regimen was H, S, and T for 2 months, followed by H and S twice per week for 10 months followed by H daily for 12 months(2 HST/10H_2S_2/12H). In 1977, ethambutol (E) was introduced to replace thiacetazone and patients were classified as either new cases or retreatment cases. Regimens for new patients lasted for 2 years; initially HSE daily for 3 months, followed by HE for 9 months, and H alone for 1 year. Rifampicin (R) and pyrazinamide (Z) were introduced at this time. Regimens for retreatment cases were HRE, or HEZ plus cycloserine or prothionamide.[83] In October 1978, Rifampicin-based regimens were applied in the treatment of both new (5HRE/5H) and retreatment cases (2HRE/8H_2 R_2E_2).[67] Treatment was mainly supervised by public health workers but directly observed therapy was not in place. In 1978-1980, of the 12,533 new patients treated with (5HRE/5H), 79.8% were successfully treated and 14.3% lost to follow-up; the

respective figure for 1,805 retreatment cases was 69.9% and 20.9%.[84] In 1990, 6-month Short-course chemotherapy (2HRZE/4HRE) was applied, and in 1993, fixed dose combinations were introduced.

Contact examination was done in the 1970s. Isoniazid preventive therapy for 6 months was offered to children <15 years old who were tuberculin skin test positive (induration of 10 mm among those without a BCG scar and 20 mm among those with).[83]

1.13 From prevalence survey to surveillance of tuberculosis

Registration of tuberculosis cases in the earlier period was incomplete and did not accurately reflect the epidemic of tuberculosis in Taiwan. Poverty, poor access to care, and insufficient capacity of tuberculosis services resulted in under-detection of tuberculosis cases. Economic development in Taiwan saw the improvement in quality, capacity, accessibility and affordability of the health care system. Increasing numbers of tuberculosis patients were treated outside the vertical tuberculosis system through different insurance programs. To strengthen surveillance of tuberculosis, all reported tuberculosis cases were registered since 1st September 1991, and notification of extrapulmonary tuberculosis became mandatory since 1st March 1997.[79]

To improve the completeness of reporting, various efforts have been made, including issuing administrative orders, promoting notification of tuberculosis in official meetings and scientific conferences, and revising the reporting form to facilitate reporting of extra-pulmonary tuberculosis. All these efforts contributed to increased

tuberculosis reporting. However, the overall picture of tuberculosis case finding and reporting changed considerably after the implementation of the national health insurance program.

1.14 National Health Insurance in Taiwan

Since the 1950s, several health insurance programs have been established in Taiwan. The top three programs were Labor Insurance, Government Employee Insurance, and Farmer's Health Insurance, which covered approximately 55% of the total population.[85, 86] Those who were not covered by any insurance program were children <15 years old, the elderly aged 65 years or more and those who had no regular job. Acting on the National Health Insurance (NHI) Law passed by the Legislative Yuan (Parliament) in 1994, the Department of Health set up the Bureau of National Health Insurance to implement the NHI Program in Taiwan. The NHI Program was a single payer health insurance system operated by the government under the principle of mandatory and universal enrollment. The proportion of the population insured under the NHI Program was initially 92% when it was launched in March 1995, quickly reached 96% by December 1996, and has been around 99% till the present time.[86, 87] With the implementation of the NHI program, most hospitals and clinics (more than 90%) have signed contracts with the Bureau of NHI, and fee-for-service claim payments are reimbursed by the Bureau of NHI on a monthly schedule.

The health care system in Taiwan is a market-oriented system regulated by the laws of supply and demand; health providers (clinicians) are free to set up their practice and patients are free to seek health services from any clinician. A referral system was

established but tiered referral procedures were not mandatory; patients who prefer to visit tertiary care hospitals can do so without any referral even for simple illnesses such as upper respiratory infection.[85, 86, 88, 89] The establishment of the NHI program fundamentally changed the landscape of tuberculosis services in Taiwan. NHI program facilitated accessibility and affordability of health services among those who need it most, especially the elderly aged 65 years or more, who accounted for 42% of reported tuberculosis cases in 1997[79] and 49.6% in 2009.[90] Because tuberculosis patients can receive treatment for tuberculosis in any health care facility under the coverage of NHI program, and because county hospitals, regional hospitals and tertiary care hospitals were equipped with advanced medical technology and staffed with well trained medical personnel that usually outperformed the vertical tuberculosis program, tuberculosis patients may not be willing to be referred to the vertical tuberculosis program for further management . General health care facilities may be reluctant to refer tuberculosis patients to the official tuberculosis control system because reimbursement from the NHI program was based on a fee-for-service mechanism. As a result, the number of tuberculosis patients receiving anti-tuberculosis treatment at general health care facilities increased continuously over time and eventually outnumbered those treated in the vertical tuberculosis control system .[82]

1.15 Strengthening surveillance of tuberculosis through NHI

After the implementation of the NHI program, NTP took advantage of the NHI program to further strengthen notification of tuberculosis. NTP worked with the Bureau of NHI to introduce the no-notification-no-reimbursement (NNNR) policy and the notification-fee (NF) policy.[91] The NNNR policy, stating that notification of

tuberculosis is a requirement for reimbursement, was announced in May 1997 and implemented from July 1997. The NF policy, stating that 250 New Taiwan dollars (USD$ 8) for each confirmed tuberculosis case would be given to reporting clinicians/hospitals, was implemented from October 1997. The announcement of the NNNR policy in May 1997 coincided with a prompt increase in reported cases in the second quarter of 1997. Upon the implementation of the NNNR policy, reported cases reached a historic peak in the third quarter of 1997. In 1997, there were a total of 15,386 incident tuberculosis cases, with a notification rate of 71.1 per 100,000.

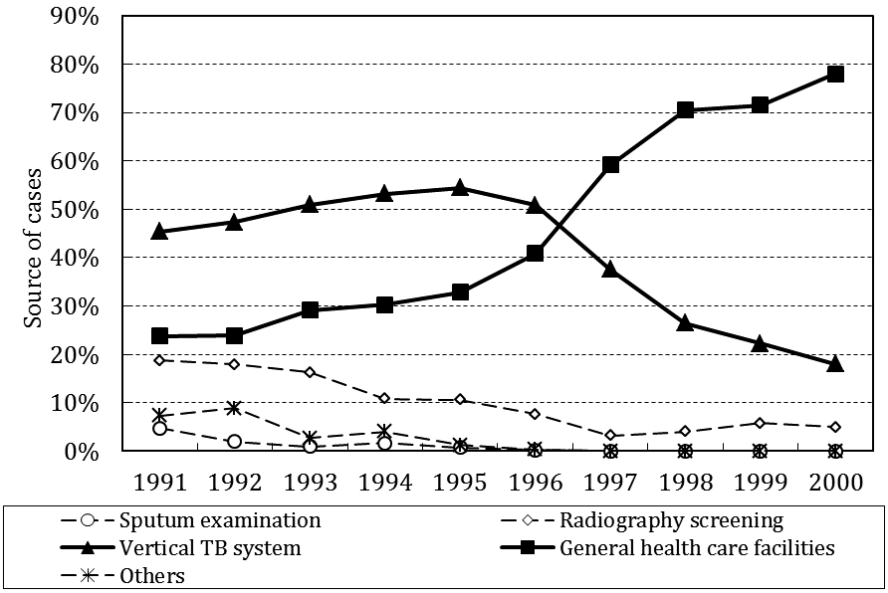

Figure 9. Source of registered tuberculosis cases in Taiwan, 1991-2000

The increase in reported cases has been primarily due to improvements in notification, especially from general hospitals/clinics, rather than to a resurgence of tuberculosis in Taiwan. The increase in numbers of cases reported from general hospitals/clinics reflected an immediate impact of the NHI policies on tuberculosis

notification, with no increase in reported cases within the official TB system. In the early 1990s, around 50% of tuberculosis cases were registered through the official tuberculosis system, which decreased to less than 20% in the year 2000; in contrast, around 30% of tuberculosis cases were reported by general hospitals/clinics in early 1990s, which increased to about 80% in the year 2000 (figure9).[90] Thereafter, notification of tuberculosis became a better tool than before in monitoring the epidemic of tuberculosis in Taiwan.

1.16 Time for a change

Tuberculosis services in Taiwan in the 1950s-1970s were in line with WHO policies. In 1980s, while Taiwan shared the spirit of the Alma Ata Declaration[42] and took action to strengthen the primary health care system, integration of managerial functions of tuberculosis services did not take place and the vertical tuberculosis program continued operation in Taiwan. In 1989, the Tuberculosis Control Bureau was renamed the Chronic Disease Control Bureau (CDCB), and the district (county) tuberculosis control dispensary was renamed the county chronic disease control dispensary, with its function expanded to include screening and health education of diabetes and hypertension. While there was no disruption of tuberculosis services in the 1980s in Taiwan, it has been increasingly difficult to efficiently operate a vertical tuberculosis program in an evolving health care system, especially after the implementation of the national health insurance program. As the majority of tuberculosis patients were diagnosed and treated outside the vertical program through national health insurance, patients who were referred to the vertical program decreased to a minority, mainly those who did not participate in the NHI program, those with major adverse reactions, those who were difficult to treat and

those who had drug-resistant tuberculosis. The evolving health care environment imposed several challenges on the vertical program.

First, the quality of the diagnosis and treatment of tuberculosis in the general health care system was difficult to ensure. Information on reported tuberculosis cases provided by general health care facilities was incomplete and difficult to obtain. Sputum examination was frequently not done and the proportion of bacteriologically-confirmed pulmonary tuberculosis cases among notified pulmonary tuberculosis cases was low (36.3% in 1999[82]). However, CDCB and its regional branches had limited budget for program operation and insufficient administrative authority in dealing with the health care system. CDCB was administratively under the Provincial Department of Health, at the same level of Provincial hospitals.

Second, life expectancy at birth of males increased from 59.6 years in 1955 to 72.7 years in 2000, and that for females from 62.8 years to 78.4 years.[92] The top 5 leading causes of death were gastro-intestinal diseases, pneumonia, tuberculosis, heart disease and cerebrovascular diseases in 1952, but have changed to malignant neoplasms, cerebrovascular diseases, heart diseases, accidents, and diabetes mellitus in the year 2000. Health authorities did not give priority to tuberculosis. Integration of tasks (expanded program on immunization, maternal and child health, non-communicable diseases, etc) of public health nurses at township/village health stations took place in the 1980s. Tuberculosis workers formerly enrolled under the vertical tuberculosis program were tasked with additional duties and shared tuberculosis-related activities with other public health nurses. Consequently, tuberculosis was easily neglected and case-holding was getting difficult to organize, especially for tuberculosis patients treated in the general health care system. The

proportion of tuberculosis patients with successful treatment was 77.1% among patients notified in 1996, 78.4% in 1997, 75.1% in 1998, 76.6% in 1999, and 74.2% in 2000; the respective proportion of patients who were lost to follow-up was 11.3%, 8.9%, 8.1%, 6.6%, and 7.0%.[68, 71, 79, 82, 93] Interruption of treatment was particularly a problem in the treatment of multidrug-resistant tuberculosis and the proportion who interrupted treatment for 2 months or more was as high as 29% for the cohort treated in 1992-1996.[14]

In addition, the construction of CDCB was built on the property of National Taiwan University, who planned to use the land to build a new Children's Hospital and had been requesting return of the land for years. CDCB had land of its own, which was occupied by another institute. The Provincial government remained indecisive for years concerning whether to construct a new building for CDCB. Eventually, CDCB temporarily rented a building in Taipei County and moved there in January 1998. Staff of CDCB was heavily demoralized and many of them left the program.

1.17 Integration of tuberculosis services, 2001

Taiwan Centers for Disease Control (CDC), Department of Health, was established in the year 2000. Taiwan CDC as part of central government enjoys a much higher level of administrative authority than CDCB. Since the mandate of Taiwan CDC is to control communicable diseases, integration of tuberculosis control into Taiwan CDC had been an issue for elaboration. The official tuberculosis control system was considered to have two distinct but inter-related functions: 1) clinical services including diagnosis and treatment of tuberculosis, and 2) public health function, including policy, planning, case finding, surveillance, advocacy, health education, prevention, case

holding, contact tracing, recording and reporting. CDCB had a hospital with 100 bed capacity and staffed with several well trained medical doctors (the majority were qualified internists and pulmonologists) who not only participated in the implementation of the tuberculosis program but also provided medical care services, especially for drug-resistant tuberculosis and difficult-to-treat tuberculosis. As second-line anti-tuberculosis drugs were not available at most general health care facilities, the majority of multidrug-resistant tuberculosis patients were referred to CDCB and its three regional branches for management.

Different options of integration of tuberculosis program into Taiwan CDC were elaborated. Eventually, it was decided that Taiwan CDC would take over the public health function but not the clinical function of CDCB. Most clinicians of CDCB and its regional branches left the program to work in general hospitals. Drastic re-structuring from a vertical tuberculosis program to a fully integrated approach started in July 2001 when Taiwan CDC formally took over the National Tuberculosis Program and was completed when the clinical functions of CDCB in Taipei were closed in August 2002.

1.18 Challenges of tuberculosis services after integration, 2002 onward

Under the vertical tuberculosis program, there were medical officers and senior public health nurses assigned to each county/city as supervisors. The records of reported tuberculosis cases were reviewed by medical officers to verify the accuracy of case notifications (whether or not they fitted the definition for tuberculosis). Medical officers also offered advice when clinicians of general health care facilities had difficulty in deciding whether anti-tuberculosis treatment was required. Senior

public health nurses supervised tuberculosis case management, as well as recording and reporting. In the 1990s, it was already noticed that chest radiography examinations were heavily used, overdiagnosis and misdiagnosis of tuberculosis were not infrequent, and bacteriologically examinations were neglected. Strengthening mycobacteriology laboratory services has been listed as an urgent issue by the former CDCB.[93] After Taiwan CDC took over NTP in 2001, most medical officers and senior public health nurses were not recruited in Taiwan CDC. A quality-assured laboratory system was not in place. New mechanisms of supervision and monitoring were not established. Completeness and accuracy of notification data were not ascertained. Diagnosis and treatment of tuberculosis were left to all clinicians in general clinics/hospitals, under a naïve assumption that all clinicians know how to diagnose and treat tuberculosis.

Taiwan CDC promoted the concept that according to the communicable disease control law, not only confirmed tuberculosis cases must be reported but also individuals with suspected tuberculosis. Subsequently, notification of tuberculosis increased. However, inexperienced clinicians at general health care facilities had no regular channel of consultation for the diagnosis and treatment of tuberculosis. Many patients who were not treated with anti-tuberculosis drugs were notified to health authorities and Taiwan CDC. A substantial number of notified patients, who were either treated or not treated with anti-tuberculosis drugs, had their diagnosis of tuberculosis changed. In 2003, a total of 22,362 suspected and confirmed tuberculosis cases were notified, of which 6,612 (29.6%) had their diagnosis changed and were thus regarded as 'non-notifiable'.[94]

Clearly, several challenges related to laboratory services, diagnosis, treatment, case

management, and surveillance of tuberculosis emerged after re-structuring. Constraints of tuberculosis services that emerged following the integration of vertical tuberculosis program into general health care system need to be identified and addressed to ensure efficiency and effectiveness of the new approach. Questions included:

1. Was the quality of smear microscopy satisfactory?
2. Were all culture positive patients treated with anti-tuberculosis drugs?
3. Were tuberculosis patients advised to stop anti-tuberculosis treatment before completing a treatment course and what were its associated factors?
4. Were prescribing practices for anti-tuberculosis drugs in the treatment of tuberculosis adequate?
5. What were the proportions of patients who had treatment interruption and died during anti-tuberculosis treatment and their associated factors?
6. Was the classification of notified tuberculosis cases accurate?

2. Study aims

2.1 Broad Objective

To assess tuberculosis services and surveillance after the integration of the vertical tuberculosis program into general health care system in 2001.

2.2 Specific Objectives

1. To evaluate quality of smear microscopy of 4 mycobacteriology laboratories who provided slides for a training course in 2004. (Paper 1)
2. To assess tuberculosis-related deaths without treatment in Taipei in 2003. (Paper 2)
3. To investigate factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion in Taipei in 2003. (Paper 3)
4. To evaluate prescribing practices for anti-tuberculosis drugs in the treatment of tuberculosis in Taipei in 2003. (Paper 4)
5. To investigate outcome of tuberculosis and factors associated with treatment interruption and death in Taipei in 2003. (Paper 5)
6. To assess accuracy in the classification of notified tuberculosis cases in Taipei in 2003. (Paper 6)

3. Methods

Table 1 shows outcome, determinants and analytic approaches of papers 1-6. Figure 10 shows study population of papers 2-6.

Table 1. Outcome, determinants and analysis of original papers

Paper	Outcome	Determinants	Analysis
1	1. Smear with proper size, thickness and staining. 2. Major and minor errors per laboratory	None	1. Descriptive analysis that presents numbers and proportions
2	1. Failure to initiate anti-tuberculosis treatment in reporting health facilities	Sex, age, sputum smear, type of case, concomitant diseases (pneumonia, sepsis/respiratory failure, cardiovascular disease, hepatic disease, and cancer)	1. Pearson's chi square test, 2. Fisher's exact test 3. Multivariable logistic regression analysis
3	1. Starting anti-tuberculosis treatment on the basis of each type of clinical investigation 2. Decision to stop anti-tuberculosis treatment before completion (change diagnosis)	Sex, age, type of reporting facilities, cancer, treatment interruption for 2 consecutive months, transferred	1. Pearson's chi square test, 2. Multivariable logistic regression analysis

Table **1**. Outcome, determinants and analysis of original papers (continued)

Paper	Outcome	Determinants	Analysis
4	1. Frequency of correct dosage, lower than recommended dosage and higher than recommended dosage of each drug	Sex, age, body weight, type of case, sputum smear, liver disease, renal disease	1. Pearson's chi square test. 2. Multinomial logistic regression models
5	1. Outcome of treatment (treatment success, died, failed, treatment interruption/ still on treatment, transferred out), 2. Excess mortality 3. 1-year mortality	Sex, age, sputum smear, sputum culture, TB treatment history, visited other health facilities, concomitant diseases, Diabetes, respiratory disease, cardiovascular disease, infectious disease, cancer, renal disease, hepatic disease	1. Pearson's chi square test 2. Standardized mortality ratio 3. Kaplan-Meier survival estimates, 4. Log rank test 5. Cox proportional hazards model
6	Official classification of reported tuberculosis cases by type of case, with specific interest on proportion of not-a-case classified as new TB case, definite cases classified as not-notifiable, and untreated individuals with suspected TB classified as new cases	None	1. Descriptive analysis that presents numbers and proportions

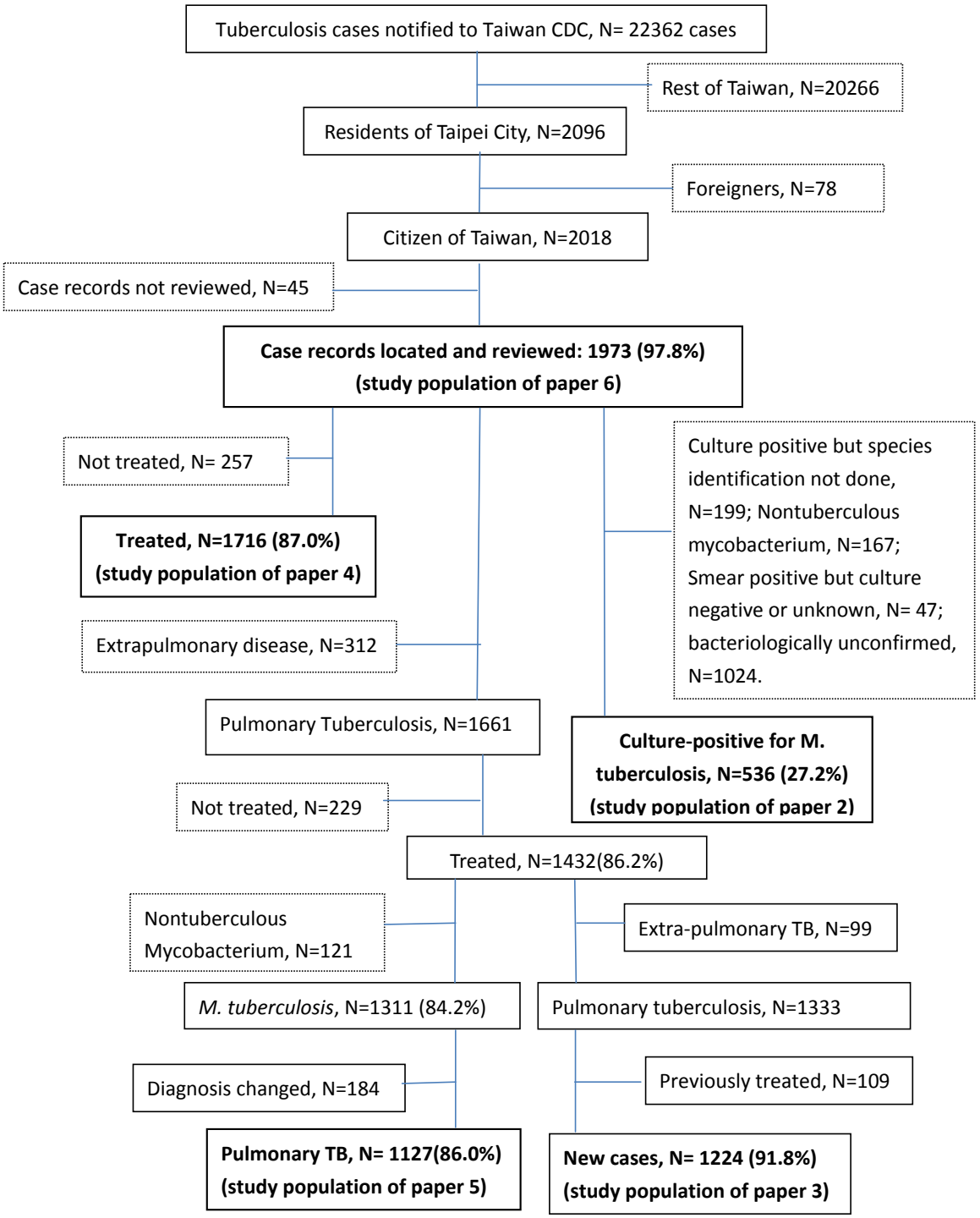

Figure 10. Flow chart of study population of papers 2-6

3.1 Quality of sputum smear microscopy in Taiwan. (Paper 1)

Four sets of slides collected from routine services at four mycobacteriology laboratories for a training course on quality assurance of smear microscopy were used for this study.[95] Participants of the training course used a systematic sampling method to choose 100 to 120 slides from a set of 600 to 800 slides for evaluation. Participants judged the size, thickness, and staining (de-staining) of smears as G (good or acceptable) or P (poor), and re-checked slides blinded to the microscopy results reported by the testing laboratories. Discordant slides were re-examined by a second re-checker in order to make the final decision. The internationally-recommended classification of errors was used.[96] High false positive and high false negative results were classified as major errors, while low false positive, low false negative, and quantification errors were considered to be minor errors. Outcome assessed were the proportion of slides with proper size, thickness and staining as well as the number and proportion of both major and minor errors per laboratory. No determinant associated with outcome was analyzed because the number of laboratories was small. Analysis was descriptive that present number and proportion of relevant outcome. Data reported by course participants were validated by course facilitators.

3.2 Study population and data management of papers 2-6.

Study population of papers 2-6 came from a cohort of suspected and confirmed tuberculosis cases whose official residence was Taipei City notified to health authorities in 2003 (2003 Taipei Cohort, Figure 10). Characteristics of these notified cases were investigated by review of their medical charts at the reporting health facilities. An official document was issued from Taiwan CDC to all health facilities to

obtain approval for carrying out the review. None of the reporting facilities refused to give approval. A structured questionnaire was designed and pilot tested. A team of 22 persons was organized and trained for data collection. Data were entered into the computer using EpiData 3.1 (The EpiData Association, Odense, Denmark). The complete data set was re-entered by a different person. Validation of the two computerized data sets was carried out using Epidata 3.1. Discrepant records were checked and corrected according to the original data on the questionnaires. STATA Version 8.0 (STATA Corporation, Houston, TX, USA) was used for statistical analysis.

3.3 Tuberculosis-related deaths without treatment. (Paper 2)

Tuberculosis cases that were culture positive for *M. tuberculosis* of the 2003 Taipei cohort were included in this study. Cases were classified as treated or not treated with anti-tuberculosis drugs after review of their case records. Outcome of interest was failure of initiation of anti-tuberculosis treatment for culture-positive TB patients in reporting health facilities. Determinants were sex, age, sputum smear, type of case, concomitant diseases (pneumonia, sepsis/respiratory failure, cardiovascular disease, hepatic disease, and cancer). A multivariable logistic regression model was constructed to assess factors associated with no treatment.

3.4 Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion. (Paper 3)

Newly diagnosed pulmonary tuberculosis cases from the 2003 Taipei cohort who did not have concomitant extra-pulmonary disease and who had not previously been treated for tuberculosis were included in this study. The procedure of clinical investigation leading to a decision to start treatment for pulmonary tuberculosis was

classified as follows:

1. Chest radiograph (CXR): immediate start of treatment after CXR, based solely on CXR findings.
2. Smear: start of treatment after CXR and a positive AFB smear.
3. Other: start of treatment after further investigations (such as bronchoscopy, pathology and polymerase chain reaction), but before culture result. Sputum AFB smear was negative or not done/ reported.
4. Culture: start of treatment after positive sputum culture.

Cases were classified by bacteriological status, as follows:

1. 'Definite' cases: presence of *M. tuberculosis* confirmed by culture.
2. 'Other confirmed' cases: *Mycobacterium* isolated but species determination not performed, and sputum smear-positive for AFB but culture not performed.
3. 'Not a case': only environmental mycobacteria isolated on culture.
4. 'Indeterminate': all other cases, including smear-positive, culture-negative cases.
5. Bacteriologically-confirmed cases: definite cases and other confirmed cases.

The proportion of patients starting anti-tuberculosis treatment according to each type of clinical investigation was assessed. Univariate analysis of factors associated with basis for diagnosis was done by chi square test and multivariate analysis by logistic regression. The proportion of patients who had their diagnosis of TB changed by a clinician and anti-tuberculosis treatment discontinued before completion was assessed. Factors associated with clinician's decision to stop anti-tuberculosis treatment before treatment completion (changed diagnosis) were analyzed by chi

square test and multivariate logistic regression.

3.5 Inconsistent dosing of anti-tuberculosis drugs in Taipei. (Paper 4)

The full 2003 Taipei cohort was included in this study. A medical audit of patients' medical charts was performed to collect pretreatment body weights and regimens prescribed at commencement of TB treatment. The dosages prescribed were then compared with recommended dosages. Outcomes were correct dosage, lower than recommended dosage and higher than recommended dosage of each drug. Categorical variables were analysed using Pearson's chi square test. $P < 0.05$ was considered statistically significant. Significant determinants were entered into multinomial logistic regression models in which the outcome variable had three categories (correct dosage, lower than recommended dosage and higher than recommended dosage) and a final fitted model was determined by backward elimination using the likelihood ratio test.

3.6 Tuberculosis outcomes in Taipei: factors associated with treatment interruption for 2 months and death. (Paper 5)

Pulmonary tuberculosis cases of the 2003 Taipei cohort who were treated with anti-tuberculosis drugs were included in this study. Treatment outcome was classified using the following definitions:

1. Treatment success: cured, for patients who were sputum culture-negative for *M. tuberculosis* at the last month of treatment and on at least one previous occasion, or treatment completed, for patients who had completed treatment but who did not meet the criteria to be classified as cured or failed.
2. Failed: patients who remained or became again sputum culture-positive for *M.*

tuberculosis at 5 months or later during treatment.

3. Died: patients who died for any reason during the course of treatment.
4. Defaulted: patients who either 1) interrupted treatment for at least 2 consecutive months (interrupts) or 2) were still on treatment 15 months after commencing anti-tuberculosis treatment (remained on treatment).
5. Transferred out: patients who had been transferred to another recording/reporting unit and for whom the treatment outcome was not known.

To assess the risk of death, all patients were followed up from the time of effective treatment until death or last contact. Cases with a follow-up of $\geqslant$1 year were censored at 1 year. Excess mortality of TB patients was determined by comparison with national mortality rates in 2003 published by the Department of Health. Kaplan-Meier survival estimates and log rank test were used to evaluate factors associated with death. All significant variables were entered into a multivariate Cox proportional hazards model, and a final fitted model was determined by backward elimination using the likelihood ratio test. The final model was checked by diagnostics including link test, graphical methods and residual analysis.

3.7 Accuracy of classification of notified tuberculosis cases in Taiwan (Paper 6)

All suspected and confirmed tuberculosis cases notified to health authorities in Taiwan in 2003 were identified from the national tuberculosis registry at Taiwan CDC. Reported cases of Taipei city was compared with those of rest of Taiwan. The full 2003 Taipei cohort were investigated by review of their medical charts at the reporting health facilities. Classification of reported cases by Taiwan CDC (Died

before registration, Treatment completed before registration, Diagnosis changed by physician, Non-notifiable (administrative coding), Newly-diagnosed case) were cross-tabulated with type of cases defined above (definite cases, other confirmed cases, indeterminate, and not-a-case) to assess accuracy in the classification of notified cases.

Ethics approval

Study 1 used data collected in a training course on quality of smear microscopy and did not access any individual information on patients; therefore, ethics approval was waived. Papers 2-6 reviewed medical charts and did not involve any patient interviews; these studies were approved by the Review Board of Taiwan CDC and funded by Taiwan CDC. An official document was issued by Taiwan CDC to all health facilities that reported TB cases to obtain approval for review of patient records; all of the reporting facilities gave approval.

4. Synopses of papers

4.1 Quality of sputum smear microscopy in Taiwan (paper 1)

The Eastern Region of the International Union Against Tuberculosis and Lung Disease (The Union) organized an international training course on quality assurance of sputum smear microscopy for tuberculosis control in Taipei from 19 to 27 August 2004.[95] Four mycobacteriology laboratories in the northern part of Taiwan collected slides from their routine work of sputum smear microscopy for the training course. Three laboratories provided a set of 600 slides and the fourth a set of 800 slides. This provided an opportunity to evaluate the quality of sputum smear microscopy in the collaborating laboratories.

A total of 433 slides were evaluated for their quality. The size of the smear prepared in one laboratory was uniformly judged to be too small. A substantial proportion of slides had at least a part of the smear sloughed off. Some slides had poor smearing, some smears were uneven, some too thin, some too large, and some incompletely decolorized. Of the 433 slides, 177 (41%) had proper size of smear, 194 (45%) proper thickness and 212 (49%) proper staining. Re-checking of the 433 smears (220 non-re-stained and 213 re-stained) by participants revealed seven as high false positive. These had to be excluded from the analysis because of the sloughing-off of the smears. Two of the 4 laboratories had at least one high false negative and 3 laboratories had at least one low false negative result.

We concluded that 1) the 2 laboratories with high false negative results needed a supervisory visit to determine the causes and 2) the National Tuberculosis Program

should pay due attention to the quality of sputum smear microscopy and develop a formal plan for external quality assessment of sputum smear microscopy in Taiwan.

4.2 Tuberculosis-related deaths without treatment (paper 2)

In 2003, 2,018 citizens of Taipei City diagnosed with tuberculosis were notified. To investigate tuberculosis patients who died without anti-tuberculosis treatment, the case records of 1,973 (97.8%) patients were located and reviewed, of whom 536 (27.2%) were culture-positive for *M. tuberculosis*. Of the 536 patients, 507 (94.6%) were treated with anti-tuberculosis drugs in reporting health facilities and 29 (5.4%) were not. Out of these 29 patients, 26 (89.7%) died, 2 (6.9%) were re-notified at a later point in time (one at month 13 after culture examination and another at month 18) and 1 (3.5%) was lost to follow-up. Of the 26 patients who died, 18 (69.2%) died within 1 month of culture examination. Among those 507 patients who were treated, 71 (14.0%) died during anti-tuberculosis treatment. Overall, of the 536 tuberculosis patients who were culture-positive for *M. tuberculosis*, 97 (18.1%) died, of whom 26 (26.8%) died without anti-tuberculosis treatment. In multivariable regression analysis, patients aged 65 years or more, patients with negative smears or smears not done, sepsis and/or respiratory failure and liver disease were significantly less likely to receive anti-tuberculosis treatment as compared with other groups.

This study probably underestimated the magnitude of tuberculosis deaths without treatment, as autopsies were rarely performed and those who did not undergo sputum examination would not be included.

4.3 Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion. (Paper 3)

Notification of tuberculosis is mandatory in Taiwan. Reported tuberculosis cases are classified as non-notifiable if the reporting clinician changes the diagnosis of tuberculosis and reports a decision to stop anti-tuberculosis treatment before completion of a full course of treatment. We conducted a study to investigate clinicians' practice in diagnosing pulmonary tuberculosis and to determine factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion of a full course (change of diagnosis) in Taipei City.

Of 1,126 pulmonary tuberculosis patients who were treated with anti-tuberculosis drugs, 512 (45.5%) started treatment immediately based solely on CXR findings; treatment for 214 (19.0%) was based on a positive sputum smear for acid-fast bacilli, for 261 (23.2%) on other findings and for 139 (12.3%) on a positive mycobacterial culture. Of the 1,126 pulmonary tuberculosis patients, 156 (13.9%) had their diagnosis of tuberculosis changed by a clinician. The proportion of cases with a changed diagnosis was significantly different between groups of patients according to their basis for diagnosis; it was highest among those treated based on "other" findings (20.7%) followed by those based on CXR findings (14.8%), positive culture (7.9%) and positive smear (7.0%). Multivariate analysis showed that patients whose diagnosis was based on CXR or other findings, female patients, patients who interrupted treatment for at least 2 months, patients who continued care at other health facilities (transferred) and patients with lung cancer were significantly more likely to have their diagnosis changed than other groups.

Among the various categories of patients, indeterminate cases were most likely to have their diagnosis changed (24.4%), followed by patients who were smear-positive but culture not done (7.7%), culture positive but species not identified (5.9%) and definite cases (3.3%). Of the 156 patients with a change of diagnosis, 83 (52.5%) had their diagnosis changed by the reporting facility and 73 (46.8%) by other facilities. "Definite cases" were most likely to have their diagnosis changed by other facilities (84.6%). We concluded that a substantial proportion of patients were prescribed anti-tuberculosis treatment based on CXR findings alone, and a considerable proportion of them were advised to stop treatment before completing a full course, findings that require the immediate attention of Taiwan's National Tuberculosis Program.

4.4 Inconsistent dosing of anti-tuberculosis drugs in Taipei. (Paper 4)

We investigated prescribing practice of anti-tuberculosis treatment in Taipei. A total of 24 different anti-tuberculosis regimens were prescribed for the treatment of tuberculosis in 1,700 reported tuberculosis patients aged 15 years or more. Of 1,700 patients, 1,096 (64.5%) had their body weight recorded. Of 506 patients prescribed a three-drug fixed-dose combination (FDC), the dosage was adequate in 374 (73.9%), too low in 100 (19.8%) and too high in 32 (6.3%). Patients with a positive smear were significantly less likely to be prescribed a lower-than-recommended dose of 3-drug FDC (relative risk ratio [rrr] 0.5, 95% confidence interval[CI] 0.3-0.8); patients weighing 50 kg or more were significantly less likely to be prescribed a higher-than-recommended dose (rrr 0.01, 95%CI 0.001-0.08); and patients with liver disease co-morbidity were significantly more likely to be prescribed a lower-than-recommended dose (rrr 3.7, 95%CI 1.3-10.6).

Of 75 patients prescribed a two-drug FDC, the dosage was adequate in 57 (76.0%), too low in 15 (20.0%) and too high in 3 (4.0%). Of 481 patients prescribed rifampicin, the dosage was adequate in 302 (62.8%), too low in 152 (31.6%) and too high in 27 (5.6%). Patients weighing ≧50 kg were more likely to be prescribed a lower-than-recommended dose of rifampicin (rrr 3.7, 95% CI 2.0-6.7) and were less likely to be prescribed a higher-than-recommended dose (rrr 0.03, 95% CI 0.01-0.14); patients with co-morbidity with renal disease were significantly more likely to be prescribed a lower-than-recommended dose of rifampicin (rrr 2.6, 95% CI 1.5-4.7). Of 451 patients prescribed isoniazid in single drug preparation, the dosage was adequate in 396 (87.8%), too low in 29 (6.4%) and too high in 26 (5.8%).

We concluded that the prescribing practices for anti-tuberculosis drugs were substandard and needed improvement.

4.5 Tuberculosis outcomes in Taipei: factors associated with treatment interruption for 2 months and death (paper 5)

Outcomes of anti-tuberculosis treatment in Taiwan were generally determined 18 months after the close of the year in which these cases were registered. Classification of treatment outcome in Taiwan did not fully follow international recommendations. Those who remained on treatment when outcome analysis was carried out were classified together patients lost to follow-up (defaulters), but patients who interrupted treatment for at least 2 consecutive months (international definition of default) were not reported as such. The Taiwan CDC reported the outcomes of 1,278 tuberculosis cases notified in Taipei in 2003 as follows: 81.3% treatment success,

17.0% died, 0.2% failed, 0 defaulted and 0.6% transferred out.

We assessed outcome of 1,127 pulmonary tuberculosis patients and investigated risk factors associated with treatment interruption for 2 consecutive months or more and death. Treatment outcomes were as follows: 73.1% treatment success, 16.8% died, 2.8% failed, 5.8% interrupted treatment for at least 2 months and 1.5% were still on treatment 15 months after commencing treatment. Treatment outcome was significantly associated with age group, sputum smear status, sputum culture status, visiting other health facilities during treatment and concomitant diseases. Of the 65 patients who interrupted treatment for at least 2 months, seven (10.8%) did so within 1 month after treatment initiation, 17 (26.2%) between 1 and 3 months. No factor was identified to be associated with treatment interruption for at least 2 months except visiting other health facilities during treatment.

Of the 189 patients who died, 72 (38.1%) died within 1 month of treatment, 69 (36.5%) between 1 and 3 months. Tuberculosis patients had a standardized mortality ratio of 8.7 (95%CI 7.5–10.0). In multivariate analysis, factors significantly associated with death were age (adjusted hazard ratio [adjHR] 1.06. 95%CI 1.05–1.08), sputum culture not performed / unknown (adjHR 2.07, 95%CI 1.47–2.92), and co-morbidity with respiratory disease (adjHR 1.68, 95%CI 1.24–2.27), infectious disease (adjHR 2.80, 95%CI 2.07–3.78), renal disease (adjHR 2.58, 95%CI 1.82–3.66) or cancer (adjHR 3.31, 95%CI 2.35– 4.65), as compared with other patients.

In contrast with official reports of no treatment interruption, 5.8% (95% CI 4.4–7.1) of patients interrupted treatment for 2 months or more. A high proportion of deaths was due to old age and co-morbidity.

4.6 Accuracy of classification of notified tuberculosis cases in Taiwan (Paper 6)

We conducted the study to address the following question: 'How accurate (logically consistent) is the classification of cases among Taiwan-born individuals resident in Taipei City who were reported to the National Tuberculosis Register? The 'null hypothesis' tested was: there is more than 95% concordance of classification of cases notified as compared with classification derived from logical consistency.

Of 1,973 patients evaluated, 782 (39.6%) were bacteriologically confirmed, 1,024 (52%) were not bacteriologically confirmed (indeterminate) and 167 (9%) were not tuberculosis cases (in whom non-tuberculosis mycobacteria [NTM] were isolated). Of the 1,973 cases, 1,716 (87%) had been treated with anti-tuberculosis drugs, while 257 (13%) had not been treated. Of the 782 bacteriologically confirmed cases, 68 (8.7%) were misclassified as non-notifiable (32 [4.1%] had their diagnosis changed by a clinician and 36 [4.6%] by administrative coding). Of the 167 cases in whom NTM were isolated, 72 (43.1%) were misclassified as tuberculosis cases. Of the 257 untreated individuals with suspected tuberculosis, 31 (12.1%) did not have any evidence of tuberculosis (20 indeterminate and 11 NTM cases) and were questionably classified as newly diagnosed cases. Thus, at least 140 (14.8%) were 'misclassified' based on logical in-consistency and only 809 (85.2%, 95%CI 82.8–87.4) were correctly classified. The null hypothesis was rejected and we concluded that there was substantial misclassification of notified tuberculosis cases in Taipei in 2003.

5. Discussion

To systematically address findings and implication of these studies, overall discussion of each paper addresses general perspectives, strengths, weaknesses, and impact of the study, as well as further actions required. There were common strengths of these papers. First, these studies were done independently without any interference of health authorities. Taiwan CDC as the funding agency played no role in data analysis and publication. Second, quality of data collection and management were assured through training and double data entry. Third, a very high proportion of the eligible population was included to avoid selection bias. Fourth, clear definitions were applied in outcome assessment to avoid information bias. Fifth, potential determinants were analyzed to address confounders. Finally, findings of these studies have contributed to policy change. An over-riding weakness of these studies was that the study population was restricted to 4 laboratories (paper 1) and Taipei (papers 2-6) and findings may not be generalized to the whole Taiwan.

5.1 External Quality Assessment of smear microscopy

External Quality Assessment (EQA) is a process to assess laboratory performance, which includes panel testing (evaluating performance by slides from the central laboratory to peripheral centers), blinded rechecking (monitor performance by a sample of slides from the peripheral laboratories to a higher-level laboratory for rereading) and on-site evaluation.[96] The objective of EQA is the identification of laboratories with serious problems resulting in poor performance, not the identification of individual slide errors or the validation of individual patient diagnoses.

This was the first study ever carried out on the quality of smear microscopy in Taiwan. Four mycobacteriology laboratories collected slides from their routine work for the training course. These slides likely were representative of the actual performance of smear microscopy of these laboratories. Course participants followed advice of international laboratory experts in using internationally recommended methodology to evaluate these slides. Findings were confirmed by instructors of the training course and likely represent an un-biased assessment of these slides.

There were some limitations of this study. It did not include all mycobacteriology laboratories in northern Taiwan. The four laboratories enrolled were not a random sample of all laboratories. It was an opportunistic study taking advantage of a training course. Therefore, findings of this study may not be generalizable to other laboratories in Taiwan. However, the finding of the exercise in the training course was alarming. A high proportion of smears was judged to be of poor quality. Two (50%) of the 4 laboratories had at least one high false negative and 3 (75%) laboratories had at least one low false negative result. Given that these 4 mycobacteriology laboratories were considered to be the most experienced mycobacteriology laboratories in northern Taiwan, these negative findings call for corrective action.

These findings obtained immediate attention of Taiwan CDC who subsequently conducted 3 workshops on EQA of sputum smear microscopy in each of the northern, central and southern regions of Taiwan in 2005. A pilot smear EQA program that involved Taiwan CDC-contracted mycobacteriology laboratories was also launched in 2005. Of the 1,017 slides sampled in 2005, 637 (63%) had proper smear size, 492 (48%) proper thickness and 884 (87%) proper staining. Rechecking of 981 readable slides in 2005 identified 3 (0.3%) high false-negatives, 3 (16.7%) low false-positives

and 26 (2.8%) low false-negatives. Of the eight laboratories, only two (25%) reached 80% sensitivity in 2005; 2 (25%) had at least one major error and 7 (78%) had at least one minor error.[97]These findings were similar to our findings.

After conducting the rechecking program in 2005, an extensive technical training course was offered at the national reference laboratory. One medical technologist from each contracted laboratory attended the course. The content of the course included slide preparation and reading, internal quality control and assessment. A certificate was given to participants who passed the technical evaluation. During an on-site evaluation, discordant slides were returned to each laboratory, and one of the laboratory technologists analyzed these discordant slides in the presence of the laboratory technologists during on-site evaluations. Laboratory facilities and procedures for slide preparation were also evaluated. These efforts resulted in improvement in the rechecking program in 2006. For the 972 slides rechecked in 2006, 972 (100%), had proper smear size, 748 (77%) proper thickness and 809 (99.6%) proper staining. Of the 9 laboratories that participated, 2 laboratories reached 80% sensitivity in 2005, which increased to 4 in 2006. However, 3 (0.3%) high false-negatives, 8 (28.6%) low false-positives and 12 (1.3%) low false-negatives were still identified. Of the 9 laboratories, 2 (25%) had at least one major error and 8 (89%) had at least one minor error.[97] The average number of slides examined in laboratories using the Kinyoun staining method was approximately 40 (range 25–50) per technologist per day, whereas the average number in laboratories using a fluorescence staining method was 59 (range 35–100). In 3 laboratories, technologists were also responsible for performing culture and drug susceptibility testing. Heavy workload remained a major concern for those laboratories with false-negatives.

Clearly, results of the rechecking program in 2006 deserved attention. Smear microscopy remains the cornerstone for the diagnosis of pulmonary tuberculosis in adults because it identifies the most powerful sources of transmission of tuberculosis. The main problem is that it is tedious, requiring motivated staff, with increasing risk of false-negative error when large numbers of specimens are examined. [98] Therefore, an effective EQA system is essential. Performance evaluation of Taiwan CDC contracted laboratories revealed a relatively low sensitivity in detecting smears positive for acid-fast bacilli, which was detrimental to the diagnosis of pulmonary tuberculosis. False negatives were mainly due to high workload of laboratory technologists. Increased payment of smear microscopy by national health insurance, reducing workload of laboratory technologists who are responsible for smear microscopy, on-the-job training to ensure capacity in reading slides, and means to increase motivation of laboratory technical personnel may be elaborated to help improve the quality of smear microscopy. To date the EQA program is limited to only 9-10 laboratories contracted by Taiwan CDC. There are plenty of laboratories in general hospitals performing smear microscopy whose quality has never been externally assessed. It is essential to establish a quality assured microscopy network in Taiwan; strategy to ensure the quality of smear microscopy at general health care facilities must be developed.

5.2 Tuberculosis-related death without treatment

Failure of diagnosis as a factor in tuberculosis mortality has been reported previously. Among patients who died from tuberculosis, the proportion who died without treatment was 47.4% in Canada[99] and 53.1% in Norway[100]. Death before notification was noted in the 1990s in Taiwan, and was mainly due to delays in notification; it was

not specified whether patients had received anti-tuberculosis treatment before death.[91]A study in the United States reported that 5.1%[101] of TB cases were diagnosed after death; another study in San Francisco reported that 3.9%[102] of tuberculosis cases were diagnosed after death.

The problem of tuberculosis-related death without treatment has not been addressed previously in Taiwan. We observed that some notified culture-positive tuberculosis patients had not been treated with anti-tuberculosis drugs in a timely manner, and some of them died without anti-tuberculosis treatment. Therefore, we kept track of a cohort of notified culture-positive tuberculosis patients in Taipei City to investigate tuberculosis-related death without treatment. Overall, of the 536 TB patients who were culture-positive for *M. tuberculosis*, 97 (18.1%) died, of whom 26 (26.8%) died without anti-tuberculosis treatment. As reporting of tuberculosis is mandatory by law and all culture positive tuberculosis patients in Taipei in 2003 were included, the study population likely was representative of Taipei. We found that the majority (88.5%) of the tuberculosis patients who died without treatment were aged 65 years or more, and 76.9% of these died before the results of sputum culture were available. Clearly, clinicians need to maintain a high level of awareness of tuberculosis and initiate anti-tuberculosis treatment as early as possible, especially among the elderly who are very ill or with co-morbidity, if the probability of tuberculosis is high. New diagnostics with a higher sensitivity in detecting smear negative tuberculosis[103, 104] might be helpful and their utility in reducing tuberculosis-related death without treatment needs to be evaluated.

This study likely underestimated the frequency of tuberculosis-related death without treatment, as autopsies were rarely performed in Taiwan and those who did not

undergo sputum examination would not be included. Further, we did not consult laboratory registers to evaluate completeness of reporting of bacteriological confirmed cases. Laboratory registers provide information on cases with acid fast bacilli and/or *M. tuberculosis,* allowing investigation of initial defaulters as well as tuberculosis-related death without treatment. Rates of initial defaulters, defined as patients who were smear-positive on the laboratory register but who were not registered for anti-tuberculosis treatment, have been reported to be 17% in Cape Town, South Africa,[105] and 4.5% in Andhra Pradesh, India.[106]

Rates of initial loss-to-follow-up and the interval from a positive sputum result (either smear or culture) to initiation of treatment are issues to be further investigated in Taiwan. For surveillance of tuberculosis, cross-checking laboratory registers and national tuberculosis registry should be done to assess completeness of reporting of bacteriologically positive patients. Further, tuberculosis-related deaths without treatment should be highlighted in the annual reports and a strategy to prevent this from happening need to be developed.

5.3 Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion

The International Standards for Tuberculosis Care has advised that all patients suspected of having pulmonary tuberculosis should have at least two sputum specimens submitted for microscopic examination in a quality-assured laboratory and that all persons with chest radiographic findings suggestive of tuberculosis should have sputum specimens submitted for microbiological examination.[107] A survey of TB services in hospitals in seven large cities in Asia and North Africa

demonstrated that a high proportion of hospitals did not always perform sputum smear examinations for individuals with suspected tuberculosis.[108] In Korea in the 1990s, more than 50% of general practitioners did not consider sputum examination essential in the diagnosis of tuberculosis.[109] In a study in South Africa, chest radiography alone was used to diagnose pulmonary tuberculosis in 45% of the records reviewed.[110] Our study showed that clinicians' practices in diagnosing pulmonary tuberculosis in health care facilities in Taipei City were not standardized. A high proportion of individuals were put on anti-tuberculosis treatment based on CXR findings before sputum examination. This practice should be discouraged; it may lead to delays in the diagnosis of lung cancer and other diseases and result in over-diagnosis of smear- and culture-negative tuberculosis, exposing the patients to unnecessary or wrong treatment. Sputum culture contributed positively to the diagnosis of tuberculosis in this series of patients. However, positive sputum culture also resulted in anti-tuberculosis treatment being started for a considerable number of patients in whom non-tuberculosis mycobacteria were isolated. This highlighted the importance of rapid species identification so that adequate treatment tailored to the species of mycobacterium can be initiated in a timely manner, if indicated.

Change of diagnosis and de-notification of tuberculosis have rarely been previously investigated. There have been studies on adequacy of presumptive diagnosis of smear negative pulmonary tuberculosis based on radiographic findings. Gordin and colleagues analyzed 139 smear negative patients who were treated for a presumptive diagnosis of pulmonary tuberculosis and reported that 66 (48%) were determined to have current tuberculosis (16 had a positive culture, 43 had radiographic improvement, and 7 clinical improvement)[111]. Lee and colleagues investigated 101 smear negative presumptive pulmonary tuberculosis cases and

found that 61 (62.4%) had radiographic improvement (32 culture positive).[112] Our study did not specifically address adequacy of presumptive diagnosis of pulmonary tuberculosis but rather changed diagnosis and de-notification of tuberculosis at program level. Of the 1,126 pulmonary tuberculosis patients, 156 (13.9%) had their diagnosis of tuberculosis changed by a clinician and were de-notified. Patients whose treatment was started based on CXR alone were significantly more likely to have their treatment stopped by a clinician. This demonstrates why radiographic findings should not be used alone to diagnose tuberculosis. Among the various categories of patients, indeterminate cases were most likely to have their diagnosis changed (24.4%). Indeterminate patients who visited other health facilities were more likely to be advised to stop anti-tuberculosis treatment than those who continued treatment at the diagnosing facilities. This probably reflected inter-personal disagreement in the diagnosis of smear- and culture-negative tuberculosis, highlighting the importance of standardizing the diagnosis of non-bacteriologically confirmed tuberculosis. Several definite tuberculosis cases were advised to stop treatment, particularly those who continued treatment at other health facilities, and subsequently required retreatment of tuberculosis. This highlighted poor communication and inadequate coordination between health facilities. Health services need to strengthen the coordination of case management of tuberculosis patients who visit other health facilities during treatment. Among those whose treatment was stopped, several patients had in fact interrupted treatment for at least 2 consecutive months. Classifying treatment interruption as having a change in diagnosis obscured the problem of treatment interruption and lost the opportunity to address this important issue. This was unintended misclassification at central level of the surveillance system but a consequence of systematic under-detection of treatment interruption.

This likely is the first study that comprehensively investigated clinical practice in the diagnosis of tuberculosis and subsequent change of diagnosis of tuberculosis by clinicians. The limitation of this study was that we did not comprehensively follow up patients who were advised to stop anti-tuberculosis treatment to determine what happened at a later point in time.

Findings of this study contributed to the development of a policy of Taiwan CDC that bacteriologically-negative cases whose diagnosis of tuberculosis cases was judged to be questionable, cases whose diagnosis of tuberculosis was changed after initiation of anti-tuberculosis treatment and retreatment cases without bacteriological evidence should be reviewed by an expert committee at regional branches of Taiwan CDC. The expert committee consisted of several senior clinicians with substantial experience of tuberculosis. Review of questionable cases by the expert committee may contribute to improvement of diagnosis and surveillance of tuberculosis and reducing inappropriate discontinuation of treatment of definite cases. However, as the expert committee did not review all bacteriologically-negative cases at the outset of treatment, the impact of this mechanism remains to be evaluated.

5.4 Prescribing practices for anti-tuberculosis drugs in the treatment of tuberculosis

An evaluation of the routine prescribing practices and dosages for anti-tuberculosis medications was done in Kenya, Malawi, Nepal and Senegal, which reported that the proportion of patients treated with adequate dosages of anti-tuberculosis drugs varied.[113, 114]

Our study revealed that prescribing practices for anti-tuberculosis drugs in Taipei City

were unsatisfactory. Almost 40% of tuberculosis patients did not have their pretreatment body weight recorded. Among those with pretreatment body weight recorded, the dosages of anti-tuberculosis drugs prescribed were often too low or too high, a finding of serious concern. This finding challenged the naïve assumption that after integration of tuberculosis services into general health care system supervision and monitoring was not required.

Inappropriate prescribing of the 3-drug FDC may be due to the strength of the preparation available in Taiwan (isoniazid, H 80 mg + rifampicin, R 120 mg + pyrazinamide, Z 250 mg). The ratios of H, R and Z in the 3-drug FDC was 1:1.5:3.1 which deviated from the ratios (1:2:5) of recommended dosage in milligrams (mg) per kilogram (kg) body weight of H (5 mg/kg), R (10 Mg/kg), and Z (25 mg/kg).[115] The amount of H per tablet is relatively high and that of Z relatively low. The equivalent strength of the 3-drug FDC recommended by the WHO is H 75 mg, R 150 mg and Z 400 mg per tablet and the ratios of H, R, and Z are 1:2:5.3, which were more consistent with the ratios of recommended dosage of H, R, and Z. The issue of imbalanced strength also applied to one formulation of 2-drug FDC (H 100+ R 150, HR ratio 1:1.5) but not another (H 150 + R 300, HR ratio 1:2)

This is the first study on dosing of anti-tuberculosis drugs in Taiwan. As it included almost all cases in Taipei in 2003, findings of this study might be generalizable to other parts of Taiwan where monitoring and supervision were also not done. This study has several limitations: first, we did not keep track of modifications of regimens during anti-tuberculosis treatment, and clinicians may have changed the dosages prescribed. Second, we did not assess the frequency of adverse reactions among patients who received higher-than-recommended dosages. Third, we did not

evaluate the association between dosages and either treatment outcome (failure and relapse) or the development of drug resistance.

The findings of this study were reported to Taiwan CDC in December 2005. Subsequently, Taiwan CDC has taken action to address the issue of substandard regimens and inadequate dosing. Several training courses on the diagnosis and treatment of tuberculosis were held. In 2006, the information system has been revised to routinely capture body weight of notified tuberculosis cases. In 2007, public health nurses have been trained to cross-check clinicians' prescription of anti-tuberculosis drugs according to guidelines for anti-tuberculosis treatment and to communicate with clinicians in case of inconsistency. If dosing remained inconsistent after communicating with clinicians, public health nurses should report these cases in meetings of tuberculosis expert committees. The expert committee would review clinical information of these cases and made recommendations, which would be provided to clinicians. In 2007, Taiwan CDC evaluated a random sample of 108 tuberculosis patients and found that 28.7% received inadequate dosage of drugs and 14.8% received lower-than-recommended dosage of rifampicin.[116] Subsequently, Taiwan CDC collaborated with the NHI program to promote standardized regimens and reduce reimbursement for inadequate tuberculosis regimen.[117] Preliminary data show that non-standardized regimen and inadequate dosing have been reduced substantially.[118] A study assessing prescribing practices in the treatment of tuberculosis in Taipei conducted in 2011 revealed that the proportion of culture positive tuberculosis patients without recorded pre-treatment body weight was 12.6% in 2007, which decreased to 0.5% in 2008 and none in 2010. (Chiang C-Y, manuscript submitted). Among those who were prescribed with 3-drug FDC, the proportion with dosage consistent with Taiwan CDC guidelines was 83.7% in 2007,

which increased to 91.4% in 2010, and the proportion with lower-than-recommended-dosage was 7.4% in 2007, which decreased to 1.9% in 2010. (Chiang C-Y, manuscript submitted)

5.5 Outcome of Tuberculosis: factors associated with treatment interruption for 2 months and death (Paper 5)

Traditionally, outcomes of anti-tuberculosis treatment in Taiwan were determined 18 months after the close of the year in which these cases were registered. This approach was insensitive to events that have important repercussions for National Tuberculosis Programs, such as treatment interruption for 2 months and remaining sputum-positive after 5 months of treatment. The proportion of TB patients lost to follow-up was 8.9% in the cohort of patients registered in 1997. To improve TB treatment outcome, Taiwan CDC has strengthened case holding in recent years. The proportion of patients who were lost to follow-up before completing a full course of treatment decreased substantially as a result. While this is remarkable progress in streamlining the national tuberculosis program, the next step should be to identify patients who interrupted treatment for at least 2 months and to address these events efficiently. Our study revealed that among 1,016 tuberculosis patients in the 2003 Taipei cohort who were classified as treatment success by Taiwan CDC, 63 (6.2%) had interrupted treatment for 2 months (treatment interruption) and 29 (2.9%) remained sputum positive at 5 months (failed); of the 171 patients who were classified as dead, 10 (5.8%) had interrupted treatment for 2 months (treatment interruption) and 7 (4.1%) remained sputum positive at 5 months (failed). Clearly, the surveillance system overestimated the proportion successfully treated and died, but under-estimated the proportion lost to follow-up and failed.

A limitation of this study was that it included only tuberculosis cases registered in Taipei but not other parts of Taiwan. However, it clearly pointed out constraints of the surveillance system and contributed to a change of policy of Taiwan CDC in strengthening identification of patients who interrupted treatment for 2 months and patients who remained sputum positive at 5 months of treatment or later. According to official reports of Taiwan CDC, the proportion of tuberculosis patients who interrupted treatment for 2 or more months was 0.6% for patients notified in 2004, 2.3% in 2005, 3.6% in 2006, and 2.8% in 2007; the proportion of patients who were sputum positive at 5 months or later was 0.6% in 2004, 1.7% in 2005, 1.6% in 2006 and 2.9% in 2007. These did not indicate an actual increased proportion of treatment interruption or failed from 2004 to 2007; it reflected the results of strengthening identification of treatment interruption and failed.

A comparison with national mortality rates shows that all-cause mortality among TB patients on treatment was 8.7 times higher than that of the general population. In England and Wales, all-cause mortality among patients with pulmonary tuberculosis was 10 times greater than that of the age- and sex-matched general population.[119] The excess mortality in this cohort is particularly high among younger members of the population, as was reported in the Netherlands.[120] Our study revealed that the proportion of tuberculosis patients on treatment who died was relatively high (16.8%). The majority (75%) died within 3 months of treatment. The proportion who died was higher among the elderly and those with concomitant diseases. Late presentation, health system delay in the diagnosis and initiation of treatment, or rapid disease progression in the presence of co-morbidities were possible factors related to death. A strategy to reduce tuberculosis case fatality needs to be developed.

5.6 Tuberculosis surveillance system (Paper 6)

Since 1997 when CDCB published the first annual tuberculosis control report, all notified tuberculosis cases were classified into one of the following categories: 1) foreigner: those who were not citizens of Taiwan; 2) died before registration; 3) treatment completed before registration; 4) diagnosis changed: those who were initially notified but who subsequently had their diagnosis changed to non-notifiable; and 5) newly diagnosed tuberculosis cases: those who did not fit into any of the above categories. Until 2002, the records of all reported tuberculosis cases were reviewed by a medical officer assigned to each city/county to verify whether or not they fitted the definition for tuberculosis. Anti-tuberculosis treatment was initiated if a medical officer confirmed the diagnosis of tuberculosis. As such, all notified cases classified as a tuberculosis case were put on anti-tuberculosis treatment.

This practice was discontinued after the responsibility of tuberculosis program was transferred from the former CDCB to Taiwan CDC. No medical officers were tasked with the duty to verify the accuracy of case notifications and the classification did not take into account whether or not a patient was under anti-tuberculosis treatment. To calculate the notification rate of tuberculosis among citizens, a non-physician public health specialist within the Taiwan CDC downloads individual information on all cases notified in the previous year from the internet-based reporting system on 30 September each year (this was changed to April 30 since 2006, Yang S-L, personal communication), and subtracts those who are foreign citizens, those who died before registration, those whose treatment was completed before registration, and those whose diagnosis was changed by a clinician. The specialist then identifies those cases without bacteriological confirmation in whom no improvement was reported

following anti-tuberculosis treatment and those who have died but in whom tuberculosis was not recorded on the death certificate, includes these cases in the 'diagnosis changed' category (in this case by 'administrative coding'), and then finally subtracts these cases to obtain the annual notification of tuberculosis cases among Taiwanese citizens. In this practice, accuracy in the classification of notified tuberculosis cases heavily depends on the completeness and timeliness in obtaining accurate bacteriology results and clinical response to anti-tuberculosis treatment from general health care facilities.

Our study identified substantial errors in the classification of reported tuberculosis cases in Taipei. One limitation of this study was that we did not follow up those cases who were classified as non-notifiable by administrative coding to see what happened to them. However, findings of this study were likely generalizable and reflected the practice for the whole of Taiwan. Classifying cases determined as non-notifiable by administrative coding in the category 'diagnosis changed' is a questionable practice and is misleading, resulting in a substantial increase in the number of cases with 'diagnosis changed'. One of the major causes of misclassification was correct determination of whether anti-tuberculosis treatment was initiated and that clinical information has not been completely updated in a timely manner to local health authorities and Taiwan CDC.[94, 121] Consequently, bacteriologically-confirmed cases were classified as non-notifiable because positive bacteriological results, especially culture, were not reported to local health authorities and Taiwan CDC. Likewise, patients from whom NTM were isolated were not de-notified and were classified as tuberculosis cases because results of species identification were not updated. To improve accuracy of the surveillance system, the communication of information between general health care facilities and the health authority should be complete,

timely and accurate.

Since the study on misclassification of reported tuberculosis cases, Taiwan CDC has strengthened surveillance data by systemically and periodically sending reminders for updating clinical information. Further, non-notifiable cases were classified into a) diagnosis changed by clinician, b) NTM, and c) does not fit with criteria of a tuberculosis case. The number of patients in the last category has decreased substantially from 1350 (5.6%) in 2004 to 34 (0.2%) in 2009 (personal communication, Yang S-L, Taiwan CDC). It is likely that misclassification of notified cases has decreased considerably. However, Taiwan CDC should regularly carry out supervision and monitoring to ensure the quality of reporting and communication.

Apart from Taiwan, reporting individuals who have no bacteriological evidence of tuberculosis and are not treated with anti-tuberculosis drugs is rare. To strengthen tuberculosis surveillance in Taiwan, it is essential to find out whether reporting bacteriologically negative individuals who are not treated with anti-tuberculosis drugs contribute to surveillance of tuberculosis in a positive manner. Reporting of individuals with suspected communicable diseases is mandatory by the article 39 of the communicable disease control act, stating that: “when physicians or forensic physicians detect communicable diseases or suspected communicable diseases in patients or corpses during the process of diagnosis and treatment or during the examination of the corpses, they shall immediately take the necessary infection control measures and report such cases to the competent authorities in the locality”. Accordingly, Taiwan CDC indicate criteria of tuberculosis reporting[122] as the following : a) persons with signs and symptoms of tuberculosis, such as chronic cough, weight loss, fever or radiographic findings suspected with tuberculosis, b)

clinical specimens culture positive for *M. tuberculosis*, c) clinical specimen smear positive for acid-fast bacilli, d) pathological findings consistent with tuberculosis. Criteria a) was not precise and allows different reading. Monitoring and evaluation on reporting individuals who fit criteria a) is extremely difficult, if not impossible. However, a substantial number of cases who did not fulfill criteria b), c) and d) (bacteriologically / pathologically negative) and were not judged to require a course of anti-tuberculosis treatment were being notified. The majority of these cases were classified as non-notifiable and a minority might be questionably classified as tuberculosis cases, as demonstrated by our study. Public health action without clear guidance or definition is potentially confusing and misleading, and runs the risk of losing focus. It is essential to evaluate critically whether reporting of individuals who have no bacteriologically / pathologically evidence of tuberculosis and are not judged to require a course of anti-tuberculosis treatment provides any public health benefit, and whether this practice imposes confusion and unnecessary burden on public health system. To be in line with the communicable disease control act on reporting individuals with suspected communicable diseases, Taiwan CDC may seek consultation on the feasibility of defining “suspected tuberculosis that required reporting” as individuals with suspected tuberculosis who require a course of anti-tuberculosis treatment judged by a qualified clinician.

A recently published study on completeness and timeliness of tuberculosis notification in Taiwan reported that there were 209,095 patients who had tuberculosis-related ICD-9 codes in the year 2005–2007 in the NHI reimbursement database, in whom 144,718 (69.2%) were newly assigned with tuberculosis-related ICD-9 codes in the year 2005–2007. Of these 144,718 patients, 84,361 (58.3%) were not prescribed any anti-TB drugs within 6 months after being assigned

tuberculosis-related ICD-9 codes, 57,405 (39.7%) were prescribed 2 or more types of anti-tuberculosis drugs. Of these 57,405 patients, 52,763 (91.9%) were new tuberculosis cases and 4,642 (8.1%) were retreatment cases who had been notified previously. Of the 52,763 new tuberculosis cases, 1,270 (2.4%) were not notified, and of the 4,642 retreatment cases, 844 (18.2%) were not notified.[123] Taiwan CDC should elaborate whether it would be more practical and effective to ensure complete and timely reporting of: 1) all cases who are treated with 2 or more anti-tuberculosis drugs, no matter whether they are bacteriologically / pathologically positive; and 2) all cases with positive bacteriologically / pathologically finding (smear positive for acid-fast bacilli, culture positive for *M. tuberculosis,* line probe assays or Xpert® MTB/RIF positive, or pathological findings consistent with tuberculosis), no matter whether they have been treated with anti-tuberculosis drugs.

6. Conclusions and Recommendations

6.1 Conclusions

The general objective of this study was to assess tuberculosis services and surveillance after the integration of the vertical tuberculosis program into the general health care system in 2001. Several constraints of tuberculosis services were identified.

1. The quality of smear microscopy of 4 mycobacteriology laboratories who provided slides for a training course in 2004 was not satisfactory.
2. The number of tuberculosis-related deaths without treatment in Taipei in 2003 was substantial.
3. A high proportion of tuberculosis patients in Taipei in 2003 were treated with anti-tuberculosis drugs on the basis of radiographic findings and subsequently were advised to stop anti-tuberculosis treatment before completion.
4. Prescribing practices for anti-tuberculosis drugs in the treatment of tuberculosis in Taipei in 2003 was substandard.
5. Treatment interruption for 2 consecutive months and sputum positive at 5 months or later among tuberculosis patients in Taipei in 2003 was largely under-detected. A relatively high tuberculosis case fatality ratio was related to old age and co-morbidity.
6. There were substantial mis-classification of notified tuberculosis cases in Taipei in 2003, largely due to failure to take into account whether anti-tuberculosis treatment is initiated and due to incomplete update of bacteriological results and clinical response.

6.2 Recommendations

It is recommended that health authorities and Taiwan CDC:

1. Extend EQA of smear microscopy to all mycobacteriology laboratories of general health care facilities in Taiwan.
2. Address initial loss-to-follow-up and tuberculosis-related death without anti-tuberculosis treatment.
3. Assess clinicians' practice in the diagnosis and treatment of tuberculosis as well as stopping anti-tuberculosis treatment before completing a full course.
4. Conduct regular clinical audit on prescription practices of anti-tuberculosis drugs.
5. Closely monitor loss-to-follow-up and failure in the treatment of tuberculosis as well as develop a strategy to reduce case fatality of tuberculosis.
6. Critically review the policy of tuberculosis notification and evaluate the quality of surveillance of tuberculosis.

7 Epilogue: from a vertical program to an integrated approach

After taking over the responsibility of the tuberculosis program, Taiwan CDC has implemented several important activities:

1. Established a national reference laboratory (NRL) in 2004: the NRL has established the capacity in performing RFLP, spoligotyping, and MIRU-VNTR for molecular epidemiological studies of tuberculosis,[124, 125] has conducted EQA of smear microscopy in CDC contracted laboratories,[97] has carried out proficiency testing of drug susceptibility test in almost all laboratories that performed anti-tuberculosis drug susceptibility testing,[126] and has pilot tested rapid diagnosis of drug resistant tuberculosis,[127] and other laboratory-related activities.
2. Collaborated with professionals and specialists to publish guidelines for the diagnosis and treatment of tuberculosis in 2004 (2nd edition in 2006, 3rd edition in 2008, 4th edition in 2011).
3. Established an "expert committee" at each regional branch" to provide guidance in the diagnosis and treatment of tuberculosis in 2004
4. Involved the private sector by an incentive mechanism through the national health insurance program in 2004.
5. Reinforced the examination of 3 sputum specimens among all notified pulmonary tuberculosis cases in 2005.
6. Strengthened infection control for tuberculosis in 2005.
7. Strengthened tuberculosis services in aboriginal areas in 2005.
8. Monitored tuberculosis outbreaks in long-term care facilities and congregate settings in 2006.[128]
9. Launched an ambitious plan entitled "mobilization of all citizens to reduce

incidence of tuberculosis by half in 10 years" in 2006, aiming to reduce incidence of tuberculosis to 34 per 100 000 by 2015, in which 15 plans of "Find tuberculosis and Cure tuberculosis" were listed. The budget for this program (NT$ 8.4 billion for 5 years) was estimated to be 40 times more than that of CDCB before re-structuring (NT$ 40 million per year, Lin T-P, former director of CDCB, personal communication).

10. Implemented a directly-observed therapy (DOT) program in 2006. To date, more than 680 outreach workers have been hired to carry out DOT. The proportion of bacteriologically confirmed tuberculosis cases treated under DOT was 50% in 2006, which increased to 92% in 2010.[129]
11. Promoted standardization of tuberculosis regimens through national health insurance program in 2008.
12. Implemented a program for management of drug-resistant tuberculosis in 2007, which has effectively reduced treatment interruption of MDR-TB patients to a very low level.
13. Strengthened contact management in 2007.[130]
14. Initiated treatment of latent infection with *M. tuberculosis* by directly-observed preventive therapy in 2008.
15. Implemented accreditation of mycobacteriology laboratories in 2008.
16. Strengthened bio-safety of mycobacteriology laboratories in 2009.
17. Strengthened tuberculosis services among the poor in 2010.
18. Pilot tested a new mechanism of external 'tuberculosis adviser' at hospitals with a high number of notified tuberculosis cases in 2011

Correction of the constraints on tuberculosis services in the transition from a vertical system to a fully integrated approach identified by our studies would have had no

impact at all if Taiwan CDC neglected these findings. Fortunately, Taiwan CDC acted positively rather than defensively to the findings described in this thesis and has taken actions to meet the challenges.[131] Taiwan tuberculosis control reports were published annually from 1997-2001. After interruption of a few years, Taiwan CDC has begun to publish an annual tuberculosis control report.[132] In 2009, a total of 13,336 new tuberculosis cases were notified; 79% of pulmonary tuberculosis cases were either smear positive and/or culture positive.[133] Tuberculosis notification rate was 57.8 per 100,000 population, representing a 20.3% reduction since 2005. Tuberculosis notification rate was highest in Eastern Taiwan (110.7 per 100,000), by region. Males had higher rates than females (79.6 vs 35.6 per 100 000 population). Those aged 65 years or more accounted for 53.1% of total new tuberculosis cases, and those aged 45-64 years accounted for another 26.2%, reflecting age transition of tuberculosis patients from the younger age group (25-44 year-old accounts for 50.9% of tuberculosis cases registered in 1957-1961)[134] to the elderly in past five decades in Taiwan.

The proportion of new tuberculosis cases who were HIV positive was 0.7%. Treatment outcome at 12 months among those registered in 2007 was as follows: 71.1% treatment success, 18.4% died, 2.9% failed, 2.8% interrupted treatment for 2 or more months, 0.1% transferred, and 4.8% still on treatment or not evaluated. The proportion of tuberculosis patients who died was relatively high among those aged 50 years or more (figure 11).

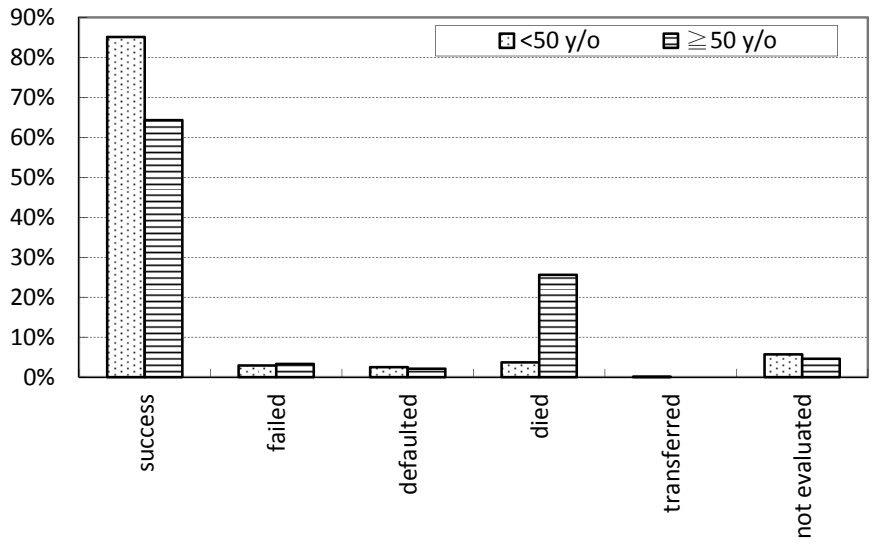

Figure 11. Outcome of smear-positive tuberculosis, 2008, Taiwan, by age group

One of the most important challenges after re-structuring the tuberculosis service system from a vertical program to a fully integrated approach was that there was no health care facility under the direct command of Taiwan CDC; tuberculosis services were provided at general health care facilities through NHI program. There was one hospital specialized in tuberculosis and lung disease (Chest Hospital in Tainan, which was one of the regional Branches of former CDCB), which was operated in a manner similar to general hospitals through the NHI program. No hospital is currently designated as a tuberculosis hospital taking tuberculosis control as primary responsibility. While reporting of tuberculosis has been mandatory, Taiwan CDC operating in parallel with the health care system has limited capacity in strengthening case finding and the diagnosis of tuberculosis within general health care system. While Taiwan CDC can strengthen health education on tuberculosis and encourage

symptomatic inhabitants to seek health care (to shorten patient delay), health care facilities are not equally competent in efficient identification of individuals with suspected tuberculosis for further examinations. A study conducted in Southern Taiwan reported that health system delay was much longer than patient delay.[135] Tuberculosis patients who visit health care facilities may not be identified; if identified, sputum examination may not be done; if it is done, the quality of sputum examination may be inadequate; if they are positive on sputum examination, they may not be put on anti-tuberculosis treatment; on the other hand, patients who have no tuberculosis may be unnecessarily treated with anti-tuberculosis drugs at the hands of inexperienced clinicians. Consequently, health system delay in the diagnosis and treatment of tuberculosis could be particularly long in some facilities; overdiagnosis of tuberculosis by inexperienced clinicians impose an unnecessary burden of registration, case management and contact tracing of public health system.

As timely diagnosis and effective treatment of tuberculosis is the cornerstone of tuberculosis service, no tuberculosis program can avoid the challenge of clinical management of tuberculosis, especially in the private sector. As tuberculosis has become a relatively uncommon disease in Taiwan, most clinicians are not efficient in timely diagnosis and proper treatment of tuberculosis. Engagement, training, monitoring and supervision of the private sector are essential. Public-public and public-private mix approaches and International Standards for Tuberculosis Care (ISTC) have been listed within the component “engage all care providers” of the Stop Tuberculosis Strategy. However, ISTC presents what should be done but does not address how the action is to be accomplished.[107] Tuberculosis programs need to develop local policies and procedures to ensure the quality of tuberculosis services. Program-relevant operational research can identify constraints with implications for

policy change, as demonstrated by our studies in relation to tuberculosis services in Taiwan. To strengthen tuberculosis services in Taiwan, an in-built budget for operational research must be protected.

There are several elements of the health care system that help address constraints of tuberculosis services in Taiwan. The communicable disease control act has been in place to ensure tuberculosis reporting. The national health insurance program not only facilitates access to care, but also provides a basis for monitoring and regulation of diagnosis, treatment and reporting of tuberculosis. Through various mechanisms of national health insurance, health authorities and Taiwan CDC have access to clinical information of tuberculosis patients (including detail bacteriological examinations, drugs prescribed and dosages administered) at almost all health care facilities. Further, tuberculosis case managers are in place in most hospitals to take care of notification of tuberculosis and play the role of focal points for on-going communication. The national tuberculosis registry is electronic and case-based, and tuberculosis notification is web-based, which facilitates efficient reporting and timely update of clinical information. The public health system has public health nurses who are in charge of case management and contact tracing. More than 680 outreach workers have been hired to perform DOT. The public-public and public-private mix can be efficient and effective if collaboration between general health care facilities, local health authorities and Taiwan CDC operate smoothly, but could go wrong if monitoring, supervision and evaluation were lacking.

Substantial progress in the fight against tuberculosis has been made after restructuring of the tuberculosis program. To further strengthen tuberculosis services in Taiwan, it is recommended that health authorities and Taiwan CDC: 1) pilot test

and subsequently scale up new diagnostics for the diagnosis of tuberculosis and drug-resistant tuberculosis; 2) investigate health system delay in the diagnosis and treatment of tuberculosis; 3) critically evaluate the quality and impact of DOT; 4) strengthen surveillance of drug-resistant tuberculosis; 5) address risk factors and social determinants of tuberculosis, and 6) seek consensus on the role of treatment of latent infection with *M. tuberculosis* in the tuberculosis program in Taiwan.

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