EVALUATION ON THE EFFECTIVENESS OF DIRECTLY OBSERVED TREATMENT SHORT COURSE AMONG NEWLY DIAGNOSED TUBERCULOSIS PATIENTS AT THE CHEST SERVICE, DEPARTMENT OF HEALTH, HONG KONG, 1996

by

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A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

Department of Health Care and Epidemiology;
Health Services Research Programme

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August 2000

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ABSTRACT

Setting:
The Chest Service, Department of Health, Hong Kong, 1996.

Problem:
The notification rate of tuberculosis in Hong Kong has failed to decline since 1990 and has remained persistently high since then. The notification rate of 1996 was 103/100,000 population, ten times those of the industrialized countries.

Objectives of the study:
1. To study the trend of tuberculosis in the past four decades
2. To determine the outcome of the tuberculosis treatment program in a random sample of patients

Study design:
Retrospective cohort study among newly diagnosed tuberculosis cases in 1996.

Results:
1. Tuberculosis notification rate has been increasing from 103/100,000 population in 1996 to 115/100,000 in 1998 (10 times those in the developed countries)
2. Age and sex differences were prominent in the distribution of tuberculosis patients in 1996
3. There were high-risk groups, namely patients with diabetes mellitus, silicosis, and alcoholism
4. The treatment completion rate at 6 and 12 months among sputum smear positive tuberculosis patients were significantly lower than the rate of 85% ($p < 0.05$) targeted by the IUATLD and the WHO for developing countries
5. Relatively high treatment default rate (8.4% of all cases) at 12 months
6. The prevalence of resistance to any four first line tuberculosis drugs was higher than other industrialized countries
7. Despite the adoption of the multiple drug treatment for 6 months since 1989, about half of tuberculosis patients received treatment for longer than 6 months
8. Only 34.4% of tuberculosis patients had fully supervised treatment

Recommendations:
1. Ensuring that every patient receives treatment through DOT in order to increase treatment completion rate
2. Reducing the number of defaulters by expanding incentives and enablers programs given to the patients
3. Focusing resources to reduce tuberculosis incidence among the elderly by conducting a pilot screening program for tuberculosis among residents in old age homes
4. Improving the adherent to treatment by enforcing the policy of 6 months chemotherapy
5. Increasing the awareness among health care professionals about the high prevalence of tuberculosis especially among the elderly
6. Development of an evaluation database on all patients being treated for tuberculosis

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like this opportunity to acknowledge the interest and support of a number of people in the preparation of this thesis. First I wish to extend most grateful thanks to my supervisors Prof. Moira Chan-Yeung, Prof. Joseph K.H. Tan, Prof. Donald A. Enarson and Prof. Kevin R. Elwood for their guidance, patience and attention to detail. I am most indebted to Prof. Moira Chan-Yeung from whom the idea of this study emerged as well as for providing me with financial support to do this study.

I am indebted to Dr. C.M. Tam of the Government Tuberculosis and Chest Service, Department of Health, Hong Kong who gave me the opportunity to collect and analyze the Chest Service data. I would also like to thank the staff in the general offices and public health units of all chest clinics, especially Ms Lucia Ku and others at the TB and Chest Service Headquarter, for their consistent and tireless effort in helping me with searching for medical records, sending and filing them. Without their efficient assistance, this thesis will not be possible.

Chest clinic	*Officer in Charge*	*Nursing officer*
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Wanchai	Mr. K.Y. Mok	Ms. Jenny Ng
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Yung Fung Shee	Mr. K.S. Yan	Ms. Ellen Yuen
South Kwai Chung	Mr. K.C. Chung	Ms. K. Chan
Yan Oi	Ms. M.K. Ng	Ms. Grace Wong
New Territory	Mr. M.B. Cheung	Ms. S.M. Lam and Ms. Maggie Kwan
Tung Chung	Ms. Jennifer Tang	Ms. M.L. Wong

Appreciation is also extended to Dr. J.M. Fitzgerald of Tuberculosis Unit, BC Centre for Disease Control who first introduces me to research on tuberculosis.

Finally I must express my deep and heartfelt thanks to my mother in law Oni Kurniawan and my brother in law Sutedjo Lubiantoro who took care of my wife and infant daughter when I was away doing this research. To Lisa and Amelia, this work is for you.

CHAPTER I

A BRIEF REVIEW ON TUBERCULOSIS

1.1. INTRODUCTION

Tuberculosis (TB) is a chronic bacterial infectious disease that is believed to have plagued mankind since Neolithic times[1]. During the medieval times, the TB epidemic was highly lethal, and was called as 'the Great White Plague'. TB death rate has been steadily declining since the beginning of this century and the decline accelerated after the introduction of anti TB chemotherapy between 1947 and 1952. When anti-TB drugs were first introduced, it was thought that the eradication of TB was within easy reach. Unfortunately, the current available data indicate that tuberculosis is still a major public health problem worldwide.

In this chapter, the epidemiology, disease transmission, pathogenesis, clinical manifestation, treatment and prevention of tuberculosis will be reviewed.

1.2. BURDEN OF THE DISEASE

TB remains one of the deadliest diseases in the world. The World Health Organization (WHO) estimates that at least 3 billion people in the world have been infected with Mycobacterium (M.) tuberculosis, the most important bacterium that causes TB infection and disease. Each year more than 8 million new cases of TB occur with approximately 3 million people dying from the disease[2]. TB was reported as the most frequent cause of death among persons aged 15 – 49 years. In 1993, WHO declared TB as a 'Global Emergency'[3].

TB is a disease with social implications. It has always occurred disproportionately among the disadvantaged such as the poor, malnourished, and the homeless. As can be seen from Tables 1.1 and 1.2, 95% of TB morbidity and mortality occur in developing countries where few resources are available to ensure proper treatment. These problems are compounded by the emergence of HIV epidemic especially in the African region[4]. With the emergence of HIV epidemic, the incidence rate of TB has increased since 1984 in some countries. The increase in TB incidence was particularly high in Africa (58 per 100,000 in 1983-1987 to 72 per 100,000 in 1990) and South East Asia (82 per 100,000 in 1983-1987 to 110 per 100,000 in 1990).

Poor case management, emergence of HIV epidemic and the rise in the incidence of drug resistance have threatened to aggravate the TB problem globally. The failure of self-management TB treatment policy has been shown to be the cause of an increase in the prevalence of infectious cases[5]. This failure has shifted management policy into a directly observed treatment. Inadequate treatment, due to patients or doctors deficiency, has been shown to increase the incidence of drug resistance TB[6]. HIV infection is the strongest risk factor identified for latent TB infection to develop into active TB disease. It has also been shown that HIV increases the risk of tuberculosis infection, either in developing or developed countries[7,8].

1.3. CAUSES AND DISEASE TRANSMISSION

Three related bacteria, M. tuberculosis, M. africanum and M. bovis, are responsible for the development of TB; of these M. tuberculosis is the most common. M. africanum is rarely found outside northwest of Africa and disease due to M. bovis is limited due to pasteurization or boiling of milk as well as an effective TB control for cattle[9]. BCG is a live-attenuated strain of M. bovis and is used as a vaccine for TB.

TB is spread from person to person through the air by droplet nuclei (i.e. particles 1 to 5 μm in diameter) that contain M. tuberculosis complex[10]. These droplet nuclei are produced when patients with pulmonary and laryngeal TB cough, sneeze, speak or sing. It can also be produced through aerosol treatments, sputum induction, aerosolization during bronchoscopy or through manipulation of the lesions in hospitals or laboratories.

Droplet nuclei containing 2 to 3 bacilli are so small that regular air current movement in a room can keep them afloat for a long time[11]. They are small enough to reach alveoli where the bacteria then replicate themselves. Although TB patients also generate larger particles containing numerous bacteria, these particles do not function as effectively as the droplet nuclei as media for disease transmission. Larger particles do not remain airborne as long as the droplet nuclei. Furthermore, large particles cannot reach the alveoli because of their size and are mostly trapped in the mucous blanket of the wall of the airway and carried to the oropharynx where they are being swallowed or expectorated[12].

Four factors determine the likelihood of M. tuberculosis transmission: the number of organisms being expelled into the air; the concentration of the organisms in the air determined by the volume of the space and its ventilation; the length of time a person inhales the contaminated air and the immune status of this person. Immunocompromised people are

more likely to become infected with M. tuberculosis and to develop disease after exposure than people with normal immunity[13].

Given the way TB is transmitted, techniques that can reduce the number of droplet nuclei, such as ventilation with fresh air, are very important in health care settings. Ultraviolet irradiation of air in the upper part of the room has been shown to reduce the number of tubercle bacilli. The most important method of eliminating TB transmission, however, is still effective chemotherapy of patients with active disease[14].

1.4. PATHOGENESIS OF THE DISEASE

Once droplet nuclei with the bacilli are being inhaled into the lung, the bacteria are implanted in a respiratory bronchiole or alveolus. Whether or not these bacteria would cause infection in the lungs depend on the virulence of the organisms and the inherent microbicidal ability of the alveolar macrophages that ingest them[10]. If the bacteria can survive this initial body defenses, it will multiply within the alveolar macrophage and divide very slowly. Within 2 to 12 weeks the bacteria can grow into 10^3 to 10^4 in number, sufficient to elicit a cellular immune response that can be detected by tuberculin skin test[15]. M. tuberculosis does not produce any known endotoxins or exotoxins; thus there is no immediate host response to the infection.

Before the host develops cellular immunity, the bacilli spread via the lymphatic system to the hilar lymph nodes and then through the blood stream to distant sites. Certain organs and tissues, such as liver, spleen and bone marrow, are more resistant to further multiplication of the bacilli. Other organs and tissues, such as upper lung zones, kidneys, bones and brains, are more susceptible to the multiplication of bacilli until specific cellular immunity limits their growth. Granulomata, which consist of activated T-cells and macrophages to limit the multiplication of M. tuberculosis, are then formed. For the majority of individuals with normal immune function, proliferation of the bacilli is arrested once cell-mediated immunity has developed[10]. The majority of chest TB infection causes no symptoms and may not be evident radiologically. A primary complex can sometimes be seen on chest x-rays [16]. Most commonly, a positive tuberculin skin test is the only sign that M. tuberculosis infection has occurred. These individuals with latent TB infection are not infectious and do not transmit the disease. Approximately 10 - 15% of individuals infected with M. tuberculosis will develop tuberculosis disease in their lifetime if they do not receive preventive chemotherapy; half of them will likely occur in the first 2-year after infection[17]. The risk of

developing disease is higher among those with silicosis, diabetes mellitus and diseases associated with immunosuppresion such as HIV infection, as well as individuals on immunosuppresive drugs and corticosteroids.

In persons with intact cell-mediated immunity, this response to infection with M. tuberculosis provides protection against re-infection. The likelihood of re-infection is a function of the risk of re-exposure, the intensity of such exposure and the integrity of the immune system. In a healthy individual who has been previously infected, any organism that is deposited in the lung is likely to be killed by the cell-mediated immune response. Clinical and laboratory evidence has indicated that disease produced by the inhalation of a second strain (re-infection) is uncommon, except among those with HIV infection[18].

1.5. DIAGNOSIS OF TUBERCULOSIS

The diagnosis of tuberculosis can be established by demonstrating the presence of tubercle bacilli on smear and culture examination, chest x-ray, or by tuberculin skin testing[19].

The detection of acid-fast bacilli in stained smears examined microscopically provides the first bacteriological evidence of mycobacterial infection. Two procedures are commonly used for acid-fast staining: carbolfuchsin method that includes Ziehl-Nielsen or Kinyoun method or fluorochrome method using auramine-O.

All specimens suspected to contain mycobacteria should be cultured as culture can detect much smaller number of bacteria than smear (as few as 10 bacteria/ml specimens). Species identification and drug susceptibility testing should also be carried out. Three different types of traditional culture media are available: egg based (Lowenstein-Jensen), agar based (Middlebrook 7H10 or 7H11) and liquid (Middlebrook 7H12). It usually takes 3 – 8 weeks before we can see any bacterial growth in these media. The development of automated culture systems, such as BACTEC 460, MGIT system, ESP Myco-ESPculture System II and BacT/ALERT MB Susceptibility Kit, allows rapid growth of bacilli within 1 – 3 weeks[16].

Specimens for mycobacterial testing can be obtained from sputum and other bodily fluid or tissue biopsy of the affected area. Sputum can be obtained directly or through sputum induction. Gastric aspiration, bronchial washings and bronchoalveolar lavage and/or transbronchial biopsy can also be obtained for patients with pulmonary disease. Other bodily fluid such as urine, blood, cerebrospinal fluid, pleural, peritoneal and pericardial fluids can be similarly processed for smear and culture. As well, tissue biopsy, such as from

lung, pericardium, lymph nodes, bone and joints, bowel, salpinges and epididymis should be considered when non-invasive techniques do not provide a diagnosis.

Chest x-ray is the most common diagnostic test. Standard antero-posterior and lateral views, sometimes with apical lordotic views are recommended. In developed countries, CT scan may identify organ involvement or cavitation in the lungs.

Nucleic acid amplification and hybridization, and high-performance liquid chromatography to identify bacterial cell wall's mycolic acid allow direct identification of mycobacterium species.

Skin testing for TB originated with Koch's discovery of old tuberculin in 1891. It involves intradermal injection of purified proteins derived from autoclaved tuberculosis bacteria (PPD), either by Mantoux or Tine methods. Even though tuberculin test was developed since 19th century, the interpretation of this test remains controversial[10]. There are 3 indications for tuberculin skin testing: to diagnose tuberculosis infection, to diagnose the disease and to act as an epidemiological tool[21]. The clinical utility of tuberculin skin test to diagnose disease is low due to the likelihood of false positive (i.e. high prevalence of TB in the community, prevalence of non-tuberculous mycobacteria, previous BCG vaccination) or false negative (i.e. severely ill patients, HIV infected patients) of the test. Even so, tuberculin skin testing has been proven to be an invaluable epidemiological tool in defining and understanding the epidemiology of TB and spread of the infection.

1.6. CLINICAL MANIFESTATION

The clinical manifestations of tuberculosis vary and depend on numerous factors. These include host factors, such as age, immune status, co-morbid illness and BCG status; microbial factors such as the virulence of the organisms and their predilection for certain tissues; and host-microbe interaction such as the site of involvement and the severity of the disease. The disease can affect the lungs and other organs (extra-pulmonary). Before the era of HIV infection, 80%-85% of TB cases were limited to the lungs and the remaining 15%-20% involved extra-pulmonary organs only or involving pulmonary and extra-pulmonary sites[19,22].

Primary TB is by definition the result of the progression of active disease directly from initial infection with M. tuberculosis. While most initial infections are asymptomatic and controlled by cell-mediated immune response, some patients may develop nonproductive cough, fever and a characteristic abnormality on the chest x-ray. The primary lesion

frequently resolves spontaneously, but reactivation occurs in 50-60% of patients who do not receive appropriate treatment. The number of bacilli present during active primary TB is thought to be low, and bacteriologic examination is frequently negative. Another manifestation of primary TB is tuberculous pleuritis, which occurs as the primary manifestation of TB in about 10% of cases[19]. In the past, tuberculous pleuritis was more frequently seen in children and young adults, but in recent times it affects mostly those older than 50 years. The natural history of this disease is spontaneous resolution with a high likelihood of reactivation[19].

Reactivation of TB is the most common form of the disease. It represents reactivation of latent infection weeks to years after the primary infection. It occurs in the upper lung zones. Multiplication of bacilli is re-initiated and causes enlargement of a previously dormant lesion. This process causes tissue destruction and caseation or liquefaction. Further bacterial growth is enhanced. Rupture of the caseous area creates a cavity that is considered a classical manifestation of adult tuberculosis[19].

Miliary TB may develop as a result of primary or reactivation of TB. The disease occurs from uncontrolled hematogenous dissemination in patients with inadequate cell-mediated immunity. It occurs mostly in infants and children less than five years of age, seniors, alcoholics, those with neoplasm, HIV infected and other immunologically compromised individuals[19].

About 15% of patients with active TB have extra-pulmonary TB. The sites most commonly involved include lymph node, pleural space, genito-urinary tract, bone and joint, meninges and in the gastrointestinal tract (including peritoneum). The likelihood of extra-pulmonary TB increases in immunocompromised individuals. The most infectious form of extra-pulmonary TB is laryngeal TB, which usually occurs as a result of lower airway disease. About 25% of extra-pulmonary cases have a previous history of TB which was inadequately treated[23]. Tuberculous lymphadenitis is the most common form of TB disease outside the lungs and is responsible for about 25% of extra-pulmonary cases.

Genito-urinary TB occurs in about 15% of extra-pulmonary TB. The disease can affect the urinary system (kidney) and genital system separately or together.

About 6% of extra-pulmonary TB affect the bones and the joints. Pott's disease is TB of the spine. At present, skeletal involvement most often occurs in the middle aged and HIV infected patients[23].

Meningitis accounts for about 5% of extra-pulmonary cases and is becoming less common. The disease predilection has shifted from children to the elderly and HIV infected patients. The mortality due to TB meningitis is about 20%[23].

Tuberculous involvement of pericardium usually results from prior hematogenous dissemination and latent reactivation of a pericardial focus. It can also be the result of spread from adjacent lung or mediastinal nodes. Without treatment, the mortality of tuberculous pericarditis is about 80%[23].

Gastro-intestinal involvement of TB can affect any area of the gastro-intestinal tract. Ileocecal involvement and tuberculous peritonitis are the most frequent manifestations. In the past, ileocecal TB was common and resulted from drinking milk containing tubercle bacilli.

1.7. TREATMENT OF ACTIVE TUBERCULOSIS

Tuberculosis treatment has evolved over time, from appeasing the supernatural spirit, bed rest and fresh air in sanatoria to modern chemotherapy[1]. Research in TB treatment has served as an important and inspirational model of how well-designed clinical trials could address important practical problems facing medical practitioners and public health officials[30].

Effective TB treatment began since the introduction of streptomycin (S) in 1944. Used alone, S was found to be highly effective at producing a clinical and bacteriological response. However, this was followed quickly by clinical deterioration and the emergence of drug resistance. After the introduction of para-aminosalicylic acid (PAS) (1948) and isoniazid (H) (1952), the emergence of drug resistance was reduced and when used in combination with S, treatment effectiveness was close to 100%[31]. Standard regimens of 18 – 24 months of combination of H, PAS and S proved to be highly effective in treating cavitary TB and preventing drug resistance. With the introduction of Rifampin (R) in 1968, shorter duration of TB chemotherapy became possible. The modern era of TB treatment began with the first series of East African/British Medical Research Council studies. This international collaboration trial and the subsequent trials demonstrated that the addition of R to H and S allowed a dramatic reduction (from 18 to 6 months) in the duration of drug therapy required to obtain a cure rate of $\geq$ 95%, the consensus 'gold standard'[32].

There are three aspects of drug activity that are relevant in treating TB; early bactericidal activity, sterilizing activity and the prevention of drug resistance. Early bactericidal activity

is the ability of a drug to reduce the number of bacilli during the early part of treatment. Sterilizing activity is the ability of the drug to kill semidormant bacteria, while the prevention of drug resistance amounts simply to suppress the growth of the entire bacterial population to prevent the emergence of bacterial mutation resistant to TB drugs[33,34]. These three aspects are important in counteracting the characteristics of mycobacteria, that is a very slow generation time, long periods of metabolic inactivity and the natural presence of drug resistance mutant in very small numbers in TB patients[35].

Table 1.3[9,30,35] summarizes the drugs used for TB treatment, the mechanism of action and their side effects. These drugs are divided into first- and second-line drugs of choice. The first-line drugs are more effective. Second-line drugs are being used in patients who have drug resistance or intolerance to the first-line drugs. Second-line drugs are not as effective as the first-line drugs and are more costly as well as having more side effects.

Due to the characteristics of the mycobacteria, TB is one of the few diseases that require a prolonged period of treatment[35]. The current standard treatment is to give medications for 6 months (short course chemotherapy) or longer and in 2 phases: initiation/initial and continuation/maintenance phase. During the initiation phase, combination of three or more drugs is being given for 1 – 2 months. The continuation phase usually involves giving 2 drugs for a period of 4 months or more. The prolonged period of treatment, the presence of side effects and the number of drugs to be taken together at the same time have led to a high probability of non-adherence[36].

Sbarbaro[37] reviewed published literature on patients' behavior towards treatment. About 4 – 100% of patients failed to adhere to medical advice; 20 – 82% failed to take medicine properly and 25 – 59% took their medication but administered it in the wrong way. He estimated that between 30 – 35% of patients would fail to follow physicians' recommendations. Studies on PAS first brought attention to non-adherence among TB patients. Only 50% of outpatients prescribed PAS had a positive urine test for metabolites of the drug[37]. Among hospitalized patients, Lepehne[37] demonstrated that 40% of patients were not taking PAS delivered to them by the hospital staff. Studies on treatment with H (Fox et al and Moulding et al), and E (Wiant et al) also found similar behavior of non-adherence when drugs were self-administered[37]. Sbarbaro concluded that adherence decreases as the treatment is prolonged and regimens become more complicated.

Non-adherence to self-administered multi-drug treatment regimens is common and is the most important cause of failure of initial treatment, persistent infectiousness and a high

relapse rate. Non-adherence may also result in the emergence and transmission of acquired drug resistance TB. Drug resistance TB requires more prolonged and expensive treatment that is also less likely to succeed[38-43]. In response to these findings, the World Health Organization[44] and the International Union Against Tuberculosis and Lung Diseases[45] stated that directly observed treatment strategy (DOT) is the best method to ensure adherence in TB treatment. In DOT, a health care worker or designated person observes the ingestion of each dose of anti-tuberculosis treatment. The adoption of DOT has been associated with reduced rates of treatment failure, relapse and development of drug resistance TB[36].

Table 1.4 provides a summary of various studies assessing the effectiveness of DOT. These studies were conducted among different populations but they all showed treatment completion rates from 85.0 % to 96.5%. With the exception of the study conducted in the Philippines[49] where the prevalence of drug resistance (single and multiple) was high, DOT yielded relatively low relapse rates (0% - 4.5%).

According to the WHO [62], the effectiveness of a chemotherapy program is determined by two factors i.e. the cure rate and the rate of acquired drug resistance. The cure rate functions as an indicator of program performance and is inversely related to the rate of acquired drug resistance. A high cure rate also eliminates sources of infection, thus reducing the incidence of TB. Further the WHO stated that the main goal of a TB control program is to achieve at least 85% cure rate in developing countries, and 90-95% cure rate in developed countries.

Various combinations of drug regimens for TB have been proposed and tested in clinical trials[63-79]. These studies showed cure rates to be greater than 85%, which are higher than the WHO's target[44], and relapse rates between 2% - 24% across different follow-up periods. In general, short course chemotherapy consists of an initial treatment using 3 - 4 drugs (H, R, Z and E or S) taken daily for 1 to 2 months followed by 2 drugs (H and R) either taken daily or 2 to 3 times weekly for 4 to 5 months. The WHO[62] and the IUATLD[45] both recommend a 6-month chemotherapy consisting of daily H, R, Z and E or S for 2 months follows by H and R 3 times weekly for 4 months.

1.8. TUBERCULOSIS PREVENTION

In order to control TB, it is vital to reduce the transmission of M. tuberculosis from infectious cases to reduce the risk of infection in the community. It is necessary to find all

active cases and to cure every active case with appropriate treatment, thereby reducing the replenishment of the infected pool. These measures will ensure a continuous reduction in TB morbidity and mortality.

General prevention of tuberculosis can be done in 2 ways: vaccination and secondary chemoprophylaxis for those with latent TB infection. Bacille Calmette-Guerin (BCG) is named after two French researchers who developed the live, attenuated strain of M. bovis in 1921. It is currently included in the WHO Expanded Programme on Immunization. BCG is being used as a vaccine to prevent TB in areas in the world with high disease prevalence.

Despite its use in millions of people globally, the efficacy of the BCG vaccine is still uncertain[24]. The results of many studies suggest that it prevents miliary tuberculosis and tuberculous meningitis in children, but protection against pulmonary TB has not been proven. Numerous trials have been conducted and the results varied, from up to 80% protection to an increased in the disease susceptibility among those vaccinated. In Canada, BCG vaccination is recommended for newborn infants of Inuit and Status Indians especially those on the reserve[21]. Mass BCG vaccination is only being carried out in Quebec and Newfoundland.

Various studies have been done to assess the efficacy of treating latent tuberculosis infection[25]. A study conducted by the International Union Against Tuberculosis and Lung Diseases (IUATLD), the largest of such preventive study so far, has demonstrated a reduction of confirmed TB cases from 21% to 75% depending on the duration of drug taken[27]. A cost-effectiveness analysis by Fitzgerald et al [28] has shown that the costs incurred per case of TB prevented were reasonable from a societal perspective. Isoniazid (INH), daily or twice weekly for 6 to 9 months, has been prescribed as the drug of choice for chemoprophylaxis. Recently, a shorter course of treatment (2 months, Rifampin (R) and Pyrazinamide (Z), daily) has also been shown to be effective in reducing the advancement of TB infection into disease among those HIV-infected[29].

On a global scale, treatment of latent TB infection is a relatively uncommon TB control strategy. In developing countries with limited resources, the highest priority is case detection and treatment of active cases. In industrialized countries, such as in Canada and the US, treatment of latent TB infection is an important and effective component of TB control program[25]. Recently, the American Thoracic Society together with the Centers for Disease Control and Prevention issued a joint statement on the treatment of latent TB infection[26].

1.9. CONCLUSION

In this era of advanced medical technology, tuberculosis still remains as one of the most important plague for humankind. The World Health Organization (WHO) estimates that at least three billion people in the world were infected with M. tuberculosis. Each year more than eight million new cases of TB occur. Approximately three million people die from the disease. TB was reported as the most frequent cause of death among persons aged 15 – 49 years.

M. tuberculosis is transmitted from person to person via droplet nuclei. Human body reacts to TB infection through the cell-mediated immune response. Individuals with immunocompromised immune system may develop a more severe disease. TB is diagnosed through the identification of M. tuberculosis in smear and culture examination of sputum or other bodily fluid or through chest x-ray. TB, as a disease entity, can affect various parts of body organs. About 80% - 85% of TB affects lung.

Due to the characteristics of mycobacteria, TB treatment requires a prolonged treatment time using a combination of drugs. These drugs have side effects, especially when in use for such a long time. Prolonged treatment time, treatment side effects and the amount of drugs to be taken each time, has led to a high probability of non-adherence. Non-adherence leads to failure of initial treatment, persistent infectiousness, high relapse rate and the emergence and transmission of acquired drug resistance TB.

In order to achieve a high treatment completion rate, the WHO and the IUATLD both proposed the adoption of DOT as the mode of treatment delivery for TB. DOT has shown to be the best mode of treatment delivery in achieving a higher treatment completion rate. Treatment of choice for drug susceptible TB is a combination of 3 - 4 drugs (H, R, Z and E or S) taken daily for 2 months followed by 2 drugs (H and R) taken 3 times weekly for 4 months.

BCG vaccination and chemotherapy of latent TB infection are parts of TB control program. Even though BCG vaccination has been done among millions of people worldwide, its efficacy in preventing pulmonary TB is still questionable. Six to nine months, daily or twice weekly INH has been shown to reduce the advancement of TB latent infection into TB disease. Recently, trial on two months RZ daily has been shown to reduce the advancement of latent TB infection among HIV-infected persons.

Table 1.1 Estimated TB incidence and HIV-attributable TB cases in 1990, 1995 and 2000.

Region	1990			1995			2000		
	Total TB cases	Rate [a]	HIV attributed	Total TB cases	Rate [a]	HIV attributed	Total TB cases	Rate [a]	HIV attributed
South East Asia	3 106 000	237	66 000	3 499 000	241	251 000	3 952 000	247	571 000
Western Pacific [b]	1 839 000	136	19 000	2 045 000	140	31 000	2 255 000	144	68 000
Africa	992 000	191	194 000	1 467 000	242	380 000	2 079 000	293	604 000
Eastern Mediterranean	641 000	165	9 000	745 000	168	16 000	870 000	168	38 000
Americas [c]	569 000	127	20 000	606 000	123	45 000	645 000	120	97 000
Eastern Europe [d]	194 000	47	1 000	202 000	47	2 000	210 000	48	6 000
Industrialized countries [e]	196 000	23	6 000	204 000	23	13 000	211 000	24	26 000
Total	7 537 000	143	315 000 (4.2%)	8 768 000	152	738 000 (8.4%)	10 222 000	163	1 410 000 (13.8%)
Increases since 1990				16.3%			35.6%		

[a] crude incidence rate.
[b] includes all countries of the Western Pacific region of WHO, except Japan, Australia and New Zealand.
[c] includes all countries of the American region of WHO, except USA and Canada.
[d] Eastern European countries and independent states of the former USSR.
[e] Western European countries, USA, Canada, Japan, Australia and New Zealand.

Source: Dolin PJ, Raviglione MC, Kochi A. (1994) Global tuberculosis incidence and mortality during 1990-2000. Bull of the World Health Organization.

Table 1.2 Estimated total TB deaths and HIV-attributable TB deaths in 1990, 1995 and 2000 assuming that regional treatment coverage rates remain at 1990 level.

Region	Deaths 1990		Deaths in 1995		Deaths in 2000	
	Total	HIV attributed	Total	HIV attributed	Total	HIV attributed
South East Asia	1 087 000	23 000	1 225 000	88 000	1 383 000	200 000
Western Pacific [a]	644 000	7 000	716 000	11 000	789 000	24 000
Africa	393 000	77 000	581 000	150 000	823 000	239 000
Eastern Mediterranean	249 000	4 000	290 000	6 000	338 000	15 000
Americas [b]	114 000	4 000	121 000	9 000	129 000	19 000
Eastern Europe [c]	29 000	< 200	30 000	< 600	32 000	< 900
Industrialized countries [d]	14 000	< 500	14 000	1 000	15 000	2 000
Total	2 530 000	116 000 (4.6%)	2 977 000	266 000 (8.9%)	3 509 000	500 000 (14.2%)
Increases since 1990			17.7%		38.7%	

[a] includes all countries of the Western Pacific region of WHO, except Japan, Australia and New Zealand.
[b] includes all countries of the American region of WHO, except USA and Canada.
[c] Eastern European countries and independent states of the former USSR.
[d] Western European countries, USA, Canada, Japan, Australia and New Zealand.

Source: Dolin PJ, Raviglione MC, Kochi A (1994). Global tuberculosis incidence and mortality during 1990-2000. Bull of the World Health Organization.

Table 1.3 First-line and second-line drugs use in treating tuberculosis.

Drugs	Abbreviation	Activity*	Known side effects
First line drugs			
1. Isoniazid	H	1, 3	drug induced hepatitis; peripheral neuropathy; Systemic Lupus Erythematosus like syndrome; hypersensitivity reaction: rash, fever; elevation of phenytoin level
2. Rifampin	R	1, 2, 3	drug induced hepatitis; hypersensitivity reaction: fever, flue-like symptoms, thrombocytopenia; gastro-intestinal (GI) upset; drug interactions
3. Pyrazinamide	PZA	1, 2, 3	drug induced hepatitis; uric acid elevation
4. Streptomycin	S	1, 2, 3	vestibular dysfunction; renal dysfunction
5. Ethambutol	E (or M)	1, 2, 3	optic neuritis
6. Thioacetazone	THA (or T)	1, 2, 3	Steven-Johnson syndrome; toxic epidermal necrolysis; exfoliative dermatitis
Second line drugs			
1. Cycloserine	-	4	psychosis; convulsions; depression; headache, rash; drug interactions
2. Ethionamide	ETH	4	drug induced hepatitis; GI upset; hypersensitivity; bloating; metallic taste
3. para-Amino-salicylic acid	PAS	1,3	drug induced hepatitis; hypersensitivity; GI upset
4. Capreomycin	-	5	auditory, vestibular and renal toxicities; hypokalemia; hypomagnesia
5. Kanamycin/Amikacin	-	4	auditory, vestibular and renal toxicities
6. Fluoroquinolones incl. Ciprofloxacin, Ofloxacin, Levofloxacin, Sparfloxacin.	-	4	GI upset; dizziness; hypersensitivity; headaches; restlessness; drug interactions

* Activity 1 = early bactericidal, 2 = sterilizing, 3 = preventing drug resistance, 4 = bactericidal, 5 = unknown (relative activities and the severity of side effects of these drugs vary).

Source: Fujiwara PI, Simone PM and Munsiff SS. (1999) Treatment of tuberculosis.

Table 1.4. A summary on the evaluation of the effectiveness of DOT on tuberculosis treatment completion.

Reference no.	Population	Size	Treatment completion (%)	Drug resistance at time of th/ (%)		Relapse during follow-up (%)
				SDR	MDR	
46	Thailand, 1981	929	93.5			0
47	South Africa, 1987	536	92.3			1.5
48	South Africa, 1991	814	89.1			
49	Philippines, 1985	144	90.2	26.0	54.0	11.5
50	Thailand-Cambodia refugee camp, 1981	58	92.7			1.7
51	New York, 1992	113	90.2	22.0	11.0	3.3
52	Rural Beijing, 1978	229	89.5	10.0	7.0	2.1
53	Harlem, NY, 1993	95	88.4	23.9	9.8	1.1
54	Baltimore, 1981	486	90.2		< 0.5	
55	Chicago, 1978	184	86.0			0
56	Hong Kong, 1983	1616	93.0	8.2	2.8	3.7
57	South Carolina, 1986	1521	96.5			
58	South Africa	150	85.5			4.3
59	Denver, 1981	160	86.2			1.6
60	Spain, 1990	102	85.2			3.4
61	Rural Hong Kong, 1979	250	85.0			0.8

Th/. = treatment. SDR = Single Drug Resistance. MDR = Multiple Drug (≥ 2) Resistance

CHAPTER II

TUBERCULOSIS IN HONG KONG

2.1. INTRODUCTION

Tuberculosis is one of the 26 diseases that must be notified by law in Hong Kong. The Department of Health, through the Government Tuberculosis and Chest Service of Hong Kong, is responsible for controlling TB. In addition to the availability of modern medical facilities, patients with TB may receive their initial investigation from herbalists or other traditional medicine practitioners as well.

In this chapter, TB notification and mortality rates, medical services available for the management of TB and the strategy for controlling TB in Hong Kong will be discussed.

2.2. TUBERCULOSIS NOTIFICATION AND MORTALITY IN HONG KONG

The rate of tuberculosis in Hong Kong was very high in the early fifties. It decreased from 697.2/100,000 in 1952 to 100.9 / 100,000 in 1995. This dramatic decrease was attributed partly to socioeconomic improvement and partly to effective TB control programs. The decline in TB notification rate has slowed since 1991. Since 1995, the rate has actually increased from 100.9/100,000 to 103, 108 and 115, in 1996, 1997 and 1998, respectively (Figure 2.1)[80].

Figure 2.2 shows mortality rate attributable to TB in Hong Kong from 1947 – 1997[80], TB mortality rate peaked in 1951 (207.9 per 100,000 population) and has since been declining sharply. Mortality rate due to TB was 3.9 per 100,000 population in 1997. The sharp decline in mortality since 1951 can be attributed partly to the success of modern chemotherapy.

2.3. MEDICAL CARE FACILITIES AVAILABLE FOR TUBERCULOSIS PATIENTS IN HONG KONG

The Government Tuberculosis and Chest Service (Chest Service) of Hong Kong, Department of Health, is responsible for controlling TB. The Chest Service was first established in 1947. Throughout the years, the Chest Service has played a prominent role in the history of tuberculosis research and has taken part in many important clinical trials in collaboration with the British Medical Research Council[61,64,65,66]. These trials have led to

worldwide acceptance of short course multi-drug chemotherapy as the standard treatment of tuberculosis.

The services provided for tuberculosis patients in Hong Kong are comprehensive. In addition to the Chest Service, there are chest hospitals, general hospitals, private practitioners and private hospitals that provide care for these patients. Every year, the Chest Service treats approximately 80 – 90% of all TB cases in Hong Kong. Figure 2.3 shows the available referral patterns for tuberculosis patients[80,82]. Patients can also attend other primary care settings, including general outpatient clinic, accident and emergency department as well as private practitioners.

In 1996, there were 2 consultant chest physicians, 8 senior medical health officers, 21 medical health officers, 14 nursing officers, 53 registered nurse, 128 enrolled nurse and 2 radiographers [80] in the Chest Service responsible for 11 full-time and 6 part-time chest clinics. Each chest clinic is staffed by physicians, nurses, medical social and clerical workers. The physicians provide diagnostic and treatment services on an outpatient basis (for any chest diseases including TB). The nursing staff in the public health team are responsible for health education of patients and their relatives, supervision of DOT and conducting contact and defaulter tracing. The medical social workers counsel patients and provide practical support such as assisting patients to apply for public assistance, including housing and home care.

The chest clinics are distributed throughout the Hong Kong Island, Kowloon and the New Territories. In the Kowloon area there are six full-time chest clinics spread out in East Kowloon, Kowloon, South Kwai Chung, Shek Kip Mei, Yung Fung Shee and Yaumati. In the New Territories, there are two full-time chest clinics in Yuen Chau Kok and Yan Oi. In the Hong Kong Island, there are three full-time chest clinics, including Wan Chai, Shaukiwan and Sai Ying Pun. Part-time chest clinics are available at Castle Peak, Cheung Chau, Sai Kung, Sheung Shui, Tai Po and Yuen Long. There is also a hospital discharge clinic in East Kowloon and Correctional Service Department in Hei Ling Chau, Stanley Prison and Shek Pik Prison. Complemented by a convenient office hours (open 6 days a week with extended hours for DOTS), the large geographical distribution of chest clinics ensures easy access for patients, including those living in smaller islands and other remote areas.

Access to chest clinics can be done through referral by other primary care or secondary care providers in public or private sectors. Patients can walk into the clinic without any

referrals and be seen on the same day. Patients are free to move between clinics for treatment and follow-up visits. Services provided at Chest Service, including prescription drugs, are all free of charge.

Since 1985 there have been about 750,000 to 790,000 patient visits to chest clinics annually, including visits to see doctors and for DOT. Thus, the total number of individuals seen at chest clinics was between 200,000 to 300,000 annually.

The chest clinics work closely with chest hospitals. Any patient with tuberculosis requiring inpatient care is admitted to one of these hospitals. There are five chest hospitals in Hong Kong: Ruttonjee Hospital (157 beds), Grantham Hospital (196 beds), Haven of Hope Hospital (114 beds), Wong Tai Sin Hospital (185 beds) and Kowloon Hospital (128 beds)[82]. Patients are usually admitted for one of the following reasons: diagnostic investigation (e.g. bronchoscopy), management of complications of the disease (e.g. severe haemoptysis), management of complication of treatments (e.g. drug induced hepatitis), management of co-morbid illness (e.g. diabetes mellitus) or adherence problems (e.g. those with mental illness). On discharge, patients who have been admitted into these hospitals (from any other hospitals or chest clinics) are usually referred back to the chest clinics for follow-up and continuation of treatment (they may also be followed up in the specialist outpatient clinics of the respective hospitals). Most hospitals and general practitioners (GPs) refer TB patients to chest clinics due to resources available at chest clinics for DOT and contact tracing. Some patients are being treated in hospitals or by GPs (approximately 5 %). However, the treatment outcomes of patients treated by hospitals and GPs are not available to the Chest Service.

2.4. STRATEGIES FOR CONTROLLING TUBERCULOSIS IN HONG KONG

Tuberculosis control is based on effective chemotherapy, case finding, BCG vaccination, health education and chemoprophylaxis. Of these strategies, the first 3 are widely and comprehensively used in Hong Kong.

Hong Kong started employing DOT for TB treatment since 1970. It was among the first in the world. Public health nurses in chest clinics are responsible for the delivery of DOT program. The clinics are opened for prolonged hours to facilitate the receipt of DOT. Some enablers are being given to those in need, such as help in applying for public assistant and transportation money.

Active case finding is being done through contact tracing and chest x-ray screening of particular populations. About 2 to 3 % of all notified TB cases are identified by contact tracing. Contact tracing is initiated once a TB case has been notified. It is done by examining household members (and close contact in schools, sometimes inmates and staffs of other institutions such as nursing homes) of active TB patients. Contacts younger than 5 year of age are tuberculin tested and examined by chest x-ray; BCG vaccination is offered if tuberculin test is negative (< 10 mm) and there is no sign of disease activity in the chest x-ray. Older contacts are only examined by chest x-ray. Screening is done for employment purposes such as schoolteachers, health care workers and civil servants. It is also being done for immigration purposes, such as those who are migrating overseas. Screening examination is also being done for prisoners and drug addicts on entry to treatment.

The Chest Service provides BCG clinics for vaccination of all newborns, re-vaccination of primary school students age 6 to 10 after tuberculin testing and direct vaccination (i.e. without prior tuberculin testing) of newly arrived refugees age equal to or less than 14 years in the refugee camps. Neonatal BCG vaccination was established in 1952; its coverage is as high as 99%[83]. Hong Kong is one of the few places in the world that still routinely offers BCG re-vaccination to primary school children. The BCG team visits each primary school once every four years to carry out this program. The practice of re-vaccination is currently under review.

Health education, especially for new patients, is the responsibility of public health nurse. Upon diagnosis of TB, the patient is being sent to see a public health nurse. The nurse provides education on transmission of tuberculosis, the importance of taking prescribed drugs for the prescribed period of time, the type of side effects to watch out for, the importance of contact examination and other relevant information. At the same time, the public health nurse collects information on possible contacts. The Department of Health in Hong Kong has been actively broadcasting television advertisement regarding TB symptoms. The advertisement contains advice for people with certain symptoms to seek helps to chest clinics. This form of health education is also being done on the local newspapers.

Even though chemoprophylaxis is largely used in countries such as the US and Canada, it is not widely practiced in Hong Kong.

2.5. CONCLUSION

A comprehensive system for treating tuberculosis patients is available in Hong Kong. The Government Tuberculosis and Chest Service of Hong Kong, Department of Health, is responsible for controlling TB.

The current policy of tuberculosis control in Hong Kong is effective chemotherapy delivered by DOT, passive case finding, newborn BCG vaccination follows by revaccination at school age, and health education. Chemoprophylaxis for those with TB infection is not being widely done in Hong Kong.

The notification rates and the mortality of tuberculosis in Hong Kong have declined dramatically since the 1950s. Hong Kong, however, still has a high incidence of TB being 10 times the rates in industrialized countries. In the past 3 years, the notification rate has been steadily increasing. Thus, it is important to evaluate the TB management program to find out the reason in order to formulate appropriate policy for the control of tuberculosis in the coming decade.

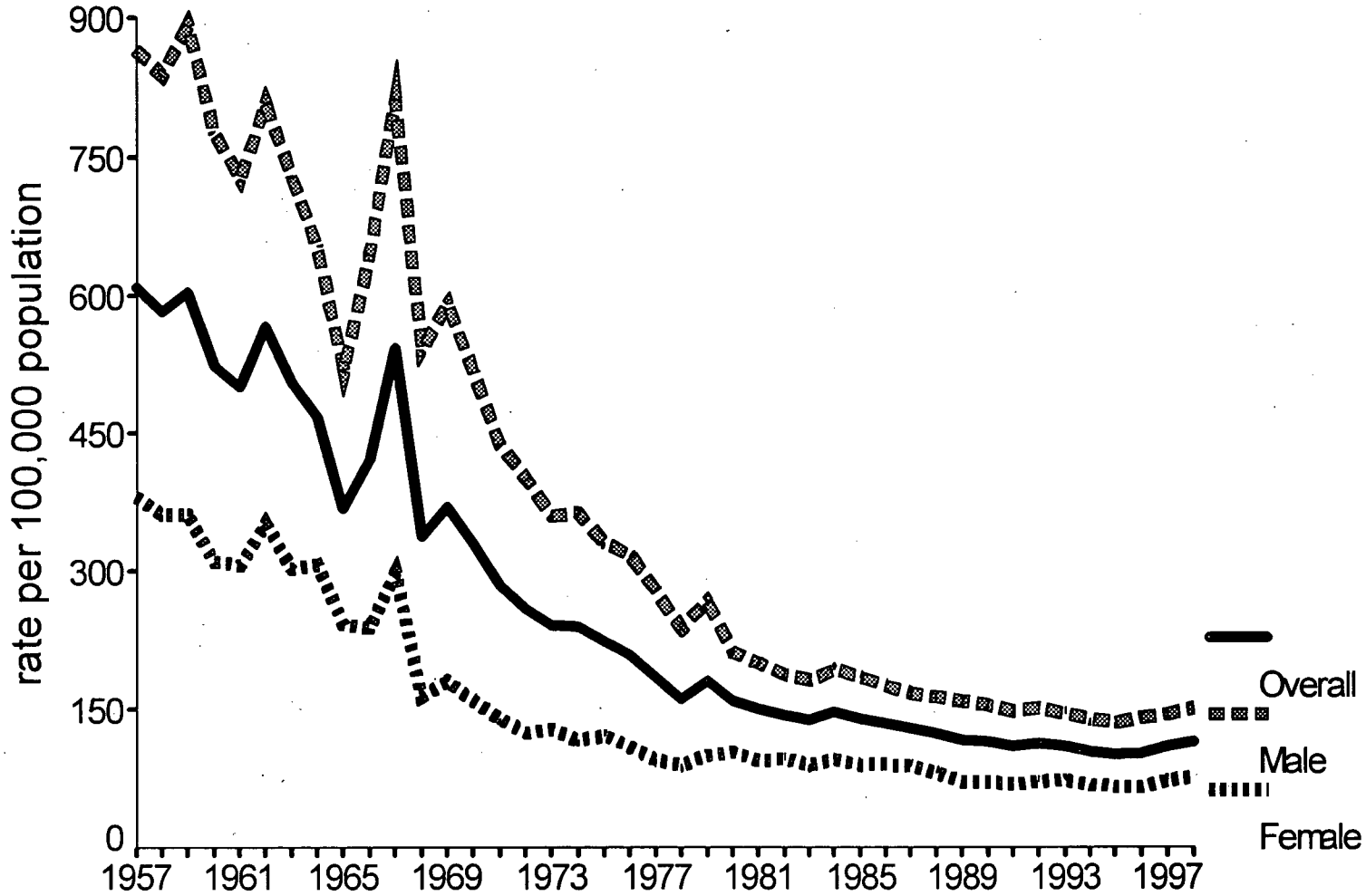


Figure 2.1. Tuberculosis notification rate in Hong Kong (1957 – 1998).

Source: Chest Service of the Department of Health. Hong Kong (1998). Annual Report.

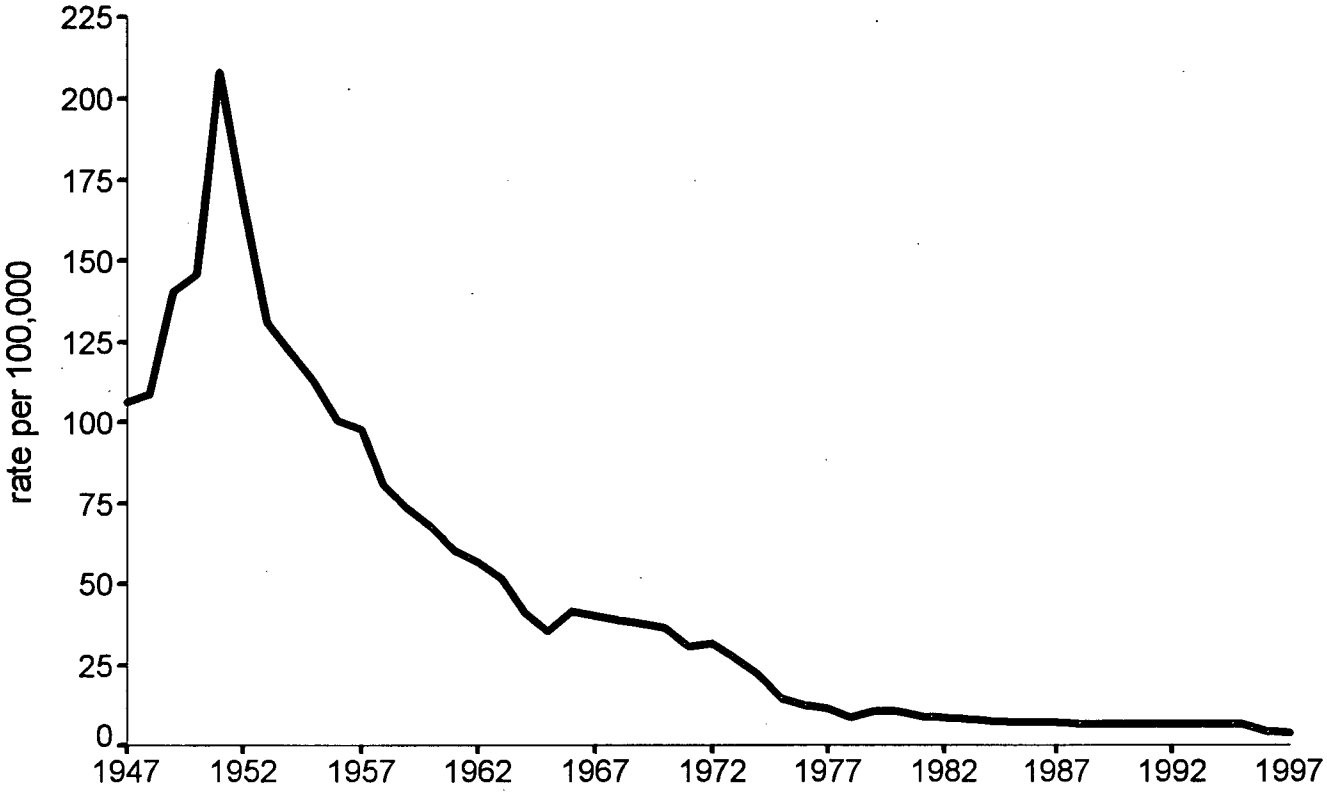
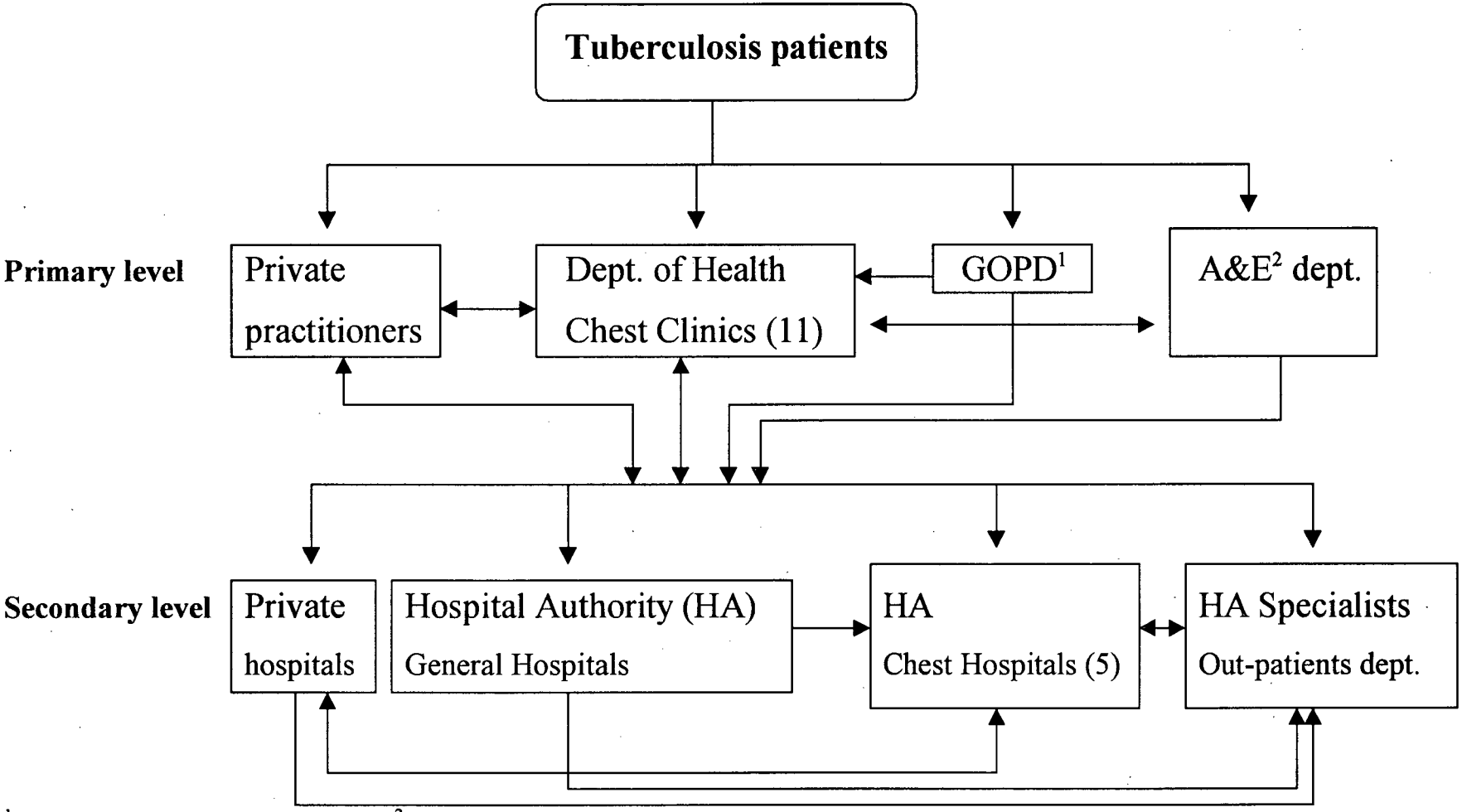


Figure 2.2. Tuberculosis mortality rate in Hong Kong (1947 - 1997).

Source: Chest Service of the Department of Health. Hong Kong (1998). Annual Report.



[1] GOPD = General Outpatient Department. [2] A&E = Accident and Emergency

Figure 2.3. Services available to patients with tuberculosis in Hong Kong (1996).

Source: Faculty of Medicine. Hong Kong University (1996). Tuberculosis in Hong Kong. Course manual.

CHAPTER III

OBJECTIVES, STUDY DESIGN, SUBJECTS AND METHODS

3.1. INTRODUCTION

The notification rate of tuberculosis in Hong Kong has failed to decline since 1990 and has remained persistently high since then. The notification rate of 1996 was 103/100,000 population, ten times those of the industrialized countries. As Hong Kong employs a comprehensive program for the management and control of tuberculosis, it is important to evaluate their current program effectiveness to determine the reasons for the persistent high rates of tuberculosis.

3.2. OBJECTIVES OF THE STUDY

The primary objectives of this study are:

1. To study the trend of tuberculosis in Hong Kong in the past four decades
2. To determine the outcome of the TB treatment program in a random sample of patients who participated in the treatment program offered by the Chest Service in 1996

The secondary objectives are:

1. To determine the factors affecting treatment outcomes
2. To determine the proportion of patients treated by DOT
3. To find out the factors contributing to non-adherence to the treatment program

3.3. STUDY DESIGN

The study design employed was a retrospective cohort study[84]. A cohort of newly diagnosed TB cases in 1996 was constructed and followed for 2 years in order to assess the treatment outcome at 6, 9, 12 and 24 months from the date of initial treatment.

A nested case-control study was conducted to investigate factors contributing to non-adherence to the treatment program. Four randomly selected controls, among those that completed treatment at 12 months and never missed treatment (100% attendance), were drawn for each non-adherent individual (case).

3.4. METHODS

3.4.1. NOTIFICATION DATA

Notification rate of tuberculosis since 1957 were obtained from the Chest Service for the study of the trend of tuberculosis during the past 4 decades.

3.4.2.THE PROGRAM REVIEW FORMS (PRF)

Since 1996, the Chest Service has started requesting physicians in the Chest Service to submit program forms for each patient with tuberculosis at the onset of treatment and at 6, 9 and 24 months after the onset of treatment (PRF 1, 2, 3, 4; appendix 1). These forms were submitted at different times, according to the schedule of treatment, to the TB headquarter at Wanchai. When the project was started in the beginning of January 1999, some of the patients had just completed 24 months follow-up examination.

Form 1 was completed at the onset of treatment. It has the name of the patient, the Hong Kong ID number or passport number if the individual was not a Hong Kong resident and the date of start of treatment. Other demographic information included age, sex, past history of treatment, the type of tuberculosis (pulmonary or extra-pulmonary), the extent of disease (if pulmonary), and the case category (new, relapse, treatment after default, failure of previous regimen and other reasons).

Form 2 was completed at six months. It provides information on the type of drug regimen planned, the frequency of drug treatment, side effects, any change from the original plan of treatment and the reasons for the change, and whether treatment had been completed or not at six months. If treatment had been completed, the proportion of treatment appointments missed by the patient during the 6-month period and the proportion of treatment that was self-administered or administered by other party than the clinic in the 6-month period were also entered.

Form 3 was completed at nine months. It included bacteriologic status before treatment, at two and five or six months from the onset of treatment, sensitivity results, and the treatment outcome of the patient at nine months. The classification of outcome is as follows: cured; treatment completed; still on treatment; changed to be treated by other doctors; defaulted; failure; and died. If treatment had been completed at nine months, the proportion of clinic appointments missed by the patient and the proportion of treatment

given not under direct supervision by chest clinic (self-administered or administered by personnel outside the clinic) were entered.

Form 4 completed at 24 months provided information on the total duration of treatment and the condition at 24 months: cured; treatment completed but relapsed before 24 months; re-treatment after default; if lost to follow up, the time from the onset of treatment; if died, the cause and the time since onset of treatment; and which agency provided the treatment for this episode of active disease.

3.4.3.SUBJECTS

In order to establish a database for random sampling, a complete listing of all patients registered with the Chest Service for treatment of TB in 1996 was necessary. To compile such a list, the four PRF forms (Forms 1, 2, 3 and 4) were put together for each patient. The data on the forms were entered into a computer file by using Epi-Info ver 6.0 (CDC, Atlanta). Epi-Info was chosen to provide compatibility with notification database available from the Statistic Unit of TB Headquarter. There were many patients missing one of the 4 forms and missing data were present in a significant proportion of the forms.

The database was then corrected for duplicate entries by employing clinic number and Hong Kong ID (HKID) number. The possibility of duplicate entries occurs due to patient movement from one clinic to another during their course of treatment.

In order to obtain a complete listing of all patients treated by the Chest Service for 1996, the computerized master list (PRF database) was matched with notification database for the year of 1995, 1996 and 1997. Matching was done by employing HKID (the first choice); clinic number for those without HKID but already assigned clinic number (second choice); or name, sex and age for those without HKID or clinic number (third choice).

Prior to matching with PRF database, the notification database of 1996 was checked for duplicate entries by employing HKID and or name and sex. 471 notifications arose from chest clinics that were not found in the PRF database. A search was then carried out among all chest clinics for the cases that were notified from the chest clinics and yet no PRF forms had been filed.

By matching PRF and notification databases, it was estimated that approximately 5812 new TB cases were seen at chest clinics in the year 1996. Until the end of December 1999, 55 records of patients were not available.

3.4.4. MEDICAL RECORDS REVIEW

By employing a simple randomization, 1000 samples were drawn from the pool of 5812 cases. Medical record review was then carried out at the various local chest clinics in order to check, to complete and to extract additional information (PRF 1A). For the purpose of this thesis, a total of 1000 records were reviewed. Supplemental data were collected during the medical record review (PRF 1A; appendix 2). PRF 1A was being completed for the purpose of this thesis. This additional data collected included occupation, marital status (single, married, other), smoking status (non-smokers, ex-smokers, current smokers, age started, age stopped, number of cigarettes per day), birth place (Hong Kong, China, other country), BCG status, mode of presentation (self attended, referral or surveys), presenting symptoms (cough, sputum, chest pain, wheeze, blood stained sputum, haemoptysis, dyspnoea, weight loss, fever, other), contact history, drug or alcohol abuse, HIV status, co-morbid illness, the actual date starting and stopping treatment, listing of drugs being prescribed, its duration and frequency, history of hospitalization during treatment, history of treatment side effects, the total actual number of DOTS appointment, missed and self-administered, listing of microbiological results and contact tracing information including age, sex, relationship, being examined and result of examination.

Of these 1000 samples, 30 had wrong diagnosis including atypical mycobacterial infection and lung cancer and they were excluded. Thus, 970 cases were available for subsequent analyses.

3.5. DATA MANAGEMENT

The data from the 4 PRF forms and PRF 1A were entered into Epi-Info Version 6 (CDC, Atlanta). Data entered were checked for accuracy by another person before analyses. Data entered on Epi-Info were then translated into SPSS (SPSS Inc., Chicago) or Stata (Stata Corp., Texas) formats by employing DBMSCopy (SPSS Inc., Chicago).

3.6. DEFINITIONS

For the purpose of this research, definitions recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD)[45] were being used in order to provide an international comparison.

A **case of tuberculosis** was defined as one who had tuberculosis micro-organisms visible on microscope examination of sputum (smear positive) or on culture if smear was negative;

or in the absence of positive bacteriology, those with clinical and radiological features compatible with tuberculosis.

Site of disease:

a. Pulmonary cases - those with tuberculosis of the lungs including those who were sputum smear positive and those sputum smear negative (provided a minimum of 3 sputum examinations have been performed)
b. Extra-pulmonary cases - all other patients, including those with tuberculosis pleurisy and miliary tuberculosis

Patient category:

a. New case – one who had never previously been treated for as much as one month
b. Relapse case - one who, having previously been treated, was declared cured prior to becoming once again sputum smear positive
c. Treatment after default – one who became sputum positive after having interrupted treatment for more than 2 months
d. Failure of previous regimen – one who never or only temporarily show sputum conversion while receiving treatment
e. Others- all other category of patients were entered under others

Extent of pulmonary disease:

a. Minimal – disease with less than one lobe involvement
b. Moderate – disease with less than one lung but more than one lobe involvement
c. Advanced – disease with more than one lung involvement

Drug resistance:

a. Initial resistance – those with resistance organisms without a history of any previous treatment for tuberculosis
b. Acquired resistance – those with resistance organisms and had a history of treatment for tuberculosis previously
c. Multiple drug resistance – those that the isolate shows resistance to at least H and R

Smear status at pre-treatment among pulmonary cases:

a. Smear positive – those whose sputum smear was positive prior to treatment
b. Remainder – those whose sputum smear was negative or smear not done prior to treatment

Outcome variables:

Treatment outcome will be measured by the proportion of smear negative (cured), smear not done (treatment completed), failure (smear positive), died, defaulted and transferred out over a period of 12 months. These outcomes are defined as follows:

a. Smear negative – cured. Those on which sputum smears was negative at one month prior to the completion of chemotherapy and on at least one previous occasion
b. Smear not done - treatment completed. Those who completed treatment but in whom smear examination results were not available on at least 2 occasions prior to the completion of treatment
c. Smear positive – failure. Those who remained or became again smear positive at 5 months or later during chemotherapy
d. Died. Those who died for any reason during the course of chemotherapy
e. Defaulted. Any patient who has failed to take medication for more than 2 consecutive months after the date of the last attendance during the course of treatment or treatment stopped by the physicians or treatment longer than 15 months
f. Transferred out. Those for whom the result treatment was unknown and who completed chemotherapy at another center or overseas to which the patient had been referred to continue the treatment

Adherence:

a. Adherence – those who finished treatment at 12 months and never missed scheduled DOT appointment (100% attendance) during the whole course of treatment
b. Non-adherence – those who missed ≥ 30 scheduled DOT appointments during the whole course of treatment

Other variables:

For the purpose of analysis for the thesis, the following were also used:

a. "True defaulters" - those who defaulted treatment for at least 2 months and were not able to be traced back or those who refused treatment

b. Treatment completed" - Those in categories 'smear negative – cured' and 'smear not done – treatment completed' were combined together as 'treatment completed' category

c. "Number of treatment appointments missed" was used to investigate adherence to treatment; these numbers were obtained by counting the actual number of DOT scheduled appointments missed by patients (data came from the treatment attendance form kept for each patient)

d. "Number of self-administered treatment" was used to investigate the actual percentage of DOT received by patients (levels of DOT).

These numbers were obtained by counting the actual number of treatment not observed by the designated health personnel (such as public health nurse at chest clinics, community health nurse) from the treatment attendance form kept for each patient. The number of self-administered treatment was expressed as the percentage of the total number of treatment appointments given for this episode of disease. Due to distribution imbalances, the percentages on the number of self-administered treatment were categorized into < 10%, 10-25%, 25-50% and > 50%, as the levels of DOT, in the subsequent analyses. Those belongs to < 10% self–administered category (including those with 0% self-administered drug) were considered as having full DOT allowing for drug self-administration on weekends. Those with more than 10% of self-administered drugs are considered as having partial DOT.

3.7.STATISTICAL ANALYSIS

3.7.1. Sample size

The primary end point in this study was to determine the cure rate by assessing the percentage rendered smear negative at 6 months. Various studies have shown that the cure rate achieved by directly observed treatment at different level of adherence range from 70% - 90% and WHO required a minimum of 85% cure rate in TB control program for developing countries or 90-95% for developed countries.

Given sample size of 970, there was 80% power to detect ± 4% difference in the smear negative (cured) with at 5% α level (two sided test). Sample size calculation was conducted on Stata release 5 for Windows 95 [85]. The sample size formula is as follows:

$$n = \left[\frac{Z_1 - \alpha\sqrt{p_o(1-p_o)} + Z_1 - \beta\sqrt{p_a(1-p_a)}}{p_a - p_o} \right]^2$$

3.7.2. Univariate analysis

Exploratory data analyses were carried out using appropriate univariate statistical techniques. Univariate χ^2, independent sample t-test and one-way anova were employed[86]. SPSS for Windows (ver. 6.1) statistical computer package was employed to do cross-tabulation, frequency, various plots and descriptive statistics.

3.7.3. Multivariate analysis

Multivariate data analyses were conducted in order to investigate factors affecting treatment outcomes (polytomous logistic regression[87,88, 89]) and risk factors of non-adherence to treatment (logistic regression[90]). In the multivariate analyses, dummy variables were created for each independent categorical variables with > 2 categories. These 2 statistical methods are briefly reviewed in the subsequent sections.

3.7.3.1.Multiple logistic regression

Multiple logistic regression was employed in order to investigate risk factors of associated with non-adherence to treatment. In classical multiple linear regression the mean value of the dependent variable is expressed as a linear function of a set of independent variables. However this method is not applicable when the dependent variable is dichotomous (such as defaulted and completed treatment). Thus, in order to fit the relationship using linear regression it is necessary to apply a transformation, which leads to the method of logistic regression.

Multiple logistic regression model takes the form of

$$\mathbf{Prob[D]} = \frac{1}{1 + \exp(-\alpha - \sum_{j=1}^{p} \beta_j x_j)}$$

(D is disease, in this case is the outcome of interest.)

Using the logistic model as described above, it is a straightforward matter to derive formulas for the various measures of epidemiological association[90]. Suppose that the exposure **x** has just two possible values which may be taken to be 0 (unexposed) and 1 (exposed), the risk of the outcome given the exposure is thus obtained by putting **x=1**, that is;

$$\mathbf{Prob[D|E]} = \frac{\mathbf{1}}{\mathbf{1+\exp(-\alpha-\beta)}}$$

(E is exposure, in this case independent variable of interest)

while the risk of the outcome given no exposure (**x=0**) is;

$$\mathbf{Prob[D|\bar{E}]} = \frac{\mathbf{1}}{\mathbf{1+\exp(-\alpha)}}$$

The relative risk may now be computed as the ratio of these two equations. However the equations for the odds and the odds ratio are much simpler. The odds of the outcome given the exposure is;

$$\frac{\mathbf{Prob[D|E]}}{\mathbf{Prob[\bar{D}|E]}} = \frac{\mathbf{Prob[D|E]}}{\mathbf{1-Prob[D|E]}} = \frac{\dfrac{\mathbf{1}}{\mathbf{1+\exp(-\alpha-\beta)}}}{\mathbf{1-\dfrac{1}{1+\exp(-\alpha-\beta)}}}$$

and this reduce after cancellation simply to $\mathbf{\exp(\alpha+\beta)}$. Similarly, the odds of the outcome given no exposure is

$$\frac{\mathbf{Prob[D|\bar{E}]}}{\mathbf{1-Prob[D|\bar{E}]}} = \frac{\dfrac{\mathbf{1}}{\mathbf{1+\exp(-\alpha)}}}{\mathbf{1-\dfrac{1}{1+\exp(-\alpha)}}} = \mathbf{\exp(\alpha)}$$

Thus the odds ratio has a simple formula

$$\mathbf{OR} = \frac{\exp(\alpha+\beta)}{\exp(\alpha)} = \exp(\beta)$$

The log odds ratio based on the logistic regression model is even simpler, that it is just β coefficient. This means that the parameter β in the model may be interpreted directly as the natural logarithm of the odds ratio.

A confidence interval (CI) of the odds ratio can also be computed from the logistic regression. This CI is obtained by exponentiating the confidence limits obtained from the parameter. To compute the CI of x_1, a dichotomous exposure variable in a model with **n** independent variables $x_1, x_2, x_3, \ldots x_n$

$$\mathbf{OR}(x_1) = \exp(\beta_1)$$

$$\mathbf{CI\ for\ OR}(x_1) = \exp(\beta_1 \pm Z_{1-\frac{\alpha}{2}} SE(\beta_1))$$

Model selection was done by employing using the hierarchical backwards elimination approach as was described by Kleinbaum[90].

Logistic regression analyses were done by employing procedure logistic available on Stata ver 5.0[89].

3.7.3.2.Polytomous logistic regression (multinomial logit model)

Suppose that the number of categories in the outcome variable is more than two (not only binomial, such as treatment outcome with 5 categories), polytomous logistic regression can be employed to analyze the models instead of logistic regression. Polytomous logistic regression model is a generalization of logistic regression[88, 89]. In logistic regression, the model for probability {Y=1|x} is as follows;

$$\mathbf{Prob}\{Y=1|x_i\} = \frac{1}{1 + \exp -(\alpha+\Sigma\beta_i x_i)}$$

Suppose Y = 0,1,2,....,k categories, then the model above can be generalized as;

$$\text{Prob}\{Y=k|x_i\} = \frac{\exp(\alpha_k+\Sigma_i\beta_{ik}x_i)}{1+\Sigma_k\exp(\alpha_k+\Sigma_i\beta_{ik}x_i)}$$

If in logistic regression there is one logit function, i.e. logit of y=0 and logit of y=1, then in polytomous regression with k categories of outcome variable, there are (k-1) logit functions in which the group coded as 0 serves as the reference outcome value[88,89]. With regard to model development strategies, multivariate modeling with polytomous outcome follows those for the binary outcome variable as discussed in section 3.7.3.1.

The outcome categories in polytomous regression model can be an ordinal or nominal scale, thus polytomous regression, particularly *mlogit procedure* from Stata ver 5.0, is applicable in this study. The purpose of the analysis of polytomous regression is to investigate the relative importance of various independent variables in affecting different treatment outcome categories.

Polytomous logistic regression analyses were being done by employing *procedure mlogit* in Stata ver 5.0[89].

3.8. ETHICAL CONSIDERATION

The study was performed in accordance to the Declaration of Helsinki issued by the World Medical Association in 1960 and revised in 1975. The Chest Service, Department of Health, Hong Kong, has endorsed the study. As well, the Ethics Committee Hong Kong University has given the study approval. All individual data generated from this study are confidential and the report has no reference to patient names or HKID numbers.

3.9.CONCLUSION

The main objective of this study was to investigate the effectiveness of TB treatment program delivered by Chest Service, Department of Health in Hong Kong by determining the outcome of the TB treatment program. The study design employed was an observational retrospective cohort. A random sample of 1000 cases was derived from all newly diagnosed TB cases registered at the chest clinics for treatment in 1996. A nested case-control design

is employed to investigate factors affecting adherence to treatment. The data collection tools, study power and the statistical analytical technique involved in achieving the objectives were discussed.

CHAPTER IV

TUBERCULOSIS TREND AND EVALUATION OF 1996 TUBERCULOSIS TREATMENT PROGRAM

4.1 TREND OF TUBERCULOSIS IN HONG KONG, 1957 - 1998

The decline in TB notification rate in Hong Kong has slowed since 1991. From 1957 – 1991, TB notification rate has been declining, on the average of 3.8% per year. Since 1995, the rate has actually increased from 100.9/100,000 to 103, 108 and 115, in 1996, 1997 and 1998, respectively (Figure 2.1). Figure 2.1 also shows that the disease rate was always been higher in male than female. The differences in rates between male and female increased with increasing age, especially among those age ≥ 60 years (Figure 4.1).

Based on the available data, one can estimate an excess of 1730 TB cases since 1996 compared to the expected rate if the trend of decline continued (Figure 4.2). Figure 4.3 shows the percentage of TB cases with the corresponding percentage of population in different age groups. The percentage of tuberculosis cases declined in the younger age groups. Of those age ≥ 60 years, there was a discrepancy between the percentage of cases of tuberculosis and percentage of population in that age group. The above findings do not suggest that improvement in reporting of tuberculosis by doctors was responsible for the increase in notification rate of tuberculosis during the past 3 years as the increase should not be localize to one age group. Even if the recent increase in notification rate was artificial, one has to address the question why the rate of tuberculosis in Hong Kong, where the gross income per capita is one of the highest in the world, has a persistent high rate of tuberculosis in the past 10 years, ten times those of other industrialized countries.

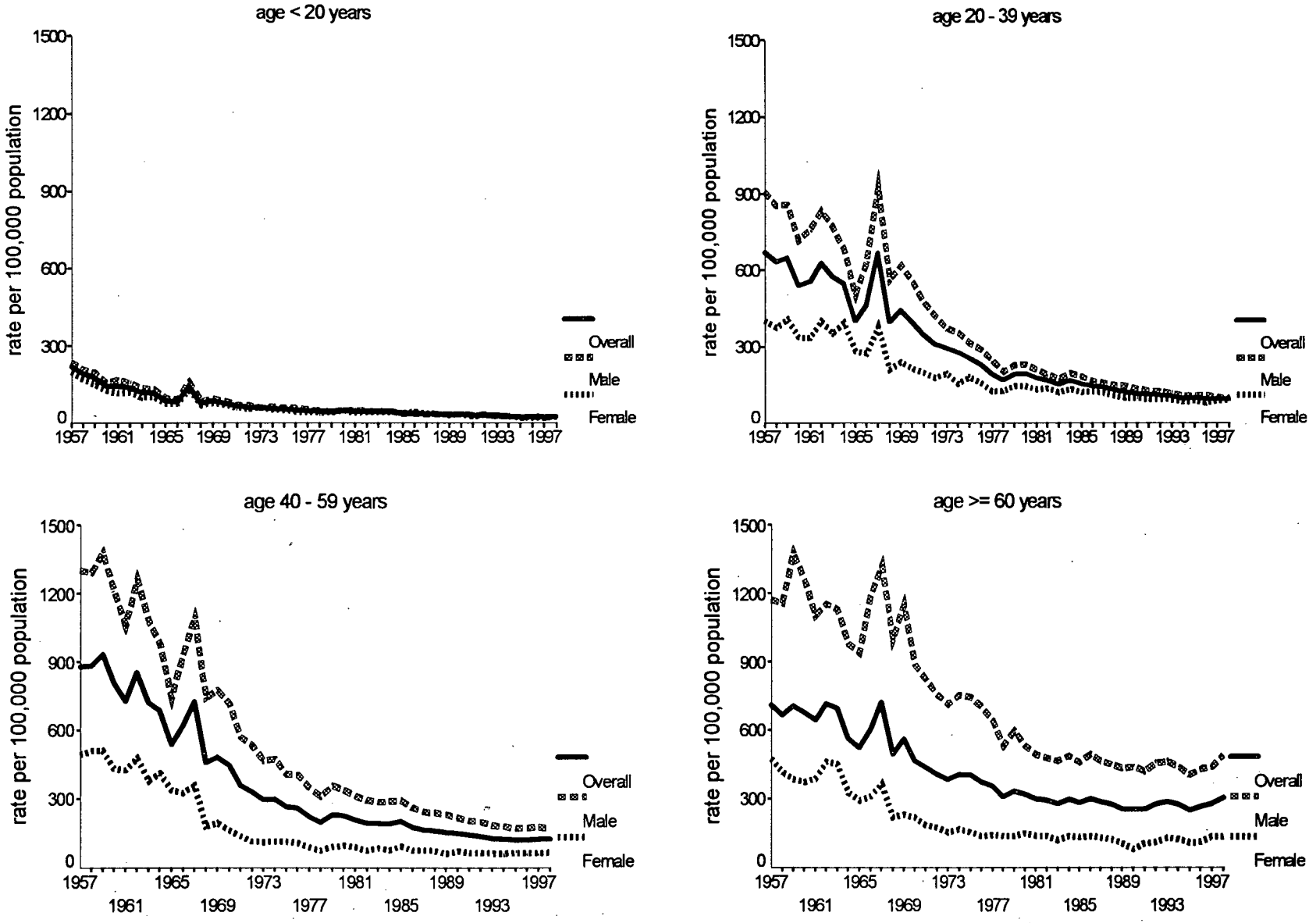


Figure 4.1. Tuberculosis notification rate in Hong Kong (1957 – 1998), by age groups.

Source: Chest Service of the Department of Health. Hong Kong (1998). Annual Report.

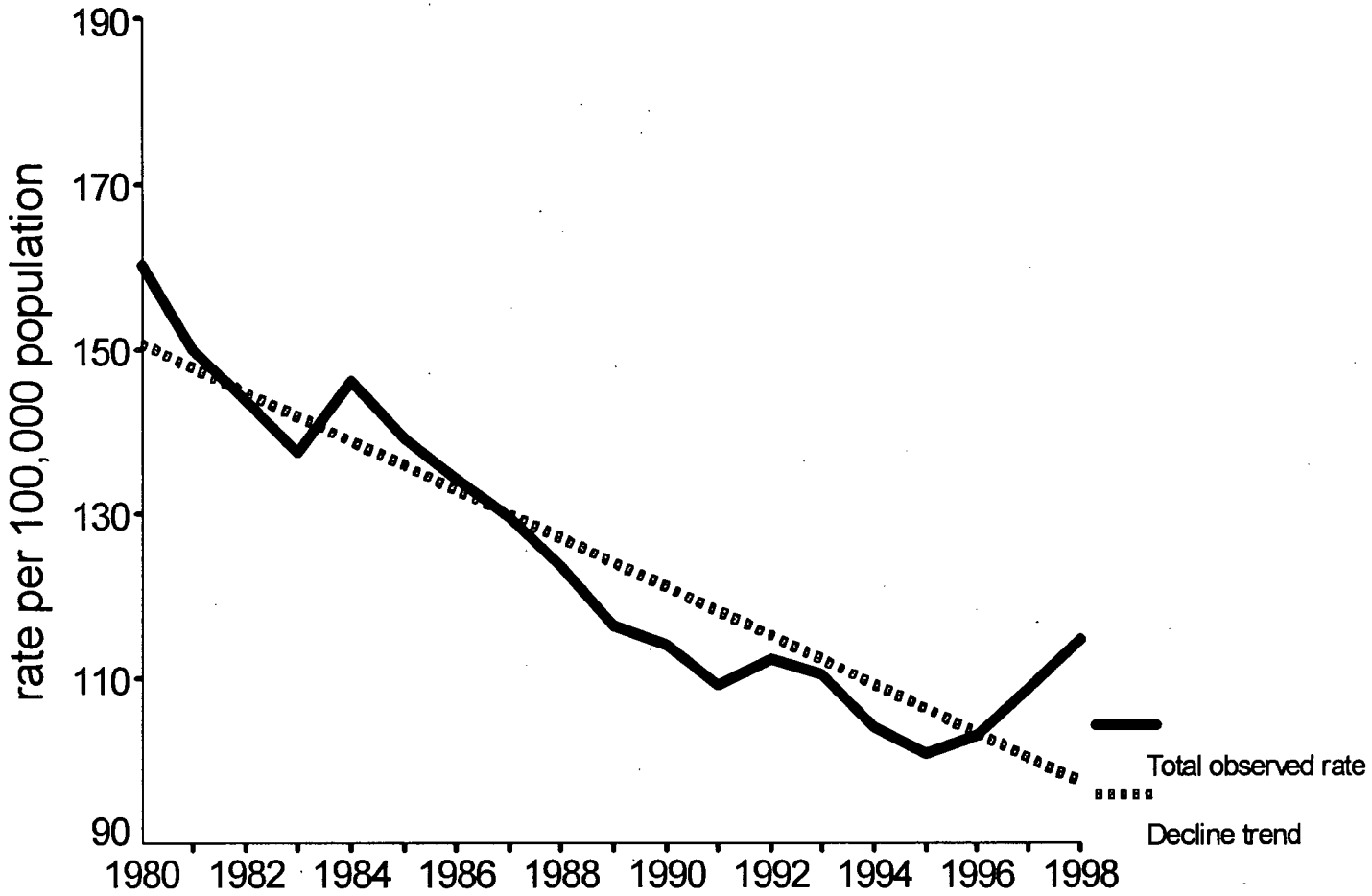


Figure 4.2. Observed and predicted trend of the tuberculosis notification rate in Hong Kong (1980 - 1998).

Source: Chest Service of the Department of Health. Hong Kong (1998). Annual Report.

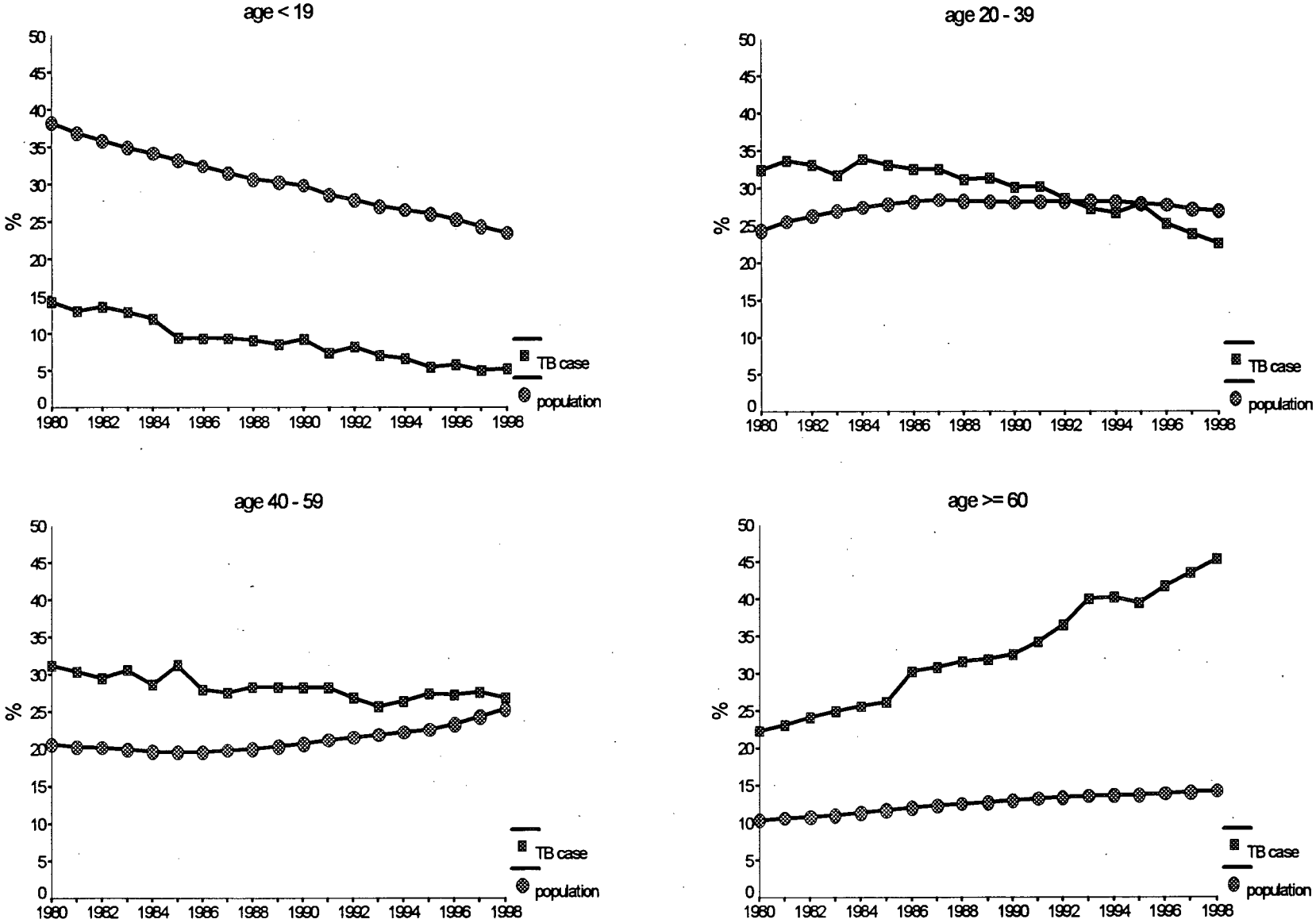


Figure 4.3. Percentage of TB cases and the corresponding population in Hong Kong (1980 – 1998), by age groups.

Source: Chest Service of the Department of Health. Hong Kong (1998). Annual Report.

4.2 EVALUATION OF 1996 TUBERCULOSIS TREATMENT PROGRAM

1000 patients were randomly sampled from a total of 5812 patients who attended the Chest Service for treatment of tuberculosis in 1996. Of these, 30 had the final diagnosis as atypical mycobacterial infection or lung cancer and they were excluded from subsequent analyses. These resulted in 970 patients being eligible for further analyses.

In this section, the characteristics of the patients, their symptoms, risk factors and co-morbid illnesses are presented.

4.2.1 CHARACTERISTICS OF THE STUDY POPULATION

4.2.1.1 Characteristics of all patients

There were more males than females (69.9% vs 30.1%, respectively) in this randomly selected samples (Table 4.1). The majority of cases were aged ≥ 60 year. Males were older than females. The majority of cases were married; males had a higher proportion of being married compared to females. Almost half of the males were current smokers while almost all of females were non-smokers. There was a significant difference in the distribution of cases in different types of occupation.

77.1% of the patients had pulmonary disease; 13.1% had extra-pulmonary and 9.8% mixed of pulmonary and extra-pulmonary disease. Females had a higher proportion with extra-pulmonary disease than males.

The majority of cases were new cases. A higher proportion of males had a history of previous treatment for TB and a history of default from treatment compared to females. 82.6% of patients were referrals from various sources such as general practitioners or public hospitals. Only 10.9% had a previous history of contact with an active case; higher in females than males.

Table 4.1. Characteristics of all patients.

	Female	Male	Total
n (%)	292 (30.1)	678 (69.9)	970 (100)
Age group:*			
- < 20 years	27 (9.2)	34 (5.0)	61 (6.3)
- 20 –39 years	134 (45.9)	187 (27.6)	321 (33.1)
- 40 – 59 years	61 (20.9)	184 (27.1)	245 (25.3)
- ≥ 60 years	70 (24.0)	273 (40.3)	343 (35.4)
Marital status:*			
- married	178 (61.6)	459 (69.7)	637 (67.2)
- others	111 (38.5)	200 (30.4)	311 (32.8)
Smoking status:*			
- non-smokers	249 (93.3)	174 (30.5)	423 (50.5)
- ex-smokers	8 (3.0)	132 (23.1)	140 (16.7)
- current smokers	10 (3.7)	265 (46.4)	275 (32.8)
Present occupation:*			
- blue collar workers	47 (16.6)	216 (33.3)	263 (28.2)
- white collar workers	67 (23.7)	94 (14.5)	161 (17.3)
- housewife	107 (37.8)	6 (0.9)	113 (12.1)
- student	23 (8.1)	24 (3.7)	47 (5.0)
- retired/unemployed	39 (13.8)	309 (47.6)	348 (37.3)
Type of disease:*			
- pulmonary TB	228 (78.1)	615 (90.7)	843 (86.9)
- extra-pulmonary TB	64 (21.9)	63 (9.3)	127 (13.1)
Case category:*			
- new case	260 (89.0)	539 (79.5)	799 (82.4)
- relapse case	27 (9.2)	112 (16.5)	139 (14.3)
- re-treatment after default	5 (1.7)	27 (4.0)	32 (3.3)
Mode of presentation:*			
- self attended	42 (14.5)	121 (18.3)	163 (17.1)
- referral	245 (84.8)	541 (81.7)	786 (82.6)
- surveys	2 (0.7)	0 (0.0)	2 (0.2)
Contact history*	40 (16.7)	42 (8.2)	82 (10.9)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

4.2.1.2 Pulmonary disease

In the following analyses, those with both pulmonary and extra-pulmonary diseases were included in those with pulmonary disease alone.

Characteristics of the patients

There were 843 patients with pulmonary TB in this randomly selected group. Of these, 95 (11.3%) had extra-pulmonary involvement as well. Pulmonary TB occurred more frequently in males than females (Table 4.2). Male patients were significantly older than females. A higher proportion of males was married, currently smoking and retired/unemployed.

The majority of pulmonary TB patients were new cases. More males had a previous history of treatment (relapse or default from previous treatment) compared to females.

Disease extent, cavitation, symptoms and co-morbid illnesses

The majority of females had minimal disease while males had more advanced disease and cavitation. More females had a contact history compared to males (Table 4.3).

23.2% of the patients with pulmonary disease had no symptoms prior to treatment (data not tabulated). The majority of those with symptoms had cough, sputum production, weight loss and blood stained sputum (Table 4.3). There was no significant difference in the occurrence and type of symptoms between females and males.

32.8% of patients had co-morbid illnesses (Table 4.4), higher among males than females ($p < 0.05$). More males were drug abuser or alcoholic. Lung cancer and liver disease occurred more commonly in males ($p < 0.05$).

Microbiological status at different times and drug resistance patterns

All patients had sputum smear and culture examination prior to treatment (Table 4.5). About a third of these patients had sputum smear and culture positive for acid fast bacilli and another third with sputum smear or culture positive for acid fast bacilli. The rest of the patients were diagnosed based on clinical or radiological findings.

Table 4.6 shows the drug sensitivity patterns. 84% of the culture positive isolates were fully sensitive to the four first line drugs (S, H, R, E). 11.7% had resistance to any one of the first four line drugs while 4.2% had resistance to more than one drug. 27.8% of

drug resistance were acquired rather than primary. Males had a higher prevalence of acquired drug resistance than females.

10 (2.0%) patients had multiple drug resistance TB as defined previously. As expected, the highest prevalence of any or mono resistance was against S, followed by H.

Table 4.2. Characteristics of pulmonary disease patients.

	Female	Male	Total
n (%)	228 (27.0)	615 (73.0)	843 (100)
Age group:*			
- < 20 years	22 (9.6)	30 (4.9)	52 (6.2)
- 20 –39 years	102 (44.7)	165 (26.8)	267 (31.7)
- 40 – 59 years	48 (21.1)	168 (27.3)	216 (25.6)
- ≥ 60 years	56 (24.6)	252 (41.0)	308 (36.5)
Marital status:*			
- married	135 (59.7)	414 (69.3)	549 (66.7)
- others	91 (40.2)	183 (30.6)	274 (33.3)
Smoking status:*			
- non-smokers	195 (92.4)	153 (29.3)	348 (47.5)
- ex-smokers	7 (3.3)	121 (23.2)	128 (17.5)
- current smokers	9 (4.3)	248 (47.5)	257 (35.1)
Present occupation:*			
- blue collar workers	37 (16.8)	190 (32.1)	227 (28.0)
- white collar workers	56 (25.5)	85 (14.4)	141 (17.4)
- housewife	81 (36.8)	6 (1.0)	87 (10.7)
- student	16 (7.3)	22 (3.7)	38 (4.7)
- retired/unemployed	30 (13.6)	288 (48.7)	318 (39.2)
Type of disease:			
- pulmonary	198 (86.8)	550 (89.4)	748 (88.7)
- pulmonary and extra-pulmonary	30 (13.2)	65 (10.6)	95 (11.3)
Case category:*			
- new case	204 (89.5)	485 (78.9)	689 (81.7)
- relapse case	19 (8.3)	105 (17.1)	124 (14.7)
- re-treatment after default	5 (2.2)	25 (4.1)	30 (3.6)
Mode of presentation:			
- self attended	37 (16.4)	118 (19.6)	155 (18.8)
- referral	187 (83.1)	483 (80.4)	670 (81.1)
- surveys	1 (0.4)	0 (0.0)	1 (0.1)
Contact history*	36 (19.1)	38 (8.1)	74 (11.2)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

Table 4.3. Disease extent, cavitation and symptoms prior to treatment among patients with pulmonary disease.

	Female	Male	Total
n (%)	228 (27.0)	615 (73.0)	843 (100)
Extent of disease:*			
- minimal	169 (74.1)	333 (54.2)	502 (59.6)
- moderate	45 (19.7)	188 (30.6)	233 (27.7)
- advanced	14 (6.1)	93 (15.1)	107 (12.7)
Cavity*	29 (13.2)	133 (22.2)	162 (19.8)
Type of symptom:			
- cough	149 (65.4)	388 (63.2)	537 (63.8)
- sputum production	111 (48.7)	291 (47.4)	402 (47.7)
- chest tightness	24 (10.5)	76 (12.4)	100 (11.9)
- wheeze	1 (0.4)	3 (0.5)	4 (0.5)
- blood in sputum	43 (18.9)	83 (13.5)	126 (15.0)
- haemoptysis	25 (11.0)	47 (7.7)	72 (8.6)
- dyspnoea	26 (11.4)	88 (14.3)	114 (13.5)
- weight loss	45 (19.7)	121 (19.7)	166 (19.7)
- fever	39 (17.1)	75 (12.2)	114 (13.5)
- malaise	0 (0.0)	5 (0.8)	5 (0.6)
- night sweat	2 (0.9)	7 (1.1)	9 (1.1)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

Table 4.4. Risk factors and co-morbid illnesses among patients with pulmonary disease.

n (%)	Female 228 (27.0)	Male 615 (73.0)	Total 843 (100)
Frequency of co-morbid illness:*			
- none	171 (75.0)	396 (64.4)	567 (67.3)
- 1 illness	40 (17.5)	162 (26.3)	202 (24.0)
- 2 illnesses	12 (5.3)	41 (6.7)	53 (6.3)
- ≥ 3 illnesses	5 (2.2)	16 (2.6)	21 (2.5)
Type of risk factors and co-morbid illness:			
- drug abuser*	2 (1.2)	26 (5.5)	28 (4.4)
- alcoholism*	1 (0.6)	48 (10.2)	25 (10.9)
- HIV	0 (0.0)	2 (0.7)	2 (0.5)
- Diabetes Mellitus	22 (9.6)	89 (14.5)	111 (13.2)
- Silicosis	0 (0.0)	8 (1.3)	8 (0.9)
- Other lung diseases except cancer	12 (5.3)	53 (8.6)	65 (7.7)
- Any type of cancer*	3 (1.3)	24 (3.9)	27 (3.2)
- Heart diseases	16 (7.0)	26 (4.2)	42 (5.0)
- Gastric ulcer	3 (1.3)	7 (1.1)	10 (1.2)
- Kidney diseases	2 (0.9)	10 (1.6)	12 (1.4)
- Liver diseases*	2 (0.9)	30 (4.9)	32 (3.8)
- Anemia	3 (1.3)	1 (0.2)	4 (0.5)
- Gout	2 (0.9)	13 (2.1)	15 (1.8)
- Bone and joint disorders	1 (0.4)	5 (0.8)	6 (0.7)
- Vision	1 (0.4)	3 (0.5)	4 (0.5)
- Mental illnesses	3 (1.3)	7 (1.1)	10 (1.2)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

Table 4.5. Microbiological data of patients with pulmonary disease.

Smear and culture n (%)	Female 228 (27.0)	Male 615 (73.0)	Total 843 (100)
at pre-treatment:			
- smear and culture positive	60 (27.5)	189 (31.6)	249 (30.5)
- culture positive only	72 (33.0)	173 (28.9)	245 (30.0)
- smear positive only	5 (2.3)	20 (3.3)	25 (3.1)
- smear and culture negative	81 (37.2)	217 (36.2)	298 (36.5)
at 2 months follow-up:			
- smear and culture positive	1 (0.7)	14 (3.6)	15 (2.9)
- culture positive only	3 (2.2)	22 (5.6)	25 (4.8)
- smear positive only	3 (2.2)	7 (1.8)	10 (1.9)
- smear and culture negative	128 (94.8)	347 (89.0)	475 (90.5)
at 5 or 6 months follow-up:			
- smear and culture positive	1 (0.6)	4 (0.9)	5 (0.8)
- culture positive only	2 (1.2)	0 (0.0)	2 (0.3)
- smear positive only	1 (0.6)	0 (0.0)	1 (0.2)
- smear and culture negative	166 (97.6)	418 (99.1)	584 (98.6)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

Table 4.6. Drug susceptibility patterns among patients with pulmonary disease prior to treatment.

n (%)	Female 132 (26.7)	Male 362 (73.3)	Total 494 (100)
Type of resistance:			
• primary	20 (87.0)	37 (66.1)	57 (77.2)
• acquired	3 (13.0)	19 (33.9)	22 (27.8)
MDR TB[#]	2 (0.9)	8 (1.3)	10 (2.0)
Resistance patterns:			
• HR	0 (0.0)	1 (0.3)	1 (0.2)
• HRE	0 (0.0)	2 (0.6)	2 (0.4)
• SHR	0 (0.0)	2 (0.6)	2 (0.4)
• SHRE	2 (1.5)	3 (0.8)	5 (1.0)
Other resistance patterns:			
• HE	1 (0.8)	0 (0.0)	1 (0.2)
• SH	2 (1.5)	7 (1.9)	9 (1.8)
• RE	0 (0.0)	2 (0.6)	2 (0.4)
• SR	0 (0.0)	2 (0.6)	2 (0.4)
• SE	3 (2.3)	3 (0.8)	6 (1.2)
Mono resistance to:			
- S	12 (70.6)	24 (58.5)	36 (62.1)
- H	5 (29.4)	12 (29.3)	17 (29.3)
- R	0 (0.0)	3 (7.3)	3 (5.2)
- E	0 (0.0)	2 (4.9)	2 (3.4)

S = Streptomycin, H = Isoniazid, R = Rifampicine and E = Ethambutol

[#]MDR TB is defined as those resistant to at least H and R.

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

4.2.1.3 Extra-pulmonary disease

Extra-pulmonary TB occurred in 222 (22.9%) patients in this sample. Of these, 95 (42.8%) had both extra-pulmonary and pulmonary involvement and 127 (57.2%) had only extra-pulmonary involvement. In this analysis those with extra-pulmonary involvement only were included.

Characteristics, symptoms, risk factors and co-morbid illnesses of the patients

There were slightly more females than males who had extra-pulmonary TB (Table 4.7). The highest prevalence was observed among those aged 20-39 years old. The majority of female patients were non-smokers. The majority of male patients were blue-collar workers or retired, while the majority of female patients were housewife.

Organ involvement and mode of diagnosis

Table 4.8 shows that the majority of patients had one extra-pulmonary organ involvement (94.6%); miliary TB occurred only in 1.8%. Pleural involvement was the most common site (43.0%), followed by lymph nodes (32.3%) (Table 4.9). Unusual sites of involvement included nasopharynx and larynx.

The diagnosis of extra-pulmonary tuberculosis was established through histological examination in the majority of patients (Table 4.9). The method of diagnosis was not found in the medical records on 16.2% of patients.

Table 4.7. Characteristics, risk factors and co-morbid illnesses among patients with extra-pulmonary disease.

	Female	Male	Total
n (%)	64 (50.4)	63 (49.6)	127 (100.0)
Age group:			
- < 20 years	5 (7.8)	4 (6.3)	9 (7.1)
- 20 –39 years	32 (50.0)	22 (34.9)	54 (42.5)
- 40 – 59 years	13 (20.3)	16 (25.4)	29 (22.8)
- ≥ 60 years	14 (21.9)	21 (33.3)	35 (27.6)
Marital status:			
- married	43 (68.3)	45 (72.6)	88 (70.4)
- others	20 (31.8)	17 (27.4)	37 (29.6)
Smoking status:*			
- non-smokers	54 (96.4)	21 (42.9)	75 (71.4)
- ex-smokers	1 (1.8)	11 (22.4)	12 (11.4)
- current smokers	1 (1.8)	17 (34.7)	18 (17.1)
Present occupation:*			
- blue collar workers	10 (15.9)	26 (44.8)	36 (29.8)
- white collar workers	11 (17.5)	9 (15.5)	20 (16.5)
- housewife	26 (41.3)	0 (0.0)	26 (21.5)
- student	7 (11.1)	2 (3.4)	9 (7.4)
- retired/unemployed	9 (14.3)	21 (36.2)	30 (24.8)
Case category:			
- new case	56 (87.5)	54 (85.7)	110 (86.6)
- relapse case	8 (12.5)	7 (11.1)	15 (11.8)
- re-treatment after default	0 (0.0)	2 (3.2)	2 (1.6)
Mode of presentation:			
- self attended	5 (7.8)	3 (4.9)	8 (6.4)
- referral	58 (90.6)	58 (95.1)	116 (92.8)
- surveys	1 (1.6)	0 (0.0)	1 (0.8)
Contact history	4 (7.7)	4 (10.0)	8 (8.7)
Had any symptoms prior to treatment	30 (46.9)	34 (54.0)	64 (50.4)
Had any co-morbid illnesses	12 (18.8)	14 (22.2)	26 (20.5)
Drug abuser	0 (0.0)	2 (4.0)	2 (1.9)
Alcoholism*	0 (0.0)	6 (12.0)	6 (5.7)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between sex.

Table 4.8. Number of organ involvement among extra-pulmonary patients.

Number of organs[#]	Frequency (%)
One	210 (94.6)
Two	5 (2.3)
Three	2 (0.9)
Five	1 (0.5)
Miliary	4 (1.8)
Total	222 (100.0)

[#]Excluding lungs

Table 4.9. Frequency of organ involvement and mode of diagnosis among patients with extra-pulmonary disease.

Site[#]	Frequency (%)	Mode of diagnosis				
		Histology	Culture	Radiology	Clinical	No data
Pleura	101 (43.0)	61 (60.4)	21 (20.8)	6 (5.9)	0 (0.0)	13 (12.9)
- pure pleura	44 (43.6)					
Lymph nodes	76 (32.3)	65 (85.5)	0 (0.0)	2 (2.6)	0 (0.0)	9 (11.8)
Genitourinary tract	9 (3.8)	3 (33.3)	4 (44.4)	2 (22.3)	0 (0.0)	0 (0.0)
Gastrointestinal tract	13 (5.5)	11 (84.6)	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)
Skin	6 (2.6)	4 (66.7)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Miliary	4 (1.7)	1 (25.0)	2 (50.0)	0 (0.0)	0 (0.0)	1 (25.0)
Bone	4 (1.7)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Spine	3 (1.3)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)
Nasopharynx	5 (2.1)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)
Larynx	5 (2.1)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)
Meninges	2 (0.8)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)
Others	7 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Total	235 (100.0)	152 (64.7)	33 (14.0)	11 (4.7)	1 (0.4)	38 (16.2)

[#] Excluding lungs

4.2.2 TREATMENT OUTCOMES

An adequate and uninterrupted treatment program until completion is important in reducing the pool of TB infection in the community and in preventing the development of drug resistance TB. In this chapter, treatment outcomes at 6 and 12 months from the initiation of treatment, the type of drugs, the frequency of drug administration and the duration of treatment will be discussed. Treatment side effects and hospitalization during treatment will be presented. Treatment outcomes were defined in accordance to IUATLD definition as was described in Chapter 3. The results will be presented separately for patients with pulmonary and those with extra-pulmonary disease.

4.2.2.1 Treatment outcomes among pulmonary patients

Outcome at 6 months:

Of the 970 cases, 843 had pulmonary disease (with or without extra-pulmonary involvement). 40.3% completed treatment at 6 months. In the smear positive group the same proportion completed treatment (Table 4.10).

Mortality occurred in 3% of patients; more frequent in males compared to females. 6.5% of all patients defaulted treatment at 6 months, again more frequent in males than females.

Outcome at 12 months:

78.5% of all patients completed treatment at 12 months. In the smear positive group, 75.6% completed treatment at 12 months (Table 4.11). The rate of treatment completion was lower than that recommended by the WHO or the IUATLD of 85% at 12 months for developing countries (for both smear positive group and all cases $p < 0.001$) and 90 to 95% for developed countries.

At 12 months, 4 (0.5%) patients had a bacteriological relapse; 2 (0.7%) from the smear positive and 2 (0.4%) from remainders groups. 40 (4.7%) of patients died, more males compared to females. 68 (8.1%) patients defaulted treatment; of these, 66 (97.0%) were 'true defaulters'. 'True defaulters' were those who defaulted treatment and were not able to be traced back or those who refused treatment

Treatment duration, side effects and hospitalization during treatment:

Patients with pulmonary disease were treated for 7.2 ± 2.9 months (Table 4.12), significantly longer in males. Even though Short Course Service Program (6 months with multiple drugs) is the treatment policy of the Chest Service, only 55.1% of patients with pulmonary disease were treated for 6 months or less.

The majority of patients received 2 different regimens (combination of drugs) during treatment. Half of the patients received drugs daily. Females were more likely to receive DOT three times weekly compared to males, during both the initiation and the continuation phase of treatment.

61.1% of patients had no side effects from treatment. 36.5% of patients required hospitalization during treatment for side effects, co-morbid illnesses or procedures that were required for treatment of co-morbid conditions.

Drug regimens given during the initiation and continuation phase:

The majority of patients received 4 or more drugs in combination (HRZE, SHRZ, and SHRZE) during an initiation phase of 2 months (data not tabulated). 36.2% of patient had an initiation phase of longer than 2 months. 85.2% received HR as the drug combination during the continuation phase (data not tabulated). During the continuation phase of treatment, 41.2% received drugs for 4 months, 37.5% for longer than 4 months while the rest for shorter than 4 months.

Defaulters:

There were 79 'true defaulters'; 66 had pulmonary disease. 39.2% of patients who defaulted did so in the first 2 months of treatment and 34.2% between the 2^{nd} to 4^{th} months (data not tabulated). Among patients with pulmonary disease, 42.5% of default occurred within 2 months of treatment. At the time of default, 13 (20.3%) were still smear positive while another 13 (20.3%) were still culture positive (data not tabulated).

4.2.2.2 Treatment outcomes among extra-pulmonary patients

Only those with extra-pulmonary involvement were included in this analysis.

Outcome at 6 months:

At 6 months, only 26.8% of patients with extra-pulmonary completed treatment; 2 (3.2%) died and 10 (7.9%) defaulted treatment (Table 4.13). There was no significant difference between males and females in the outcomes at 6 months.

Outcome at 12 months:

At 12 months, 81.9% of patients completed treatment and 5.5% were still on treatment; 1.6% died and 10.2% defaulted treatment (Table 4.13). There was no significant difference in the outcomes at 12 months between males and females.

Treatment duration, side effects and hospitalization during treatment:

Patients with extra-pulmonary TB was treated for an average of 8.3 ± 3.1 months, longer than those with pulmonary disease. Only 35.5% of patients with extra-pulmonary TB were treated for 6 months or less, the rest were treated longer (Table 4.14). Two drug regimens were prescribed for 78.0% of patients with extra-pulmonary disease. These drugs were usually being administered daily during the initiation or the continuation phase. 43.3% of patients with extra-pulmonary disease required hospitalization, and 41.4% experienced treatment side effects. Even though the difference was not statistically significant, there were more females being hospitalized or experiencing treatment side effects compared to males.

Drug regimens given during the initiation and the continuation phase:

Four or more drug combinations (HRZE, SHRZ, SHRZE) were being prescribed to 62.9% of the patients during the initiation phase (data not tabulated). Only 3.6% received drug regimen for less than 2 months during the initiation phase; the majority (56.7%) was given drugs for 2 months and the rest received drugs for more than 2 months during the initiation phase.

During the continuation phase, 40.3% of extra-pulmonary patients received treatment for ≤ 4 months, 10.2% for 5 months, 11.6% for 6 months and the rest for

longer than 6 months. 85% of patients with extra-pulmonary disease received HR during the continuation phase (data not tabulated).

Table 4.10. Treatment outcome at 6 months among patients with pulmonary disease.

Smear status at pre-treatment / Sex	Smear positive			Remainder			Total
	Female	Male	Subtotal	Female	Male	Subtotal	
	65 (23.7)	209 (76.3)	274 (32.5)	163 (28.6)	406 (71.4)	569 (67.5)	843 (100.0)
6 months follow-up:♦♥							
- smear (-) – cured	29(44.6)	44 (21.1)	73 (37.2)	78 (47.9)	163 (40.1)	241 (42.4)	314 (37.2)
- smear ND – tx completed*	4 (6.2)	4 (1.9)	26 (3.1)	4 (2.5)	14 (3.4)	18 (3.2)	26 (3.1)
- still on treatment	26 (40.0)	135 (64.6)	161 (58.8)	58 (35.6)	175 (43.1)	233 (40.9)	394 (46.7)
- died:	0 (0.0)	8 (3.8)	8 (2.9)	4 (2.5)	13 (3.2)	17 (3.0)	25 (3.0)
• tx completed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (92.3)	1 (5.9)	1 (4.0)
• tx incomplete	0 (0.0)	8 (100.0)	8 (100.0)	4 (100.0)	1 (7.7)	16 (94.1)	24 (96.0)
- defaulted:	3 (4.6)	13 (6.2)	16 (5.8)	11 (6.7)	28 (6.9)	39 (6.9)	55 (6.5)
• not found	3 (100.0)	13 (100.0)	16 (100.0)	10 (90.9)	27 (96.4)	37 (94.9)	53 (96.4)
• tx stopped	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (5.6)	2 (5.1)	2 (3.6)
- transferred out	3 (4.6)	5 (2.4)	8 (2.9)	8 (4.9)	13 (3.2)	21 (3.7)	29 (3.4)

♦ $p < 0.05$, by χ^2, or Fisher's exact test, for differences between smear (+) at pre-treatment vs. remainder, at that particular period of follow-up. ♥ $p < 0.05$, by χ^2, or Fisher's exact test, for differences between sex within smear (+) at pre-treatment, at that particular period of follow-up

* is a patient who completed treatment but in whom smear examination results are not available on at least 2 occasions prior to the completion of treatment.

tx = treatment. ND = not done. Defaulted – treatment stopped – those whose treatment were stopped by the physicians prior to treatment completion due to side effects.

Table 4.11. Treatment outcome at 12 months among patients with pulmonary disease.

Smear status at pre-treatment / Sex	Smear positive			Remainder			Total
	Female	Male	Subtotal	Female	Male	Subtotal	
	65 (23.7)	209 (76.3)	274 (32.5)	163 (28.6)	406 (71.4)	569 (67.5)	843 (100.0)
12 months follow-up: ♥							
- smear (-) – cured	40 (61.5)	98 (46.9)	138 (50.4)	109 (66.9)	246 (60.6)	355 (62.4)	493 (58.5)
- smear ND – tx completed*	14 (21.5)	55 (26.3)	69 (25.2)	22 (13.5)	78 (19.2)	100 (17.6)	169 (20.0)
- bacteriological relapse	0 (0.0)	2 (1.0)	2 (0.7)	2 (1.2)	0 (0.0)	2 (0.4)	4 (0.5)
- still on treatment	1 91.5)	14 (6.7)	15 (5.5)	4 (2.5)	17 (4.2)	21 (3.7)	36 (4.3)
- died:	1 (1.5)	15 (7.2)	16 (5.8)	6 (3.7)	18 (4.4)	24 (4.2)	40 (4.7)
• tx completed	0 (0.0)	2 (13.3)	2 (12.5)	1 (16.7)	1 (5.6)	2 (8.3)	4 (10.0)
• tx incomplete	1 (100.0)	13 (86.7)	14 (87.5)	5 (83.3)	17 (94.4)	22 (91.7)	36 (90.0)
- defaulted:	5 (7.7)	19 (9.1)	24 (8.8)	12 (7.3)	32 (7.8)	44 (7.7)	68 (8.1)
• not found	5 (100.0)	16 (84.2)	21 (87.5)	9 (75.0)	30 (93.8)	39 (88.6)	60 (88.2)
• retreated	0 (0.0)	3 (15.8)	3 (12.5)	2 (16.7)	1 (3.1)	3 (6.8)	6 (8.8)
• tx stopped	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (3.1)	2 (5.6)	2 (3.0)
- transferred out	4 (6.2)	6 (2.9)	10 (3.6)	8 (4.9)	15 (3.7)	23 (4.0)	33 (3.9)

♥ $p < 0.05$, by χ^2, or Fisher's exact test, for differences between sex within smear (+) at pre-treatment, at that particular period of follow-up

* is a patient who completed treatment but in whom smear examination results are not available on at least 2 occasions prior to the completion of treatment.

tx = treatment. ND = not done. Defaulted – treatment stopped – those whose treatment were stopped by the physicians prior to treatment completion due to side effects.

Table 4.12. Treatment duration, side effects and hospitalization during treatment among patients with pulmonary disease.

	Female	Male	Total
n (%)	228 (27.0)	615 (73.0)	843 (100)
Duration of treatment (months, mean ± SD)*	6.7 ± 2.6	7.4 ± 3.0	7.2 ± 2.9
Duration of treatment:* (n, %)			
- < 6 months	28 (12.3)	76 (12.4)	104 (12.3)
- 6 months	118 (51.8)	243 (39.5)	361 (42.8)
- 6 – 9 months	72 (31.6)	211 (34.3)	283 (33.6)
- > 9 months	10 (4.4)	85 (13.8)	95 (11.3)
No. of drug combinations being given during whole course of treatment:* (n, %)			
- one	24 (10.5)	47 (7.6)	71 (8.4)
- two	182 (79.8)	463 (75.3)	645 (76.5)
- three	22 (9.6)	86 (14.0)	108 (12.8)
- four or more	0 (0.0)	19 (3.11)	19 (2.3)
Frequency of drugs during initiation phase:* (n, %)			
- daily	114 (50.2)	355 (58.1)	469 (56.0)
- 3x/week	104 (45.8)	219 (35.8)	323 (38.5)
- mixed	9 (4.0)	37 (6.1)	46 (5.5)
Frequency of drugs during continuation phase:* (n, %)			
- daily	101 (49.5)	325 (57.7)	426 (55.5)
- 3x/week	101 (49.5)	225 (40.0)	326 (42.5)
- mixed	2 (1.0)	13 (2.3)	15 (2.0)
Had any treatment side effects (n,%)	87 (38.2)	241 (39.2)	328 (38.9)
Ever hospitalized during treatment* (n, %)	62 (27.2)	246 (40.0)	308 (36.5)

- $p < 0.05$ by χ^2, Fisher's exact test or t-test, whichever appropriate.

Table 4.13. Treatment outcomes at 6 and 12 months among patients with only extra-pulmonary disease.

n (%)	Female 64 (50.4)	Male 63 (49.6)	Total 127 (100.0)
6 months follow-up:			
- treatment completed	15 (23.4)	19 (30.2)	34 (26.8)
- still on treatment	46 (71.9)	35 (55.6)	35 (55.6)
- died	0 (0.0)	2 (3.2)	2 (3.2)
- transferred out	0 (0.0)	0 (0.0)	0 (0.0)
- defaulted	3 (4.7)	7 (11.1)	10 (7.9)
12 months follow-up:			
- treatment completed	56 (87.5)	48 (76.2)	104 (81.9)
- still on treatment	4 (6.3)	3 (4.8)	7 (5.5)
- died	0 (0.0)	2 (3.2)	2 (1.6)
- transferred out	0 (0.0)	1 (1.6)	1 (0.8)
- defaulted	4 (6.3)	9 (14.3)	13 (10.2)

Table 4.14. Treatment patterns among patients with only extra-pulmonary disease.

	Female	Male	Total
n (%)	64 (50.4)	63 (49.6)	127 (100.0)
Duration of treatment (months, mean ± SD)*	8.8 ± 3.0	7.7 ± 3.1	8.3 ± 3.1
Duration of treatment:			
- < 6 months	3 (4.7)	8 (12.7)	11 (8.7)
- 6 months	15 (23.4)	19 (30.2)	34 (26.8)
- 6 – 9 months	33 (51.6)	26 (41.3)	59 (46.5)
- > 9 months	13 (20.3)	10 (15.9)	23 (18.1)
No. of drug combinations being given during whole course of treatment:			
- one	1 (1.6)	5 (7.9)	6 (4.7)
- two	53 (82.8)	46 (73.0)	99 (78.0)
- three	7 (10.9)	10 (15.9)	17 (13.4)
- four or more	3 (4.7)	2 (3.2)	5 (3.9)
Frequency of drugs during initiation phase:			
- daily	40 (62.5)	40 (64.5)	80 (63.5)
- 3x/week	21 (32.8)	15 (24.2)	36 (28.6)
- mixed	3 (4.7)	7 (11.3)	10 (7.9)
Frequency of drugs during continuation phase:			
- daily	36 (58.1)	38 (65.5)	74 (61.7)
- 3x/week	24 (38.7)	17 (29.3)	41 (34.2)
- mixed	2 (3.2)	3 (5.2)	5 (4.2)
Hospitalized during treatment:	29 (45.3)	26 (41.3)	55 (43.3)
Treatment side effects:	30 (46.9)	24 (38.1)	54 (42.5)

* $p < 0.05$ by χ^2, Fisher's exact test or t-test, whichever appropriate.

4.2.2.3 Factors affecting outcomes for pulmonary patients

In this section, the factors affecting treatment outcomes at 12 months will be explored. In this analysis the outcome categories "smear negative – cured" and "smear not done – treatment completed" were combined together as the "treatment completed" category. The outcome categories of interest were: 1. treatment completed, 2. still on treatment, 3. died, and 4. defaulted. The analyses on patients with pulmonary disease are presented below since the number of patients with extra-pulmonary disease was too small for building the polytomous logistic model.

The results of univariate analysis are presented below.

Characteristics of patients:

There was a significant difference in the distribution of age, sex, smoking status and present occupations between different categories of treatment outcome at 12 months (Table 4.15). Those aged ≥ 60 years old and males were more likely to be still on treatment at 12 months. More males, those aged ≥ 60 years old and ex-smokers died at 12 months. There was a significant difference in the distribution of case category and extent of disease between various categories of outcome (Table 4.15). Patients with advanced disease were more likely to be in the category "still on treatment" or "died" compared to those with lesser extent of disease. Those who defaulted were more likely to have a history of previous default.

Symptoms, risk factors and co-morbid illnesses:

The presence of symptoms did not affect the treatment outcome at 12 months (Table 4.16). Those who were "still on treatment" at 12 months had a significantly higher percentage with liver disease, alcoholism, side effects from treatment and hospitalization during treatment. Patients who "died" had a significantly higher percentage with any co-morbid illness, particularly diabetes mellitus and other lung diseases except cancer. The majority of drug abusers defaulted treatment at 12 months. "Default" and "transferred out" occurred at the early stage of treatment.

Microbiology:

Patients who were "still on treatment" at 12 months had the highest percentage with positive sputum culture and multiple drug resistance (Table 4.17). There was one multiple drug resistance patient who defaulted from treatment at 12 months.

4.2.2.4 Polytomous regression on factors affecting outcomes among pulmonary patients

In order to determine the factors affecting treatment outcome at 12 months, polytomous logistic regression analysis was carried out. In this analysis, those who "completed treatment" was used as the "baseline" group for comparison. The possibilities of any effect modification were not explored due to small sample size. The final polytomous regression model is presented as Table 4.18.

The factors associated with "still on treatment" at 12 months were the presence of advanced disease at the time of presentation (RR 2.6, 95% CI 1.1 – 6.5 compared to those with minimal disease); had any co-morbid illness (RR 2.5, 95% CI 1.2 – 5.4, compared to those without any co-morbid illness); positive sputum smear and culture at pre-treatment (RR 4.1, 95% CI 1.1 – 15.3, compared to those with sputum smear and culture negative); and positive smear or culture pre-treatment (RR 6.6, 95% CI 1.9 – 23.1, compared to those with sputum smear and culture negative).

Age (RR 1.1, 95% CI 1.1 – 1.2), advanced disease (RR 3.5, 95% CI 1.3 – 9.3 compared to those with minimal disease) and the presence of any co-morbid illnesses (RR 5.6, 95% CI 2.2 – 14.6 compared to those without any co-morbid illnesses) were important factors in predicting "died" at 12 months.

The single most important factor in predicting "default" at 12 months was a history of previous default; the RR compared to new cases was 14.1 (95% CI 6.2 – 32.4).

The independent variables in this model only explained about 13.1% of the variation observed in the dependent variable (outcome categories).

Table 4.15. Characteristics of pulmonary patients by outcome at 12 months.

n (%)	Tx# completed 666 (79.0)	Still on tx# 36 (4.3)	Died 40 (4.7)	Defaulted 68 (8.1)	Transferred out 33 (3.9)
Age group:*					
- < 20 years	45 (6.8)	2 (5.6)	0 (0.0)	4 (5.9)	1 (3.0)
- 20 – 39 years	211 (31.7)	10 (27.8)	0 (0.0)	25 (36.8)	21 (63.6)
- 40 – 59 years	186 (27.9)	10 (27.8)	3 (7.5)	13 (19.1)	4 (12.1)
- ≥ 60 years	224 (33.6)	14 (38.9)	37 (92.5)	26 (38.2)	7 (21.2)
Female*	187 (28.1)	5 (13.9)	7 (17.5)	17 (25.0)	12 (36.4)
Smoking status:*					
- non-smokers	287 (49.1)	14 (46.7)	9 (27.3)	22 (37.3)	16 (59.3)
- ex-smokers	97 (16.6)	5 (16.7)	14 (42.4)	8 (13.6)	4 (14.8)
- current smokers	200 (34.2)	11 (36.7)	10 (30.3)	29 (49.2)	7 (25.9)
Case category:*					
- new case	557 (83.6)	27 (75.0)	31 (77.5)	44 (64.7)	30 (90.9)
- relapse case	95 (14.3)	8 (22.2)	9 (22.5)	10 (14.7)	2 (6.1)
- re-treatment after default	14 (2.1)	1 (2.8)	0 (0.0)	14 (20.6)	1 (3.0)
Extent of disease:*					
- minimal	411 (61.8)	15 (41.7)	17 (42.5)	40 (58.8)	19 (57.6)
- moderate	180 (27.1)	12 (33.3)	11 (27.5)	21 (30.9)	9 (27.3)
- advanced	74 (11.1)	9 (25.0)	12 (30.0)	7 (10.3)	5 (15.2)

*$p < 0.05$ by χ^2, Fisher's exact test or one-way ANOVA, whichever appropriate, for differences between categories of outcome. #tx = treatment.

Table 4.16. Symptoms, co-morbid illnesses, hospitalization and treatment side effects among patients with pulmonary disease by outcome at 12 months.

n (%)	Tx# completed 666 (79.0)	Still on tx# 36 (4.3)	Died 40 (4.7)	Defaulted 68 (8.1)	Transferred out 33 (3.9)
Had any symptoms	517 (77.7)	25 (69.4)	54 (79.4)	21 (66.6)	30 (75.0)
Had risk factors or co-morbidity:*	195 (29.3)	19 (52.8)	32 (80.0)	22 (32.4)	8 (24.2)
Type of risk factors or co-morbidity:					
- drug abuser*	15 (2.9)	2 (7.7)	1 (4.2)	10 (17.9)	0 (0.0)
- alcoholism*	33 (6.5)	7 (25.9)	2 (8.0)	7 (13.0)	0 (0.0)
- HIV*	1 (0.3)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
- Diabetes Mellitus*	83 (12.5)	7 (19.4)	11 (27.5)	7 (10.3)	3 (9.1)
- Other lung diseases except cancer*	51 (7.7)	3 (8.3)	10 (25.0)	6 (8.8)	1 (3.0)
- Any type of cancer*	14 (2.1)	1 (2.8)	7 (17.5)	4 (5.9)	1 (3.0)
- Liver diseases*	19 (2.9)	6 (16.7)	5 (12.5)	2 (2.9)	0 (0.0)
- Other illnesses*	58 (8.7)	5 (13.9)	14 (35.0)	6 (8.8)	5 (15.2)
Duration of treatment (months)*	7.6 ± 1.8	13.8 ± 4.3	4.8 ± 2.9	3.3 ± 2.7	3.2 ± 2.3
Hospitalized during treatment*	213 (32.0)	29 (80.6)	31 (77.5)	25 (36.8)	10 (30.3)
Had treatment side effects*	258 (38.7)	22 (61.1)	15 (37.5)	25 (36.8)	8 (24.2)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between categories of outcome. # tx = treatment.

Table 4.17. Bacteriology status of patients with pulmonary disease by outcome at 12 months.

n (%)	Tx[#] completed 666 (79.0)	Still on tx[#] 36 (4.3)	Died 40 (4.7)	Defaulted 68 (8.1)	Transferred out 33 (3.9)
at pre-treatment:*					
- smear and culture positive	193 (29.8)	14 (38.9)	13 (36.1)	20 (30.3)	9 (29.0)
- culture positive only	190 (29.3)	18 (50.0)	13 (36.1)	17 (25.8)	7 (22.6)
- smear positive only	16 (2.5)	1 (2.8)	3 (8.3)	4 (6.1)	1 (3.2)
- smear and culture negative	249 (38.4)	3 (8.3)	7 (19.4)	25 (37.9)	14 (45.2)
MDR TB*●	3 (0.5)	6 (16.7)	0 (0.0)	1 (1.6)	0 (0.0)

* $p < 0.05$ by χ^2, Fisher's exact test or one-way ANOVA, whichever appropriate, for differences between categories of outcome. [#]tx = treatment.
●Multiple drug resistance TB – those that the isolate shows resistance to at least H and R.

Table 4.18. Polytomous regression analysis of factors affecting outcome at 12 months of patients with pulmonary disease .

Outcome categories[#] & the related independent variables	RR	95% CI
Outcome : **Still on treatment.**		
• age (years)	0.9	0.9 – 1.1
• case category:		
- relapse vs new case	1.7	0.7 – 4.0
- re-treated after default vs new case	1.4	0.2 – 11.8
• disease extent:		
- moderate vs minimal disease	1.4	0.6 – 3.1
- advance vs minimal disease	2.6	1.1 – 6.5
• had any co-morbid illness vs none	2.5	1.2 – 5.4
• microbiology at pre-treatment:		
- smear and culture (+) vs smear and culture (-)	4.1	1.1 – 15.3
- smear or culture (+) vs smear and culture (-)	6.6	1.9 – 23.1
Outcome : **Died.**		
• age (years)	1.1	1.1 – 1.2
• case category:		
- relapse vs new case	1.3	0.5 – 3.2
- re-treated after default vs new case	0.0	0.0
• disease extent:		
- moderate vs minimal disease	1.3	0.5 – 3.3
- advance vs minimal disease	3.5	1.3 – 9.3
• had any co-morbid illness vs none	5.6	2.2 – 14.6
• microbiology at pre-treatment:		
- smear and culture (+) vs smear and culture (-)	1.3	0.4 – 3.9
- smear or culture (+) vs smear and culture (-)	1.1	0.4 – 3.2
Outcome : **Defaulted.**		
• age (years)	0.9	0.9 – 1.1
• case category:		
- relapse vs new case	1.4	0.7 – 3.0
- re-treated after default vs new case	14.1	6.2 – 32.4
• disease extent:		
- moderate vs minimal disease	0.9	0.5 – 1.9
- advance vs minimal disease	0.9	0.4 – 2.3
• had any co-morbid illness vs none	1.1	0.6 – 2.0
• microbiology at pre-treatment:		
- smear and culture (+) vs smear and culture (-)	1.1	0.5 – 2.1
- smear or culture (+) vs smear and culture (-)	1.1	0.6 – 2.0
Pseudo R^2	0.13	

[#] treatment completed was the base category.

4.2.3 LEVEL OF DOT

The IUATLD and the WHO strongly recommended Directly Observed Treatment (DOT) as the mode of treatment delivery for TB. By definition, DOT involves the witness of the ingestion of TB drugs by a health care worker or a designated person. There are different levels of DOT: "DOT plus" which involves giving incentives and enablers together with legal action against defaulters in order to secure close to 100% drugs delivery; "regular DOT" which does not provide any incentives or enablers and "partial DOT" when DOT was given only part of the treatment. Although it is the policy of the Hong Kong Chest Service to give all TB medication by DOT, in reality, it is difficult to do as some patients live far away from any clinics and are working. The purpose of this section is to determine the levels of DOT by examining the percentage of drugs being self-administered by patients.

4.2.3.1 Level of DOT for pulmonary and extra-pulmonary patients

In this analysis, patients who defaulted treatment (81, 8.4%), transferred out (34, 3.5%) and those whose treatment cards were missing (39, 4.0%) were excluded. There were 816 (84.1%) cases that completed treatment and had valid information.

Allowing for self-administration of drugs on Sundays and public holidays, > 90% level of DOT is considered to be fully supervised. Only 34.4% of all patients had > 90% of their treatment given by DOT (Table 4.19). 34.5% of pulmonary cases had > 90% of treatment given by DOT. Of these, 23 (3.3%) had 100% of fully supervised treatment. Among extra-pulmonary patients, 34.2% had > 90% under DOT. Of these, only 5 (4.5%) had 100% DOT (data not tabulated).

11.8% and 14.8% of all patients had 25-50% and < 25% fully supervised treatment respectively (data not tabulated). No difference was observed between the level of DOT between patients with pulmonary and those with extra-pulmonary disease.

4.2.3.2 Level of DOT and outcome at 24 months

There was a significant difference in the distribution of level of DOT among outcome categories (Table 4.20). The majority of patients who "died" had a low percentage of treatment by DOT. There was no dose-response relationship observed between relapse (bacteriological and or clinical) and the level of DOT. As the number of patients with

relapse at 24 months is very small, it is not possible to draw any conclusion from this analysis. A longer period of follow-up is necessary.

Table 4.19. Level of DOT by type of disease.

	Pulmonary	Extra-pulmonary	Total
n (%)	705 (86.4)	111 (13.6)	816 (100.0)
% of DOT			
- > 90%	243 (34.5)	38 (34.2)	281 (34.4)
- 75 – 90%	169 (24.0)	25 (22.5)	194 (23.8)
- 50 – 75%	103 (14.6)	21 (18.9)	124 (15.2)
- < 50%	190 (27.0)	27 (24.3)	217 (26.6)

Table 4.20. Level of DOT and treatment outcome at 24 months.

n (%)	> 90 % 281 (34.4)	75 – 90% 194 (23.8)	50 – 75% 124 (15.2)	< 50% 217 (26.6)
Outcome at 24 months:*				
- treatment completed	268 (95.4)	186 (95.9)	117 (94.4)	198 (91.3)
- bacteriological relapse	7 (2.5)	2 (1.0)	2 (1.6)	1 (0.5)
- clinical relapse	1 (0.4)	4 (2.1)	0 (0.0)	2 (0.9)
- died	5 (1.8)	2 (1.0)	5 (4.0)	16 (7.4)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between level of DOT.

4.2.4 ADHERENCE TO TREATMENT

Non-adherence to self-administered multi-drug TB regimens is common and is the most important cause of failure of initial treatment and relapse. Non-adherence may also result in acquired drug resistance, requiring more prolonged and expensive treatment that is less likely to be successful. In response to these findings, the IUATLD and the WHO have recommended DOT as the mode of treatment delivery. Despite the impressive gains in adherence associated with the use of DOT, non-adherence occurs when patients miss the treatment appointments.

Factors associated with default have been examined in the previous section. The purpose of this section is to determine factors affecting non-adherence in a nested case-control study. For the purpose of this analysis, those who defaulted from treatment (81, 8.4%), transferred out (34, 3.5%) and those missing treatment cards (39, 4.0%) were excluded. Cases (non-adherence) were defined as those who missed ≥ 30 treatment appointments during the whole course of treatment. There were 34 cases that satisfied this criterion. Four controls for each case were selected among those who completed treatment without ever missing or missing ≤ 10% of their treatment appointments. The characteristics of the patients, co-morbid illnesses and treatment aspects were explored in univariate analyses. The variables that showed a significant difference at univariate analyses will be employed further in a multiple logistic technique to build a final model. Analyses will be presented for patients with pulmonary and extra-pulmonary disease.

4.2.4.1 Characteristics of cases and controls

There were 816 (84.1%) patients who had complete information on their treatment cards. Of these, 55.0% never missed any treatment appointment; 36.9% missed ≤ 10%; 4%, 10-20%; 2.3%, 20-30% and 1.7%, > 30% of treatment appointments.

Demographic characteristics:

Cases were younger, more likely to be males and current smokers compared to controls. Married patients were less likely to be a case than those who were singles (Table 4.21). Those who were re-treated after previous default were more likely to miss a high percentage of treatment appointments.

Symptoms and co-morbid illnesses:

Those with any co-morbid illnesses were more likely to miss treatment appointments than those without any co-morbid illnesses (Table 4.22). Drug abusers and those with HIV infection were more likely to miss > 30% of treatment appointments.

Treatment aspect:

There was no significant difference between cases and controls in the number of drug regimens given, the level of DOT and the occurrence of treatment side effects (Table 4.23). Cases were more likely to have more appointments, longer duration of treatment and more frequently hospitalized during treatment than controls. It is not possible to distinguish, based on the available data, whether it was the duration of treatment or the total number of appointments that determined the frequency of missing appointments among cases.

Table 4.21. Characteristics of cases and controls.

	Control	Case
N	136 (80.0)	34 (20.0)
Age (years, mean ± SD)*	49.4 ± 20.8	40.7 ± 19.4
Age group:		
- < 20 years	10 (7.4)	4 (11.8)
- 20 – 39 years	39 (28.7)	16 (47.1)
- 40 – 59 years	35 (25.7)	4 (11.8)
- ≥ 60 years	52 (38.2)	10 (29.4)
Female*	51 (37.5)	4 (11.8)
Marital status:*		
- single	38 (28.8)	18 (52.9)
- married	92 (69.7)	16 (47.1)
- others	2 (1.5)	0 (0.0)
Smoking status:*		
- non-smokers	74 (66.1)	11 (39.3)
- ex-smokers	15 (13.4)	4 (14.3)
- current smokers	23 (20.5)	13 (46.4)
Type of disease:		
- pulmonary TB	102 (75.0)	27 (79.4)
- extra-pulmonary TB	18 (13.2)	7 (20.6)
- extra- and pulmonary TB	16 (11.8)	0 (0.0)
Case category:*		
- new case	114 (83.8)	26 (76.5)
- relapse case	21 (15.4)	5 (14.7)
- re-treatment after default	1 (0.7)	3 (8.8)

* $p < 0.05$ by χ^2, Fisher's exact test or t-test, whichever appropriate, for differences between case and control.

Table 4.22. Symptoms and co-morbid illnesses among cases and controls.

	Control	Case
N	136 (80.0)	34 (20.0)
Had any symptoms prior to treatment	93 (68.4)	21 (61.8)
Had any co-morbid illnesses*	40 (29.4)	16 (47.1)
Type of risk factors and co-morbid illness:		
- drug abuser*	2 (2.0)	5 (17.2)
- alcoholism	4 (3.9)	7 (25.0)
- HIV*	0 (0.0)	1 (7.1)
- Diabetes Mellitus	16 (11.8)	3 (8.8)
- Other lung diseases except cancer	11 (8.1)	3 (8.8)
- Any type of cancer	1 (0.7)	2 (5.9)
- Liver diseases	4 (2.9)	3 (8.8)
- Other illnesses	15 (11.0)	8 (23.5)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between case and control.

Table 4.23. Treatment aspects among cases and controls.

	Control	Case
N	136 (80.0)	34 (20.0)
Number of drug regimens:		
- 1	2 (1.5)	0 (0.0)
- 2	94 (69.1)	20 (58.8)
- 3	30 (22.1)	10 (29.4)
- ≥ 4	10 (7.4)	4 (11.8)
Number of appointments*	162.9 ± 76.4	259.1 ± 114.6
Duration of treatment (months)*	7.8 ± 1.9	10.9 ± 3.3
Level of DOT:		
- > 90%	42 (30.9)	6 (17.6)
- 75 – 90%	25 (18.4)	8 (23.5)
- 50 – 75%	19 (14.0)	9 (26.5)
- < 50%	50 (36.8)	11 (32.4)
Had any treatment side effects	53 (39.0)	11 (32.4)
Ever hospitalized during treatment*	45 (33.1)	19 (55.9)

* $p < 0.05$ by χ^2 or Fisher's exact test, whichever appropriate, for differences between case and control.

4.2.4.2 Factors affecting non-adherence

Table 4.24 shows the result of logistic regression analysis on factors affecting non-adherence. Age had a protective effect against non-adherence (OR 0.9, 95% CI 0.8 – 0.9) while the odds of non-adherence increased with increasing number of treatment appointments (OR 1.01, 95% CI 0.01 – 1.03). The odds of non-adherence among current smokers was 6.0 (95% CI 1.3 – 28.5) compared to non-smokers. Those who were re-treated after previous default had OR 34.4 (95% CI 1.4 – 870.3) of non-adherence compared to new case. The model in Table 4.24 explained about 47% of the variation in the dependent variable.

Table 4.24. Logistic regression analysis on factors associated with non-adherence to treatment.

Independent variables:	OR	95% CI
- Age (years)	0.9	0.8 – 0.9
- Number of treatment appointment	1.01	1.01 – 1.03
- Smoking status:		
- ex-smokers vs non-smokers	3.4	0.5 – 25.4
- current smokers vs non-smokers	6.0	1.3 – 28.5
- Male vs female	14.0	1.6 – 118.6
- Case category:		
- relapse vs new case	0.9	0.2 – 4.3
- retreated after previous default vs new case	34.4	1.4 – 870.3
Pseudo R^2	0.47	

4.2.4.3 Adherence and treatment outcome at 24 months

There was a significant difference in the distribution of treatment outcome at 24 months between cases and controls (Table 4.25). Those who died were more likely to be non-adherent to treatment. There was no relapse (clinical or bacteriological) occurred among cases while five patients relapsed among controls.

The importance of adherence to treatment on treatment outcome of interest i.e. relapse is not known because of the short duration of follow up and the small number of relapses.

Table 4.25. Treatment outcome at 24 months among cases and controls.

	Control	Case
n	136 (80.0)	34 (20.0)
Outcome at 24 months:*		
- treatment completed	125 (91.9)	31 (91.2)
- bacteriological relapse	3 (2.2)	0 (0.0)
- clinical relapse	2 (1.5)	0 (0.0)
- died	6 (4.4)	3 (8.8)

* $p < 0.05$ by χ^2, or Fisher's exact test, whichever appropriate, for differences between case and control

4.3 CONCLUSION

- Persistent high rate of TB in Hong Kong:

  TB notification rate in Hong Kong was 103/100,000 population in 1996 and the rate has been increasing to 115/100,000 in 1998 (10 times those in the developed countries).

- Characteristics of TB patients in 1996:
  - Age and sex differences were prominent in the distribution of TB patients in 1996. TB was found more in males than female; 69.9% of TB cases were males. 38.2% of TB patients were aged ≥ 60 year.
  - 77.1% of the patients had pulmonary disease; 13.1% had extra-pulmonary and 9.8% mixed of pulmonary and extra-pulmonary disease.
  - About 40% of patients with pulmonary TB had moderate to advanced disease at time of diagnosis.
  - Among patients with pulmonary TB, 11.7% of culture positive isolates had resistance to any one of the first four line drugs (S, H, R, E) while 4.2% had resistance to more than one drug. 27.8% of these resistance were acquired in nature. 2% of patients had MDR TB.
  - There were high-risk groups: diabetes mellitus was found in 12.2% of patients, silicosis 0.8%, drug abusers 4.0%, and alcoholism 7.4%.
- Treatment outcome:
  - Treatment completion rate: At 6 months, 40.3% of smear positive pulmonary TB patients completed treatment (smear negative – cured and smear not done treatment completed) and at 12 months 75.6% completed treatment. The treatment completion rate at 6 and 12 months among smear positive TB patients were significantly lower than the rate of 85% targeted by IUATLD and WHO for developing countries.
  - Still on treatment: 4.3% of the pulmonary TB patients was still on treatment at 12 months. Pulmonary patients who were still on treatment at 12 months were those with advance disease; any co-morbid illness, those with positive sputum smear and/or culture at pre-treatment.
- Mortality:

  4.7% died at 12 months. Death at 12 months was associated with advanced disease, age and the presence of co-morbid illnesses.

- Default:

  8.4% of all cases defaulted treatment at 12 months. 39% of default occurred in the first 2 months of treatment. The most important risk factor for default was a history of previous default.

- Duration of treatment:

  Pulmonary TB patients, on the average, received chemotherapy for 7.2 ± 2.9 months while those with extra-pulmonary TB 8.2 ± 3.1 months. 44.9% of pulmonary TB and 64.6% of extra-pulmonary TB cases received treatment for > 6 months. A longer duration of treatment was prescribed for those with co-morbid illnesses such as DM, silicosis, HIV infection, extensive disease and relapse.

- Level of DOT:

  Despite the implementation of fully supervised treatment policy since 1970s, this study found that in 1996, only 34.4% had fully supervised treatment. The rest had self-administered drugs parts of the time. The significance of the level of DOT on the relapse rate of disease is not known as the duration of follow up is too short.

- Adherence to treatment:

  55.0% of patients in this study never missed any treatment appointments, 36.9% missed ≤ 10%, 4% missed between 10-20%, 2.3% missed between 20-30% and 1.8% missed > 30% of treatment appointments. The risk factors for non-adherence to treatment (those missing > 30 times of treatment appointments) were duration of treatment, a previous history of default from treatment. The short duration of follow-up and the small sample size do not permit analysis into the association of disease relapse with compliance to treatment.

CHAPTER V

GENERAL DISCUSSION, IMPLICATION AND RECOMMENDATION

5.1. GENERAL DISCUSSION

5.1.1. Epidemiological trend of TB in Hong Kong

Over time, TB notification and mortality rates have been declining in Hong Kong. Analysis of notification rate data across time has shown that TB is high in the elderly and in men. This pattern of age and sex distribution is compatible with TB in declining phase[92,93].

During its peak, TB epidemic is characterized by very high incidence and mortality rates. At its peak, TB mainly affects young adults and often females[92]. No high-risk groups are found [92]. The most common cause of the disease is recent infection.

TB in declining phase is characterized by lower and steadily declining incidence rates. At this stage, TB incidence is highest in the elderly and especially males. At this stage, high-risk groups present. The most common cause of disease is re-activation of disease from remote infection. After reaching its peak, most community members have already been infected with TB and the incidence of TB either become steady or starts to decline. When TB is uncommon in the community, the disease is due mainly to re-activation of disease among the elderly.

One possible reason for TB re-activation among the elderly is the loss of immunity with aging[100,101]. As discussed previously (Chapter 1.4), the progression of TB infection toward disease depends on cell-mediated immune response of the individual. Throughout life, there is a progressive appearance of immune dysregulation with aging such as impairment of T cell functions as reflected the decline of T cell proliferation and secretion of INF-gamma.

The reason for the disease to affect men during the declining phase of TB epidemic is unclear. It has been suggested that the mobility and the higher possibility of being infected in the past in men may be the reason for the higher rate of TB in men. Others argue that it may reflect a difference in the access to health services between men and women in the past.

5.1.2. Persistently high tuberculosis rate in Hong Kong

TB has been perceived as a disease of the disadvantaged. The majority of TB cases occurred in poor countries. Hong Kong gross domestic product in 1996 was $US 175.2 billion with gross income per capita of $US 27,333[94]. In the same year, gross income per capita in Canada, the US, Japan, Singapore, the UK and South Korea was $ 19,970; $ 24,740; $ 31,490; $ 19,850; $ 18,060 and $ 7,660, USD respectively. Yet in 1996 the TB rate in HK was more than ten times higher than those of Canada and the US (less than 10/100,000 population); and almost doubled that of Singapore (57/100,000 population)[95]. Thus, the persistent high rate of TB in Hong Kong is not due to lack of available resources. Hong Kong was and still is a high-risk place for TB [92].

There are several possible factors that may contribute to this persistently high rate of TB in Hong Kong. These include:

a. Migration

Various studies[92,93,96] show that the prevalence of TB among migrants reflects the prevalence of TB in their homelands. Individuals from high risk countries such as China (1990 TB prevalence 523/100,000 population[97]), Thailand (1994 notification rate 79/100,000 population[98]), the Philippines (1992 notification rate 390/100,000 population[98]), Indonesia (1990 notification rate 250/100,000 population[98]) and the Middle East (1991 TB notification rate range from 4.5/100,000 population to 533.3/100,000 population[99]) come to work in Hong Kong. However, these migrants are in the 15 – 40 year old age group. Historical data show (Figure 4.3, Chapter 4) that there were population increase in this particular age group but the rate of TB in this particular age group has been declining steadily. It is unlikely that migrants are responsible for the persistent high rate in Hong Kong.

b. Changes in demographic structure

Figure 4.3 shows that demographic structure is changing, namely population in Hong Kong is getting older. In addition, the rate of disease in those over the age of 60 years has been increasing. In 1996, 35.4% of all TB cases occurred among those ≥ 60 years old; in 1998, the proportion increased to 42.6%.

c. HIV infection

Since 1982, HIV infection has emerged with the highest relative risk for TB ever recorded. The impact of HIV infection on the increase of TB incidence was first noted in the US[102]. In the US, prevalence of TB has been declining on the average of

5% annually since 1950s. In 1985 to 1991, the prevalence has increased by 18%. The occurrence of TB among individuals with HIV infection was the major factor contributing to the changes in the pattern of TB decline. The impact of HIV infection was also noted mainly in sub-Saharan Africa (Table 1.1, Chapter 1).

In Hong Kong, HIV did not contribute to the persistence high rate of TB. In 1996, there were only 6 TB patients with HIV infection. By mid 1999, the cumulative number of HIV infected individuals in Hong Kong was 1255 and the total number with AIDS was 409.

d. Over-crowding

Hong Kong is one of the most densely populated places in the world. Hong Kong is only about 1000 km^2 in size with population amounting to 6,409,800 in 1996.

Various studies have shown that over-crowding is one of the identified risk factors for TB[103,104]. The probability of exposure to M. tuberculosis is a function of the number of cases of pulmonary TB in the community, the density of the bacteria in expectorated sputum, the density of bacteria in the air surrounding the infectious person (a function of ventilation and size of the inhabited space), the number of people presents and the duration of contact with the individuals with the disease[93].

5.1.3. High rate of tuberculosis in the elderly population

Differences in the distribution of TB across age groups were found in this study. The highest incidence of TB occurred in those aged ≥ 60 years especially among men. In the developed world and increasingly among countries in the Pacific Rim and South East Asia, elderly men are the largest group with the disease and the largest possible source of infection in the community[118].

The presentation of the disease in the elderly is often atypical, for example, the disease tend to be more insidious in onset, fever often absent and haemoptysis less common. Chest x-ray changes may also mislead the physicians since the disease is frequently present in the mid or lower lung zones[118]. The findings of this study are in accord with others. Tuberculosis in the elderly in Hong Kong is often recognized at a late stage, thus prolonging their period of infectiousness to others.

The reason for the high rate of TB or perhaps the increase susceptibility to TB among the elderly is unclear. In Hong Kong, tuberculosis in the old age group is most likely to be due to reactivation rather than to recent infection; however, further study using

molecular biology method will be required to support that[123]. Risk factors that determine whether an infected elderly will develop disease are unknown, but it probably relate to time when TB prevalence was still very high, the presence of co-morbid illnesses, the use of immunosuppressive drugs, the nutritional status and the immunocompetence of the individuals[119]. Studies by Alvarez et al[120,] and Umeki[121] have shown that elderly patients more often had diabetes mellitus, gastrectomy and malignancy than younger patients, and they are more likely to be receiving immunosuppressive drugs and had malnutrition. The present study supported their findings that elderly patients have co-morbid illnesses known to be associated with an increased risk for tuberculosis. These conditions may adversely affect cell-mediated immunity, thus predisposing patients to re-activation of old TB infection or to progression of new infection to disease.

Poverty in the elderly has also been identified to be associated with higher rates of TB. Kearney et al[122] have shown that in Leeds, those aged ≥ 65 years living in areas defined as Urban Priority Areas had twice the rates of TB compared to the same age group living in the rest of the city. It has been argued that as people get older, their income and ability to look after themselves often declines. These factors may lower resistance to disease and therefore contribute to an increase in TB. Poverty and overcrowding associated with poverty are two important risk factors for some of the elderly people in Hong Kong.

Another possibility is institutional care. More elderly people in Hong Kong are now living in old age homes. A previous study has demonstrated a high rate of tuberculosis (1000 to 2000/100,000) in old age homes in Hong Kong[127]. In these situations, recent infection could be a cause of disease; again molecular studies of isolates will answer this question. It should be pointed out that there are at present only 50,000 places in old aged homes and there are slightly over 1 million people in Hong Kong over the age of 60 years. The contribution of cases from nursing homes is limited.

Because of the high prevalence of tuberculosis in the old age groups in Hong Kong and the increasing population in this age group, it is important that this group should be targeted for preventive measures.

5.1.4. Sex differences in distribution of tuberculosis in Hong Kong

This study has demonstrated that men had higher rates of tuberculosis than women did in all age groups. The differences between men and women increased with age. For those over the age of 60 years, the rate in men is 4 times those of women.

The reason for sex differences in tuberculosis is not clear. In general, a higher proportion of men found in TB notification worldwide[123]. In developed countries, tuberculosis mortality rates among young adult aged 15 – 44 were initially higher in women than men[124]. With the decline in the risk of infection in these countries, TB mortality rates became highest in elderly men. The cumulative experience of PPD skin test surveys has shown that in most situations, the prevalence of infection is higher in men than women, beginning in adolescence. Thus there is a higher annual risk of infection in young men than women and a higher notification rate of disease among men from the aged of 15[125].

It has been hypothesized that the difference in the prevalence of infection among men and women is due to differences in the numbers of contacts inside and outside of the households. Until adolescence, men and women have similar numbers of contacts with people outside the household and family; after adolescence, males have more frequent external contacts[125].

Comparison of infection rates with disease rates in some settings suggests that women may have a higher rate of progression to disease in their reproductive years, whereas men have higher rates of progression when they are older[126]. Due to the higher prevalence of infection among men from early adulthood onward, a higher proportion of the PPD positive men may have had earlier self-limited disease that was re-activated in old age. The present study has identified that the prevalence of alcoholic and drug abuse is higher among male than female patients in Hong Kong. Heavy alcoholic consumption may depress immune system[125] and drug abuse is a well known risk factor for tuberculosis.

Hudelson[124] suggests that the differences in the prevalence of TB among men and women may be due to socio-economic and cultural factors. Socio-economic and cultural factors may be important in 2 ways: 1) in determining overall sex differences in rates of infection, progression to disease, treatment and treatment outcome; and 2) in terms of barrier to detection and successful treatment of TB. Greater migration by men may put them at a higher risk of contact with other TB-infected individuals. Sex differences may exist in rates of treatment compliance, namely a higher default rate among men.

In Hong Kong the low rate of tuberculosis in women is not due to underreporting as a higher proportion of women had minimal disease at the time of diagnosis suggesting that they were diagnosed early. The difference between men and women could very well be related to the effects of sex hormones on the immune system which is vital for body

defense[125]. The finding that men in the old age group are at a much higher risk for tuberculosis is helpful in focussing the target group for prevention programs.

5.1.5. Treatment completion rate

To reduce disease transmission and eventually to eliminate TB, it is necessary to cure infectious TB patients, i.e. those with smear positive pulmonary TB. The WHO and the IUATLD stated that the first and foremost goal of a TB control program is to achieve at least an 85% treatment completion rate in developing countries or 90 – 95% in developed countries in patients with sputum smear positive[45,62]. In Hong Kong, only 78.5% of patients with pulmonary TB completed treatment at 12 months; the proportion was the same for the smear positive group. The proportion that completed treatment in Hong Kong fell short of the WHO and the IUATLD standard even for developing countries.

Of those who did not complete treatment, 8.1% of all or 8.8% of previously smear positive pulmonary TB patients defaulted treatment. The proportion of 8% of patients defaulting treatment is not a high figure compared to a number of programs that give self-administered drugs. However, this proportion is very high compared to the experience in China giving medication by DOT[106]. The WHO program in China was based on outpatient fully supervised treatment. It involved the cooperation of village doctors, who were being paid in a small amount, as designated persons to observe drugs administration and follow-up of patients. All new smear positive cases were treated with SHRZ for 2 months followed by 4 months of HR. In 1991, this program achieved treatment completion rate of 93.4% among sputum smear positive pulmonary TB patients. Only 1.6% of patients defaulted from treatment. Very close supervision from village doctors who lived nearby can achieve a very high treatment completion rate and a low default rate.

The reasons for not completing treatment other than default in Hong Kong included those who died, and those who transferred out of the system and being treated elsewhere and those who were still on treatment at 12 months. Thus the only way to improve treatment completion rate is to reduce the number of people defaulting from treatment and to improve on the current DOT strategy that is being practiced by the Hong Kong Chest Service.

5.1.6. Default from treatment

Default from treatment is a major problem in management of TB patients. Although animal and in-vitro studies suggest that patients with active TB remain contagious for 2 weeks after the initiation of treatment[117], this has not been proven in clinical settings. Patients with smear positive disease are likely to be contagious much longer. It has been estimated from previous studies that one smear and culture positive case of pulmonary TB may infect, on the average, 12 individuals and each culture positive case may infect 6 individuals annually[93]. It has also been estimated that about 15% of TB infected individuals will develop disease which in turn infect others. Any patients who defaulted from treatment while they are still smear or culture positive should be considered infectious. While it is not known whether default from treatment is the reason of persistent high rate of tuberculosis in Hong Kong, these patients certainly provide a pool of infectious individuals in the community. The single most important factor predicting default from treatment was a history of previous default. The Chest Service should take active steps to reduce the rate of default from treatment, particularly the recurrent offenders.

5.1.7. Non-adherence to treatment

The most important factor in influencing the response to chemotherapy with effective regimens is adherence to treatment[113]. Self-administered treatment of long duration frequently fails because patients tend to stop treatment especially after they became symptoms-free, or to take the drugs irregularly. Factors affecting adherence to treatment are complex and involve poorly understood human behaviors, clinic business hours, the type and duration of treatment, side effects and costs to patients[111]. On the other hand, adherence also involves the efforts from health care providers, particularly involving physicians. Despite ample evidence supporting the effectiveness of short-course chemotherapy for TB, many physicians, including those in Hong Kong, did not follow the recommendations on drugs combination, dosages, frequency of administration and duration of treatment[110].

Defaulting from treatment, the most extreme kind of non-adherence, has been discussed in the previous section. This study also addressed patients who did not disappear completely but tended to skip treatment appointments. The most important risk factors for non-adherence were the length of treatment, being a male and a current smoker. A

history of default from previous treatment was another important risk factor. Special attention should be paid to patients who have a previous history of default from treatment.

A similar study using the same criterion for non-adherence (missing ≥ 30 treatment appointments), conducted in Denver[38], found that only alcohol abusers (OR 4.2, 95% CI 2.4 - 7.4) and the homeless (OR 4.0, 95% CI 2.5-6.4) were associated with increased risk of non-adherence, adjusted for sex, Asian ethnicity, born in the US and residence of inner city. Non-adherence was found to be associated with poor treatment outcome, i.e. microbiological failure, clinical failure and relapse.

In Hong Kong, non-adherence was not associated with treatment failure or relapse. However, the result on relapse should be interpreted with caution since the duration of follow-up was relatively short.

5.1.8. Drug resistance among pulmonary TB

One of the consequences of non-adherence to treatment is the development of drug resistance. The prevalence of resistance to any four first line TB drugs in Hong Kong in 1996 (16%) was higher than industrialized countries such as UK (8.2%)[108] and Singapore (3.9%)[95]. The prevalence of MDR TB in Hong Kong was also higher than Singapore (0.8%). Streptomycin and Isoniazid have been used for a long time in Hong Kong. It is understandable that resistance rates for these 2 drugs were higher than the resistance rates toward R and E. In the last 10 years TB notification in Singapore was between 48 to 57 per 100,000 population i.e. about half the notification rates in Hong Kong for the same periods of time. As the incidence of disease and of drug resistance reflects the quality of the TB management program, the results of the present study indicates that the TB management program and the DOT strategy in Hong Kong should be improved.

5.1.9. Duration of treatment

Despite the adoption of the Short Course Service Program (multiple drug treatment for 6 months) in Hong Kong since 1989[107], the majority of TB patients, whether pulmonary or extra-pulmonary, received treatment longer than 6 months.

Various scientific bodies in the world recommended a standard treatment of only 6 months for the majority of TB cases. The Joint Tuberculosis Committee of The British

Thoracic Society (BTS)[111], the American Thoracic Society (ATS) and the Centers for Disease Control[112] recommended that a six month short course regimen, with four drugs (HRZE) in the initial phase should be used for all forms of TB, except for TB meningitis and multiple drug resistance TB. Prolonged treatment beyond 6 months was not recommended for patients complicated by silicosis, diabetes mellitus, liver disease, renal disease, HIV infection and pregnancy. The treatment guidelines of the WHO[6] and the IUATLD[45] are essentially the same with those issued by the BTS and the ATS. Further, various clinical trials jointly conducted by British Medical Council and the Chest Service in the past had identified the effectiveness of the short course chemotherapy with appropriate drugs[64,65,66]. A 3-month, 4-months and 6-months chemotherapy conducted in Hong Kong, among previously smear negative cases (regardless of the culture results), has proven that 4 months treatment was sufficient to treat previously smear negative pulmonary TB cases[107]. During 5 years follow-up, those who were being treated for 4 months had 2% relapse rate the same with those being treated for 6 months.

Physicians at the Chest Service in Hong Kong tended to prescribe more prolonged treatment program. It is not known whether prolonged treatment would yield a lower relapse rate. Given the unproven effectiveness of prolonged treatment, and the findings in this study that the longer the duration of treatment, the poorer the adherence to treatment, the Chest Service should take steps to reinforce its policy of short course chemotherapy in treatment of tuberculosis.

5.1.10. DOT

Treatment completion in TB is very important in order to prevent relapse, development of chronic disease and drug resistance. Although DOT has been recommended by the WHO and the IUATLD recently, it originated in the late 1940s and early 1950s when the British Medical Research Council used it in clinical trials for TB treatment in Africa, Asia (including Hong Kong) and London. In the WHO assessment of worldwide TB control in 1995, 75 of 180 countries responding to WHO survey had implemented DOT[112]. The adoption of DOT has been associated with reduced rates of treatment failure, relapse disease and the emergence of drug resistant TB. In a smaller scale, experience in New York City found that the application of DOT was followed by a 21% decrease in case rate and a 39% decrease in the rate of drug resistant isolates[115]. The wide spread uses of DOT maybe an important factor in the recent decrease of TB

incidence in the US[116]. Prior to the emergence of HIV infection in the 1980s, the US did not implement DOT.

Despite the impressive gains in treatment adherence associated with the adoption of DOT, non-adherence with DOT occurs when patients fail to show themselves for the administration of chemotherapy. In 1998 The US Public Health Tuberculosis Guidelines Panel evaluated evidence on the relative effectiveness of DOT in achieving treatment completion for pulmonary TB[36]. The panel chose 27 studies that satisfied the criteria with treatment completion for pulmonary TB as an outcome. There were 5 randomized or semi-randomized studies, 12 prospective trials without controls, 7 retrospective studies, 2 case-control studies and 1 cross-sectional report. The Panel found that the 12 studies based on comprehensive, patient-centered DOT strategies, such as fully supervised DOT with multiple incentives and enablers, reported the highest treatment completion rates (enhanced DOT). The completion rates ranged from 86% to 96.5% for a variety of patient populations, including alcoholics, substance abuse patients, incarcerated patients, homeless persons, and patients infected with HIV. The rate of TB relapse reported in these studies ranged from 0% to 11.5%. For the 4 studies of DOT without extensive enablers and incentives, treatment completion rates ranged from 85% to 87.5% and reported rates of relapse ranged from 0.8% to 4.9% (DOT). With modified DOT, supervision was used for only part of the treatment period (during hospitalization phase of therapy), and thereafter, patients were self-supervised. The last strategy appeared to be less effective with treatment completion rates ranging from 78.6% to 82.6%.

Although fully supervised DOT is the treatment delivery policy of the Hong Kong Chest Service for TB patients, this study has shown that in 1996 only 34.4% of patients received DOT for the whole duration of treatment, the remaining patients received self-administered drugs part of the time. With the short duration of follow up, it is not possible whether over 90% DOT or partial DOT affects the rate of disease relapse.

5.2. IMPLICATIONS AND RECOMMENDATIONS

1. Even though economically a developed country, Hong Kong is still being classified as a high-risk place for TB. In 1996, TB notification rate was 103/100,000 population and has been increasing since. There are several possible factors responsible for the persistent high rate of TB, namely:
   a. High TB incidence among the elderly and the aging population in Hong Kong;

b. Over-crowding;

c. A rate of default from treatment of 8% in 1996 and has not changed over the years. 39.4% default occurred during the first 2 months when the patient's sputum was still positive for the mycobacteria;

d. The presence of a large source of TB infection

2. The rate of tuberculosis among those over the age of 60 years was high and especially men; the notification rate of men over the age of 60 was 448/100,000 reaching epidemic proportion

3. The treatment completion rate in Hong Kong in 1996 was lower than what is recommended by the WHO as the goal for developing countries. This low treatment completion rate could be partly accounted for by default from treatment

4. Default from treatment occurred in 8% of patients. 39.4% defaulted while their sputum was still positive on smear or culture for M. tuberculosis suggesting that they were still infectious to people in the community. It is possible that these individuals contributed to the persistent high rate of tuberculosis in Hong Kong. Every effort should be made to reduce the rate of default from treatment

5. The average duration of treatment was longer than 6 months. For those with relapse disease, extra-pulmonary involvement, co-morbid illnesses, drug resistant TB, the duration of treatment was even longer, often 9 or 12 months. There is an association between the degree of non-adherence and the duration of treatment, the longer the duration of treatment, the higher the degree of non-adherence. The Chest Service should reinforce the policy on short course chemotherapy

6. Although the policy of the Chest Service is to give treatment to all patients by the DOT strategy, in reality, this is not true. A substantial percentage of patients received self-administered treatment part of the time. While analysis failed to show any association between treatment failure and relapse of disease and the percentage of drugs given by DOT, it is not known whether if all medications were given by DOT to all patients, the rate of default might reduce

The following are recommendations for the Chest Service based on results of this study:

1. <u>Improving DOT program</u>

The persistent high incidence of disease and the moderate rate of drug resistance suggest that the DOT strategy that is being practiced by the Chest Service is not adequate.

Treatment completion rate for pulmonary TB patients was well below the recommended rate from the WHO and the IUATLD. It is necessary to ensure that every patient receives treatment through DOT in order to increase treatment completion rate, thus reducing the rate of drug resistance. The available incentives and enablers program at the Chest Service can be expanded to cover a larger population particularly for the elderly

2. Reducing the number of defaulters

   More incentives and enablers should be given to the patients who require them in order to reduce the number of defaulters. It is necessary for the community locally to debate the possibility of enforcing the Health Act for communicable disease control. The possibility of legal sanction including compulsory quarantine for patients with infectious tuberculosis when collaborative efforts failed and all barriers to treatment for the patient has been removed

3. Focusing resources to reduce TB incidence among the elderly

   This study has shown that the majority of pulmonary TB cases occurred among the elderly. Historical notification rates data also showed that the rates of TB among those aged 60 years or older have been increasing over time. A pilot program for screening for tuberculosis among residents in old age homes should be conducted using chest x-ray and sputum examination. Collaboration with Geriatric division in every hospitals as well as private practitioners should be developed for such programs

4. Reducing the duration of treatment

   The policy of short course chemotherapy of 6 months for patient with tuberculosis should be enforced to improve adherence to treatment. It is necessary to evaluate whether prolonged treatment among patients with co-morbid illnesses is worthwhile. The evaluation can be done in a 5 years follow-up of this cohort of 1996 TB patients

5. Education

   Doctors and nurses and other paramedical staff should be educated about the high prevalence of tuberculosis in Hong Kong especially among the elderly. In addition, they need to know that the clinical presentation of tuberculosis in the elderly can be atypical. Early diagnosis and early treatment is necessary to reduce the pool of infectious patients in the community.

6. Development of an evaluation database on all patients being treated for TB

   The evaluation should be on all patients including those being treated by private practitioners and by physicians in public or private hospitals. The form should contain the

following information: name, HKID, case category, bacteriology, drug regimen, duration of treatment and outcome. The evaluation form should be submitted at the end of treatment, or when patients defaulted, died or transferred out. The addition of such administrative work would not add a large burden to the annual Chest Service budget. A clerk can be assigned specifically to be responsible for contacting, collecting and entering data. It has been proven that the Epi-Info program is sufficient to handle a large amount of information. The evaluation data can be easily linked to the already established notification database.

5.3. CONCLUSION

Tuberculosis notification rate in Hong Kong is still high and has been increasing since 1996. This study has identified several possible factors that may contribute to this persistently high rate of TB. These factors are high rate of TB among the elderly and the relatively high rate of default among those being treated for TB.

This study has not been able to show the association between duration of treatment, adherence to treatment and its impact on relapse. As such, it is necessary that the 1996 TB patient cohort is followed-up further to assess the impact of duration of treatment, adherence to treatment and relapse of the disease. It can simply be done by computerizing 1997, 1998, 1999 and 2000 PRFs data and linked it with 1996 PRF database that has been done during this study. Further study among the elderly by employing RFLP technique is necessary in order to investigate the pattern of disease transmission.

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Appendix 1. Program Review Form 1.

PRETREATMENT (PRF FORM 1) (To be completed at DOS (date of starting treatment)) PRF1-1-7-96(Rev)

Name: _____

Clinic No.: __ __ - __ - __ __ __ __ __ - __ Sex: *M / F* * Age: __ __ DOS: __ __ / __ __ / 19 __ __

HKID No.: __ - __ __ __ __ __ __ - (__) or *Passport / Birth Certificate* * No.: _____

Expected date of completion of PRF FORM 2 (6-MON): __ __ / __ __ / 19 __ __

PRF FORM 3 (9-MON): __ __ / __ __ / 19 __ __

PRF FORM 4 (2-YR): __ __ / __ __ / 19 __ __

Part A: Previous treatment

- within past five years *Y / N / Unknown**

  total duration = *(< 1 month) / (1 month - 1 year) / (> 1 year)**

- more than five years ago *Y / N / Unknown**

  total duration = *(< 1 month) / (1 month - 1 year) / (> 1 year)**

Part B: Disease classification (more than one item may be ticked)

Pulmonary Tuberculosis	○		
Extra-pulmonary Tuberculosis			
meninges	○	bone and joint	○
pleura	○	lymph node	○
abdomen	○	genito-urinary tract	○
skin	○	miliary tuberculosis	○
others (please specify)_____			○

Part C: Extent of disease (For pulmonary tuberculosis only)

(1) Minimal Disease (< RUL)	○	Cavity: *Y / N**
(2) Moderate Disease (> RUL)	○	
(3) Advanced Disease (> a lung)	○	

Part D: Case category

New Case ○

Retreatment Case

- Relapse:
  - within 5 years from DOS of last course of treatment ○
  - more than 5 years from DOS of last course of treatment ○
- Treatment after default ○
  - The last anti-TB treatment has been given:
    - with DOS on __ __ / __ __ / 19 __ __
    - PRF has been filled in for that DOS: *Y / N**
- Failure of previous regimen ○

Others (please specify)_____ ○

Completed by Dr. _____ **on** __ __ / __ __ / 19 __ __

Appendix 2. Program Review Form 2.

6-MON (PRF FORM 2) (To be completed at 6 months from DOS) PRF2-1-7-96(Rev)

Clinic No.: __ __ - __ - __ __ __ __ __ - __ DOS: __ __ / __ __ / 19 __ __

HKID No.: __ - __ __ __ __ __ __ - (__) or *Passport / Birth Certificate* * No.: _____

Part E: Regimen used

(1) SCSP (as originally planned)

(a)

Intensive phase						Maintenance phase					
2 mo	○	HRZ	○	daily	○	4 mo	○	HR	○	daily	○
4 mo	○	HRZE	○	3x/wk	○	2 mo	○	Others	○	3x/wk	○
__ mo	○	HRZS	○	mixed	○	__ mo	○	_____		mixed	○
		Others	○								
		_____									

(b) Duration of deviation from the above regimen: ≤2 wk / >2 wk *

If > 2 wk, the reasons being (more than one item may be ticked):

- Adverse effects of drugs:
  - Gastro-intestinal upset ○
  - Skin rash ○
  - Visual ○
  - Impaired liver function ○
  - Vestibular ○
  - Arthropathy ○
  - Others _____ ○
- Drug resistance ○
- Poor drug compliance ○
- Others (please specify)_____ ○

(2) Non-SCSP (as originally planned) _____ (fill in regimen, if possible) ○

Reason(s) for choosing non-SCSP _____

(3) Has patient been allocated to any treatment regimen for research study for this episode? *Y / N* *

Part F: Condition at 6 months (from DOS)

(1) Treatment completed, or to be completed in ≤ 2 weeks ○

(2) Still on treatment because (more than one item may be ticked):

- SCSP treatment has been modified (see Part (E)(1)(b)) ○
- Concomitant medical conditions (e.g., silicosis, etc) ○
- Relapse case ○
- Extrapulmonary disease ○
- Others (please specify) _____ ○

(3) Defaulted or refused treatment at chest clinic for more than 2 months since _____ month from DOS ○

(4) Others (please specify) _____ ○

→ **(NB**: *If "Treatment completed, or to be completed in ≤ 2 weeks" is ticked, please select "Need to fill in by nurse" in the following box; otherwise, select "No need".)*

(Please see explanatory notes before completion of this box.) *Need / No need * to fill in by nurse*

Part G: Percentage of treatment defaulted in the 6-mo period

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○

Part H: Percentage of treatment given but not under supervision by chest clinic or chest hospital in the 6-mo period

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○ (superv. by other parties)

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○ (suppl. to patient/relative)

By (1) Dr. _____ on __ __ / __ __ / 19 __ __ (2) Nurse _____ on __ __ / __ __ / 19 __ __

Appendix 3. Program Review Form 3.

9-MON (PRF FORM 3) (To be completed at 9 mo from DOS) PRF3-1-7-96(Rev)

Clinic No.: __ __ - __ - __ __ __ __ __ - __ DOS: __ __ / __ __ / 19 __ __

HKID No.: __ - __ __ __ __ __ __ - (__) or *Passport / Birth Certificate* * No.: _____

Part I: Sputum results

	Pre-treatment			At 2 month			At 5 or 6 month		
	positive	negative	unknown	positive	negative	unknown	positive	negative	unknown
smear	○	○	○	○	○	○	○	○	○
culture (MTB)	○	○	○	○	○	○	○	○	○
culture (NTM)	○			○			○		

Part J: Pre-treatment sensitivity test results

	S	R		S	R		S	R
S	○	○	Z	○	○	Cyclo	○	○
H	○	○	Ofl	○	○	Others	○	○
R	○	○	Ethi	○	○	_____	○	○
E	○	○	Kana	○	○	_____	○	○

Source of ST: YFS ○ TGH ○ RH ○ HOH ○ Others ○

Part K: Treatment outcome at 9 months (from DOS)

(1) Cured (more than one item may be ticked) ___
- bacteriological conversion ○
- radiological improvement ○
- other evidence of clinical response ○

(2) Treatment completed ○ ___ → Total interval of treatment (from DOS to date of stopping treatment) = 6 mo / 7 mo / 8 mo / 9 mo *

(3) Still on treatment ○
(4) Changed to be treated by GP/other doctors ○
(5) Defaulted ○
(6) Failure ○
(7) Died (from _____) ○
(8) Others (e.g. incorrect diagnosis)
_____ ○

↳ *(**NB**: If the total interval of treatment is 9 months, please select "Need to fill in by doctor" in the following box and then complete Part L onwards; otherwise, select "No need" and then end of form.)*

Part L: If the total interval of treatment = 9 months, the regimen used is: *Need / No need * to fill in by doctor*

(1) (a)

Intensive phase						Maintenance phase					
2 mo	○	HRZE	○	daily	○	7 mo	○	HR	○	daily	○
4 mo	○	HRZS	○	3x/wk	○	5 mo	○	HRE	○	3x/wk	○
__mo	○	HRZES	○	mixed	○	__mo	○			mixed	○

(b) Duration of deviation from the above regimen: *≤2 wk / >2 wk* *

(2) None of the combinations of the above ○

*(**NB**: If any one combination of Part L (1)(a) is ticked, please select "Need to fill in by nurse" in the following box; otherwise, select "No need".)*

(Please see explanatory notes before completion of this box.) *Need / No need * to fill in by nurse*

Part M: Percentage of treatment defaulted in the 9-mo period

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○

Part N: Percentage of treatment given but not under supervision by chest clinic or chest hospital in the 9-mo period

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○ (superv. by other parties)

≤5% ○ 6-10% ○ 11-20% ○ 21-30% ○ ≥31% ○ (suppl. to patient/relative)

By (1) Dr. _____ **on** __ __ / __ __ / 19 __ __ **(2) Nurse** _____ **on** __ __ / __ __ / 19 __ __

Appendix 4. Program Review Form 4.

2-YEAR (PRF FORM 4) (To be completed at 2 yr from DOS) PRF4-1-7-96(Rev)

Clinic No.: __ __ - __ - __ __ __ __ __ - __ DOS: __ __ / __ __ / 19 __ __

~~HKID~~ No.: __ - __ __ __ __ __ __ - (__) or *Passport / Birth Certificate* * No.: _____

Part O: Total interval of treatment given (from DOS to date of stopping treatment)

(1) ≤ *9 months* / _____ *months* * ○

(Date of stopping treatment = __ __ / __ __ / 19 __ __)

(2) Still on treatment ○

(3) Not applicable because patient has defaulted treatment before completion ○

Part P: Condition at 2 years (from DOS) (more than one item may be ticked):

(1) Cured or treatment completed, with no relapse ○

(2) Cured or treatment completed, but with relapse at _____ months since DOS

- Bacteriological relapse ○
- Radiological relapse ○
- Other evidence of relapse

_____ ○

(3) Retreated (after default) at _____ months from DOS ○

(4) Treatment failure case ○

(5) Lost to follow up at _____ months from DOS ○

(6) Died (from _____) at _____ months from DOS ○

(7) Others _____ ○

Part Q: The anti-TB medication for this episode has been given by the following parties (more than 1 item may be ticked):

(1) Chest clinics ○

(2) HA hospitals
- TB & Chest units ○
- other units ○

(3) Private doctors ○

(4) Medical practitioners outside Hong Kong ○

(5) Others

_____ ○

Completed by Dr. _____ on __ __ / __ __ / 19 __ __

Appendix 5. Program Review Form 1-A.

PRF Form 1-A

1. Clinic no : _____ 2. Name : _____

3. Current address : Apt # : _____ Building : _____

Street : _____ Area : _____

4. Occupation : _____

5. Marital status : 1. single 2. married 3. other _____ 5

6. Smoking status : 1. Non-smoker _____ 6

2. Ex-smoker

age started _____ Age stopped _____ No. of cigarette/day _____

3. Current smoker

age started _____ No. of cigarettes/day _____

7. Birth place : 1. Hong Kong _____ 7

2. China

3. Other, please specify _____

7 a. Did you travel to China in the past 24 months ? Y. Yes N. No _____ 7a

If **yes,** how many times did you travel to China in the last 24 months _____ x

which cities did you go to _____

8. BCG status/ BCG scar Y. Yes N. No _____ 8

9. Mode of presentation : 1. Self attended _____ 9

9.1. due to ...1. symptom 2. check up _____ 9.1

2. Referral

9.2 by ... 1. GP 2. Hospital Authority 3. Govt. clinic 4. Contact 5. Pre-employment 6. Pre-emigration 7. Others _____ 9.2

3. Surveys

9.3 through ... 1. School 2. Firm 3. Other _____ 9.3

Presenting symptoms : Y. Yes N. No.

10. Cough _____ 10

11. Sputum _____ 11

12. Chest pain _____ 12

13. Wheezing _____ 13

14. Blood stained sputum _____ 14

15. Haemoptysis _____ 15

16. Dyspnoea _____ 16

17. Loss of weight _____ 17

18. Fever _____ 18

19 Other, please specify _____ _____ 19

20. History of contact. 1. Yes 2. No. 3. Not known _____ 20

21. Substance abuse :

21.a Drug Y. Yes N. No. _____ 21a

21.b Alcohol Y. Yes N. No. _____ 21 b

22. HIV status : 1. Positive 2. Negative 3. Not tested _____ 22

23. Other concomittant disease, specify _____ 23

23.a. Other concomittant disease, specify _____ 23.a

24. Other concomittant disease, specify _____ 24

24.a. Other concomittant disease, specify _____ 24.a

Treatment :

25. Date th/ start (dd/mm/yy) ____/____/____ 25

26. Date th/ completed (dd/mm/yy) ____/____/____ 25

Regimen used :	Duration (mo)	Regimen	Frequency
27. Intensive phase.			
a.	_____	_____	_____
b.	_____	_____	_____
c.	_____	_____	_____
d.	_____	_____	_____
e.	_____	_____	_____
f.	_____	_____	_____
g.	_____	_____	_____
28. Maintenance phase.			
a.	_____	_____	_____
b.	_____	_____	_____
c.	_____	_____	_____
d.	_____	_____	_____
e.	_____	_____	_____

Was the patient hospitalized during treatment ? _____, if **Yes**, when _____

29. Drug side effects Y. Yes N. No _____ 29

if **yes,** please specify :	side effects	when did it start	Does it change the regimen
a.	_____	_____	_____
b.	_____	_____	_____
c.	_____	_____	_____
d.	_____	_____	_____
e.	_____	_____	_____

f. _____ _____ _____

g. _____ _____ _____

h. _____ _____ _____

i. _____ _____ _____

Compliance :

30. Total no. of appointment _____ 30

31. Total no. of appointment missed _____ 31

32. Reminders sent by Chest Clinic Staff. Y Yes N. No _____ 32

33. Total no. of self administered drugs _____ 33

Microbiological results: 1. Positive 2. Negative

	Date	Smear result	Culture result
34.	_____	_____	_____
35.	_____	_____	_____
36.	_____	_____	_____
37.	_____	_____	_____
38.	_____	_____	_____
39.	_____	_____	_____
40.	_____	_____	_____
41.	_____	_____	_____
42.	_____	_____	_____
43.	_____	_____	_____

Outcome :

44. Loss to follow-up (i.e 2 consecutive months has not been able to be contacted) _____ 41

45. Defaulter (i.e. 2 consecutive months did not take medication or was still on th/ 15 months after being entered into registry) _____ 42

Contact tracing :

46. Total number of contacts _____ 43

Characteristics of contact persons.

- Relationship : 1. Wife 2. Husband 3. Daughter 4. Son 5. Mother 6. Father 7. Sister 8. Brother 9. Grandfather 10. Grandmother 11. Granddaughter 12. Grandson 13. Daughter in law 14. Son in law 15. Father in law 16. Mother in law 17. Brother in law 18. Sister in law 19. Maid 20. Co-worker 21. Other
- Sex : 1. Male 2. Female
- Finding : 1. Positive 2. Negative

- Examined : 1. Referred clinic 2. Elsewhere

	Relationship	Age (years)	Sex	Examined	Findings	Prev. case no	New case no.
47.							
48.							
49.							
50.							
51.							
52.							
53.							
54.							
55.							
56.							
57.							
58.							
59.							
60.							