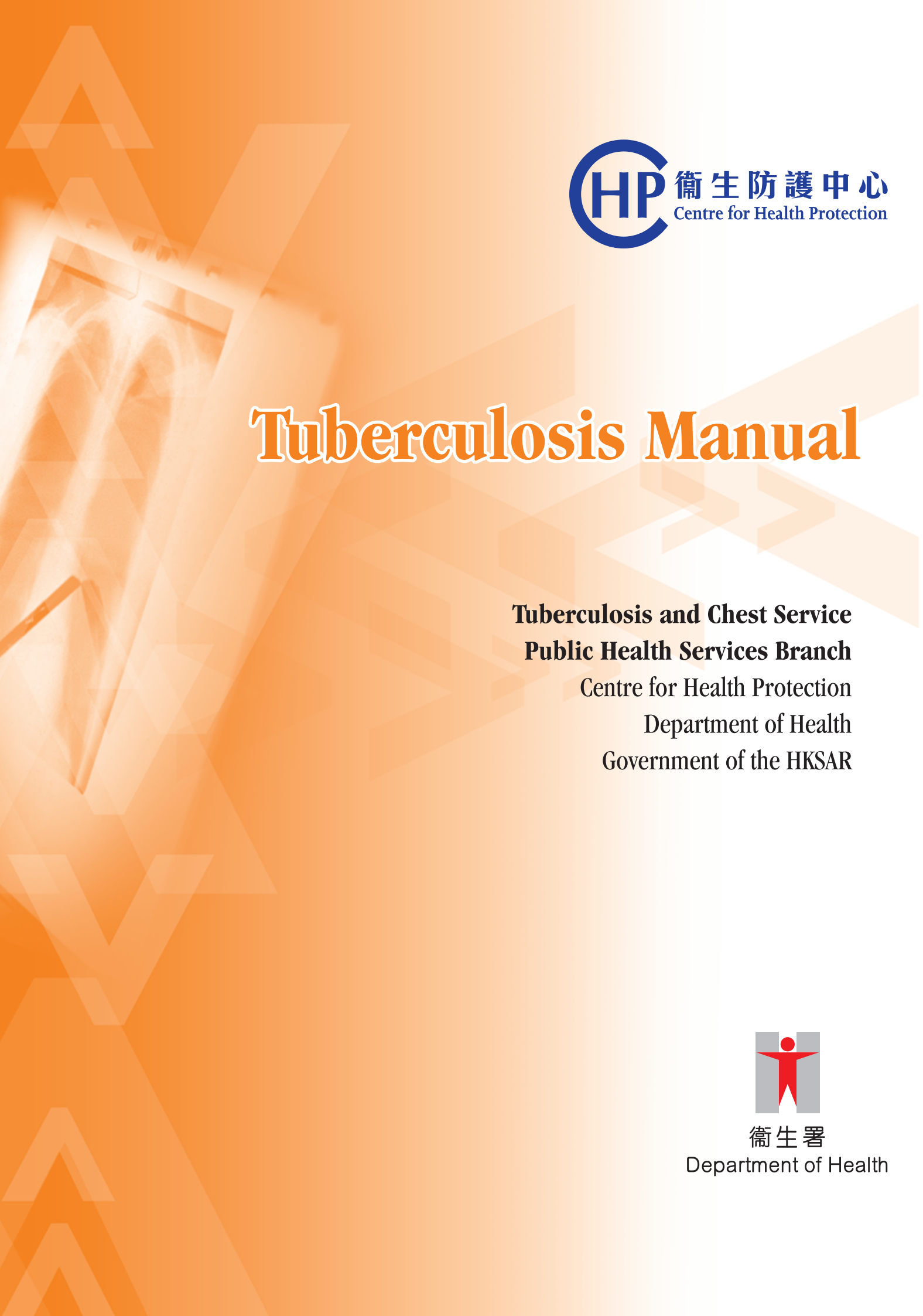


衞生防護中心
Centre for Health Protection

Tuberculosis Manual

Tuberculosis and Chest Service
Public Health Services Branch
Centre for Health Protection
Department of Health
Government of the HKSAR

衞生署
Department of Health

衞生防護中心
Centre for Health Protection

Tuberculosis Manual

Tuberculosis and Chest Service
Public Health Services Branch
Centre for Health Protection
Department of Health
Government of the HKSAR

衞生署
Department of Health

TUBERCULOSIS MANUAL

(Hong Kong SAR 2006)

ISBN 962-8868-10-1
978-962-8868-10-0

Published in February 2006
Printed in Hong Kong SAR

Address:
Tuberculosis and Chest Service
Wanchai Chest Clinic
99 Kennedy Road
Hong Kong SAR

PREFACE

Tuberculosis (TB) is a long-existing infectious disease. With the advent of effective treatment in the form of short course service programmes in 1970s, it was once thought that the disease could be eliminated quite soon. However, since late 1980s and early 1990s, for a number of reasons, TB became resurgent alongside rampant drug resistance and HIV co-infection in various parts of the world. In April 1993, the World Health Organisation declared TB as a global emergency. Today, TB remains an important infectious disease worldwide.

In Hong Kong, the TB notification rate has become rather "stagnant" in the last decade, despite an overall downward trend in the past 50 years. The rate now stands just below 100 per 100,000 population, with around 7,000 cases each year. With such an endemicity, medical practitioners in various fields are likely to encounter TB cases from time to time.

Local guidelines have been promulgated on various aspects of TB from time to time. This manual is prepared as another step to facilitate the clinical management of TB in the local settings. Apart from the professional staff of the TB and Chest service, a large number of experts in different fields have contributed much of their effort and time in making the publication of this manual possible. The chapters are based on a careful review of information from multiple sources, including overseas and local studies, international guidelines, expert opinions and local experiences where appropriate. Through the dedication of the contributors, vigorous attempt has been made to strive for high-standard evidence-based medicine suited for the control of TB in the local scene.

With the huge volumes of literature on this important topic, this manual does not mean to be a comprehensive text. Instead, it aims to serve as a handy synopsis of updated guidelines and resources for the reference of local professionals. Although the contributors have tried to ensure that the information is up-to-date at the time of writing, there remains an ongoing need to keep abreast of new scientific advances and changes in practices. Readers are therefore encouraged to refer to other relevant sources or visit our TB website at www.info.gov.hk/tb_chest for updated information wherever necessary.

CM Tam
CC Leung
(Editors)

Hong Kong SAR 2006

LIST OF CONTRIBUTORS

KF Au *MBChB(CUHK), MRCP(UK)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
CK Chan *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
HS Chan *MBBS(HK), FHKAM(Medicine)*
Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hospital Authority
KS Chan *MBBS(HK), FHKAM(Medicine)*
Department of Pulmonary and Palliative Care, Haven of Hope Hospital, Hospital Authority
M Chan-Yeung *MBBS(HK), FHKAM(Medicine)*
Department of Medicine, Queen Mary Hospital, University of Hong Kong
MY Chan *Senior Medical Technologist*
Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health
SL Chan *MBBS(HK), FHKAM(Medicine)*
Private practitioner (Specialist in Respiratory Medicine)
YC Chan *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Unit, Wong Tai Sin Hospital, Hospital Authority
KC Chang *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
DSC Hui *MD(UNSW), FHKAM(Medicine)*
Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong
KM Kam *MBBS(HK), DABMM*
Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health
CW Lam *MBBS(HK), FHKAM(Medicine)*
Department of Respiratory Medicine, Ruttonjee Hospital, Hospital Authority
WS Law *MBChB(CUHK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
SN Lee *MBChB(CUHK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
CC Leung *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
ECC Leung *MBBS(HK), FRCP(Canada)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
TYW Mok *MBBS(HK), FHKAM(Medicine)*
Respiratory Medical Department, Kowloon Hospital
WH Seto *MBBS(Singapore), FHKAM(Pathology)*
Department of Microbiology, Queen Mary Hospital, Hospital Authority
LB Tai *MBChB(CUHK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
CM Tam *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
CY Tam *MBBS(HK), FHKAM(Medicine)*
Department of Medicine, Tuen Mun Hospital, Hospital Authority
KWT Tsang *MD(Glas,Hons), FRCP(Edin,Glas,Lond)*
Department of Medicine, Queen Mary Hospital, University of Hong Kong
MY Wong *MBChB(CUHK), MRCP(UK)*
Tuberculosis and Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health
PC Wong *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Unit, Grantham Hospital, Hospital Authority
WS Wong *Senior Medical Technologist*
Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health
WW Yew *MBBS(HK), FHKAM(Medicine)*
Tuberculosis and Chest Unit, Grantham Hospital, Hospital Authority
CW Yip *BSc, PhD*
Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health
WC Yu *MBBS(HK), FHKAM(Medicine)*
Department of Medicine, Princess Margaret Hospital, Hospital Authority
RWH Yung *MBBS(HK), FHKAM(Pathology)*
Infection Control Branch, Centre for Health Protection, Department of Health

Acknowledgement

We would like to thank our colleagues in the Hospital Authority, the two Universities and the Department of Health for their support, contribution, and comments during the preparation of the various chapters of this TB manual: Dr. KF Au, Dr. CK Chan, Dr. HS Chan, Dr. KS Chan, Prof. M Chan-Yeung, Ms. MY Chan, Dr. SL Chan, Dr. JWM Chan, Dr. YC Chan, Dr. KC Chang, Dr. KL Choo, Dr. CM Chu, Dr. SS Ho, Prof. DSC Hui, Dr. KM Kam, Dr. FY Kong, Dr. CW Lam, Dr. WS Law, Dr. SN Lee, Dr. ECC Leung, Dr. HM Ma, Dr. TYW Mok, Dr. WH Seto, Dr. L So, Dr. LB Tai, Dr. CY Tam, Prof. KWT Tsang, Dr. ML Wong, Dr. MY Wong, Dr. PC Wong, Mr. WS Wong, Dr. KS Yee, Dr. WW Yew, Mr. CW Yip, Dr. WC Yu, Dr. RWH Yung. The advice from Dr. PY Leung (Controller, Centre for Health Protection) and Dr. PY Lam (Director of Health) is also very encouraging. Last but not least, the high-spirited nursing team and clerical staff of the TB & Chest Service have provided all the necessary assistance and support to make this publication possible.

from
The Editors

LIST OF ABBREVIATIONS

ACH	Air changes per hour
ART	Anti-retroviral therapy
ARI	Annual risk of tuberculosis infection
ATS	American Thoracic Society
BCG	Bacille Calmette Guérin
CI	Confidence interval
DH	Department of Health
DOT	Directly observed treatment
DOTS	Directly observed treatment, short course
ERS	European Respiratory Society
FDA	Food and Drug Administration (of the United States)
FDC	Fixed-dose combination tablets
HA	Hospital Authority
HAART	Highly active anti-retroviral therapy
HEPA	High efficiency particulate air filter
HCW	Health care workers
HIV	Human immunodeficiency virus
IUATLD	International Union Against Tuberculosis and Lung Diseases
MDR-TB	Multidrug-resistant tuberculosis
MOTT	Mycobacterium other than tuberculosis
MTB	Mycobacterium tuberculosis
OR	Odds ratio
PCR	Polymerase chain reaction
PPD	Purified protein derivative
PHLC	Public Health Laboratory Centre (of Department of Health)
RFLP	Restriction fragment length polymorphism
RR	Relative risk
ST	(Drug) sensitivity or susceptibility tests
TB	Tuberculosis
TB&CS	Tuberculosis & Chest Service (of Department of Health)
TBCCC	TB Control Coordinating Committee (of Department of Health)
TBSC	TB Subcommittee (of the Hospital Authority)
TST	Tuberculin test or tuberculin skin test
WHO	World Health Organisation

LIST OF TABLES

LIST OF FIGURES

CONTENTS

CHAPTER 1

HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY OF TUBERCULOSIS

CM Tam, CC Leung, SL Chan

Summary points:

1. Tuberculosis is a disease of the past, and is still an important disease of the present, and will likely continue to be a major public health problem in the foreseeable future globally and locally.
2. The epidemic curve of tuberculosis is probably similar in shape to that of many other infectious diseases, but with a much longer time span.
3. To tackle this global epidemic, the World Health Organisation has declared tuberculosis as a global emergency in 1993. Since then, special projects on "Stop TB initiatives" have been conducted in various parts of the world.
4. The rate of tuberculosis in Hong Kong has shown an overall downward trend in the past 40 to 50 years, but become rather "stagnant" since the 1990s. Possible contributory factors include strengthened surveillance, ageing of the population, ageing of the tuberculosis epidemic, and increased population movement.
5. The observed rates among recent immigrants do not appear to be higher than that of the general population locally.
6. Results from unlinked anonymous testing show that HIV-TB coinfection constitutes only a minority of the annual tuberculosis notifications.
7. With the use of directly observed treatment, the problem of multidrug-resistance can be contained at a relatively low level.
8. Tuberculosis mortality also declined over the years. However, delay in seeking care, atypical presentation, poorer drug tolerance, co-existing diseases, and psychosocial problems are likely factors contributing to less favourable outcomes among the elderly.

Historical Perspective

Tuberculosis (TB) is an old disease. Fragments of the spinal column from Egyptian mummies show evidence of TB over four thousand years ago.[1] Large scale epidemic of the disease occurred in the recent centuries. In 1958, Grigg pointed out that the shape of the epidemic curve for TB is the same as that for any other infectious disease, if one adjusts the time scale to allow for the roughly 300 year duration of a TB epidemic.[2] The TB epidemic started in Europe over three centuries ago. The TB morbidity and mortality began to fall well before introduction of BCG vaccine and effective treatment. The TB epidemic in Asia started much later, and hence is probably in a different epidemiological stage as compared with the rest of the developed world. The duration of ancestral selection for resistance to *Mycobacterium tuberculosis* (MTB) probably plays a significant role in affecting the TB epidemic curve. The findings from a recent local study on the relationship between TB and host genetics corroborate this postulation.[3]

The introduction of sanatorium care in the mid-19th century provided the first real step in the battle against this dreadful disease. In 1882, Robert Koch discovered the tubercle bacillus, but few weapons were available against this important human enemy. Artificial pneumothorax and other surgical methods to reduce the lung volume were developed in the late 19th century. Subsequently, the French bacteriologist Calmette, together with Guérin, used specific culture media to lower the virulence of the bovine TB bacterium, and there came the BCG vaccine still in widespread use today.[4] In 1943, streptomycin was discovered and in the next year, it was administered for the first time to a critically ill TB patient with very impressive effect.[5] However, with streptomycin

monotherapy, resistant mutants began to appear within a few months. Other anti-TB drugs were subsequently introduced, and it was soon demonstrated that emergence of resistant mutants could be prevented with a combination of anti-TB drugs.[5]

In Hong Kong, TB became a notifiable disease in 1939. In 1947, the first public service for TB was established at the Harcourt Health Centre, followed by a few subsidiary clinics in Aberdeen, Stanley, Tai Po and Yuen Long. The Kowloon Chest Clinic was opened in 1951, and the Wanchai Chest Clinic replaced the Harcourt Health Centre in 1954. Initially, these centres provided limited facililties, such as provision of vitamins, tinned food, milk powder and rice. A restricted number of artificial pneumothorax and artificial pneumoperitoneum were done. In 1951, surgery and thoracoplasty for TB was started, and later lung resection was also conducted. Specific treatment with anti-TB drugs was first introduced in 1950, with the use of para-aminosalicylic acid. Later streptomycin was introduced in 1951 and isoniazid in 1952. Effective combination chemotherapy then became available. However, in the 1950's and 1960's, only about one quarter of patients completed treatment and the danger of unsupervised treatment became increasingly recognised.[6] Supervised treatment, which was the forerunner of directly observed treatment (DOT), was introduced on a trial basis in 1960s. Since 1970s, supervised treatment was delivered as part of the TB service. The 6-month standard four-drug short course regimen with isoniazid, rifampicin, pyrazinamide, and streptomycin (or ethambutol) was introduced as early as 1979.

The Recent Tuberculosis Situation Globally

With the availability of effective short course chemotherapy in the 1970s, apparently TB became under control with decrease in incidence in many parts of the world. In industrialised countries, the steady drop in TB incidence began to level off in the mid-1980s and then stagnated or even began to increase. Much of this rise could be at least partially attributed to a high rate of immigration from countries with a high incidence of TB. Forty-one percent of the notifications in England and Wales in 1993 were in those of Indian subcontinent origin. Their notification rate was 128 per 100,000 in 1993, nearly 30 times that of the white population.[7] In the United States, routine surveillance indicated that from 1986 to 1995, foreign born cases of TB in the United States increased by 61%, and foreign born cases as a percentage of all cases increased from 22% to 35%.[8]

While only one out of ten immunocompetent people infected with MTB will develop active TB in their lifetimes**,** among those infected with HIV, one in ten per year will develop the disease.[9] In many industrialised countries, such co-infected cases make up only a minority of the TB cases. However, in developing countries, the impact of HIV infection, especially in the 20 to 35 age group, is of increasing concern. The combined attack by these two dreadful pathogens can be devastating on the health of the population as well as the vitality of the economy.

Drug resistance occurs as a result of tubercle bacillus mutations. Since it is very unlikely that a single bacillus will spontaneously mutate to become resistant to more than one drug, giving multiple effective drugs simultaneously will inhibit the multiplication of these resistant mutants. Unfortunately, patients may be denied of or fail to complete an effective combination regimen in many parts of the world. As a consequence, the emergence of multidrug-resistant tuberculosis (MDR-TB) became an area of increasing concern.

In late 1980s and early 1990s, TB has become resurgent in various parts of the world alongside rampant drug resistance and HIV co-infection. The World Health Organisation (WHO) declared TB as a global emergency in April 1993 and called for international collaboration in the fight against the disease. In the 51st World Health Assembly in May 1998, a resolution was made to urge all member states to turn their policies into action and to make strong political commitment on TB control. A few months later, WHO issued a special project called "Stop TB Initiative". In September 1999, "TB crisis" was declared in the Western Pacific Region and the project of "Stop TB in the Western Pacific Region" was initiated. In 2005, WHO estimated that one third of the world's population is currently infected with the tubercle bacilli, and more than eight million people get TB every year, of whom 95% live in developing countries. An estimated two million people die from TB every year.[10]

The Recent Tuberculosis Situation Locally

The notification rate of TB in Hong Kong has shown an overall downward trend in the past 40 to 50 years (Fig 1.1). The rate decreased from a peak of 697.2 per 100,000 in 1952 to around 100.9 in 1995, and thereafter ran a fluctuating course and became rather "stagnant". In 2004, the total number of notified cases is 6,238, at a rate of 90.6 per 100,000. Hong Kong is classified as a place of intermediate TB burden with good health infrastructure in the Western Pacific Region.[11]

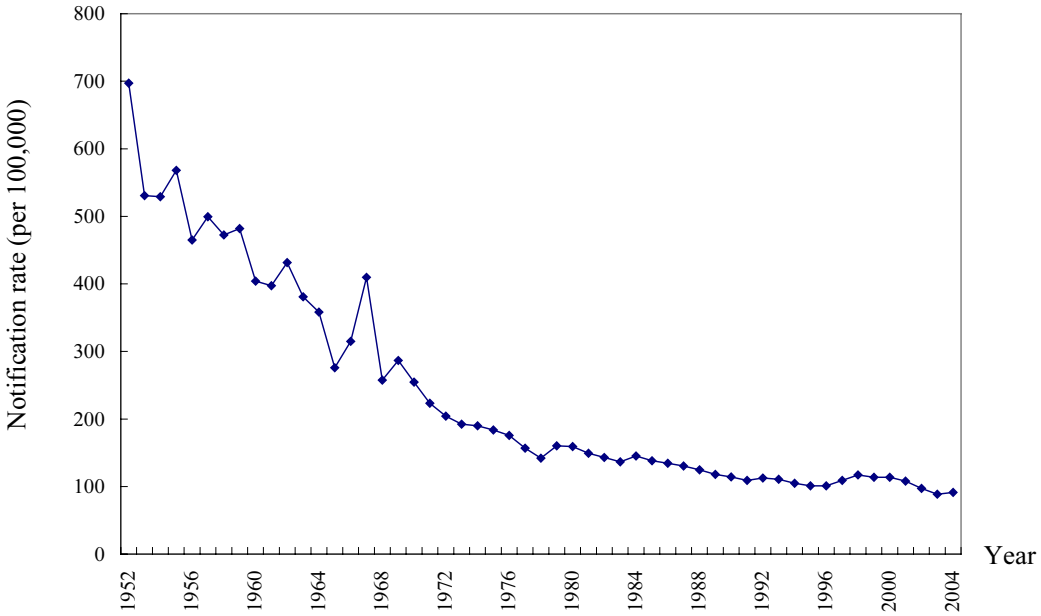


Figure 1.1. Tuberculosis notification rate (per 100,000) (1952-2004)

With the rapid decline in disease incidence brought about by effective treatment in the last few decades in Hong Kong, there has probably been decreasing exposure to the tubercle bacilli for successive birth cohorts. The notification rate for young children under 5 years old tends to reflect the ongoing risk of infection. Although the absolute numbers may have been affected by the almost universal neonatal BCG vaccination undertaken locally, it is reassuring to note the drastic decline from 38.8 per 100,000 in 1965 to only 2.7 per 100,000 in 2004 (Fig 1.2). The decreasing tuberculin-positive rate among the 6- to 9-year olds from 79.5% in 1967 to 16.9% in 2000 also strongly suggested a very significant decline in the risk of infection (Fig 1.3).

Ageing of the Population

The population of Hong Kong is getting older as it undergoes demographic transition, which is a result of decreasing birth rate and increasing life expectancy. In 1965, 3.6% of the population was aged 65 or over, and the corresponding figure in 2004 has increased to 11.9%. With the high prevalence of TB in Hong Kong and Mainland China in the past decades, many of our elderly are likely to have been exposed to the tubercle bacilli in the past. With an ageing population and the relative affluence of the society, chronic degenerative and debilitating diseases are increasingly encountered. In a survey conducted in 1999, about 25% of all notified TB cases were found to have medical conditions that could predispose to the development of TB.[12] These included diabetes mellitus, malignancies, chronic renal failure, treatment with cytotoxics and steroids, silicosis, and others. While there was a declining trend in the overall TB notification rate in the past five decades, the actual number of notifications for those aged 65 or above increased from 1,158 (15.3% of total notifications) in 1985 to 2,431 (39.0% of total notifications) in 2004 (Fig 1.4). The factors that underscore such significant change in the profile of patients may also help to explain why Hong Kong is experiencing stagnation of the TB trend in the recent decade, just like other places with intermediate TB burden, e.g. Japan, Singapore, and Malaysia (Fig 1.5).

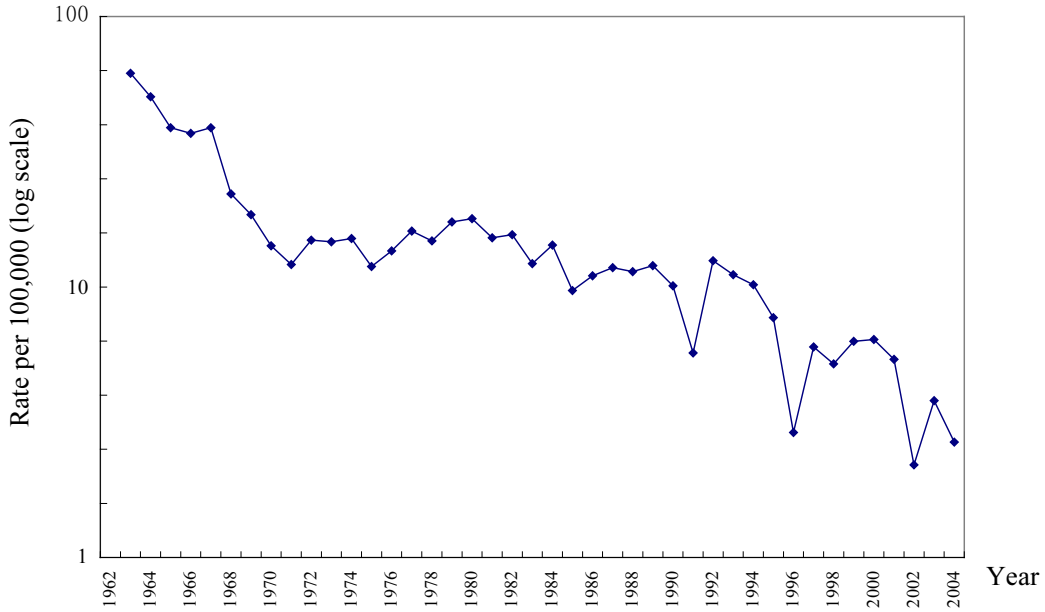


Figure 1.2. Tuberculosis notification rate among children under 5

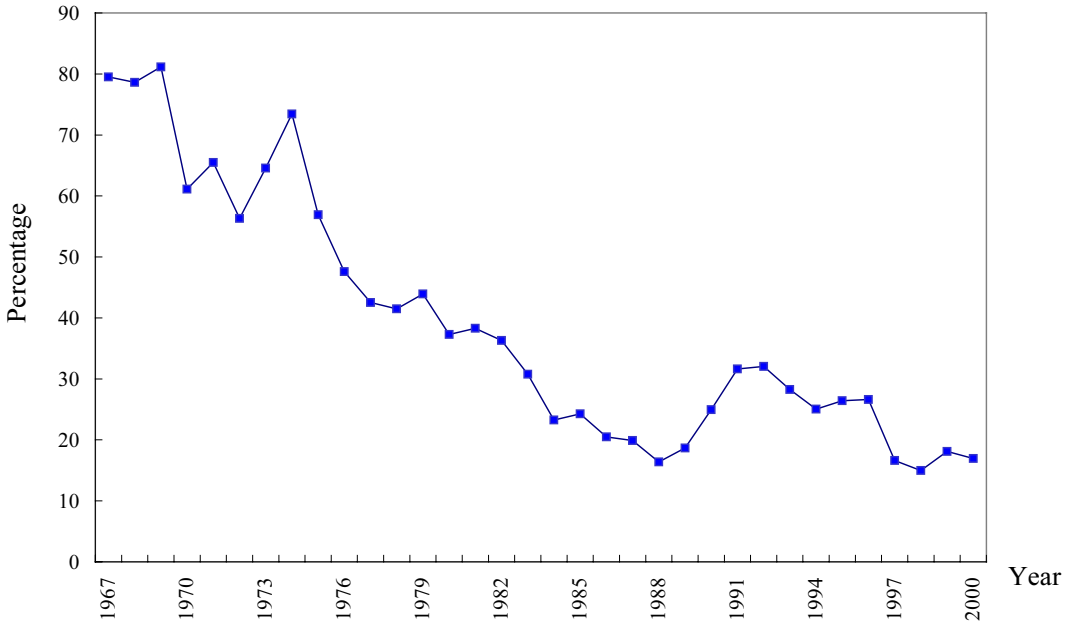


Figure 1.3. Tuberculin-positive rates among primary school children (1967-2000)

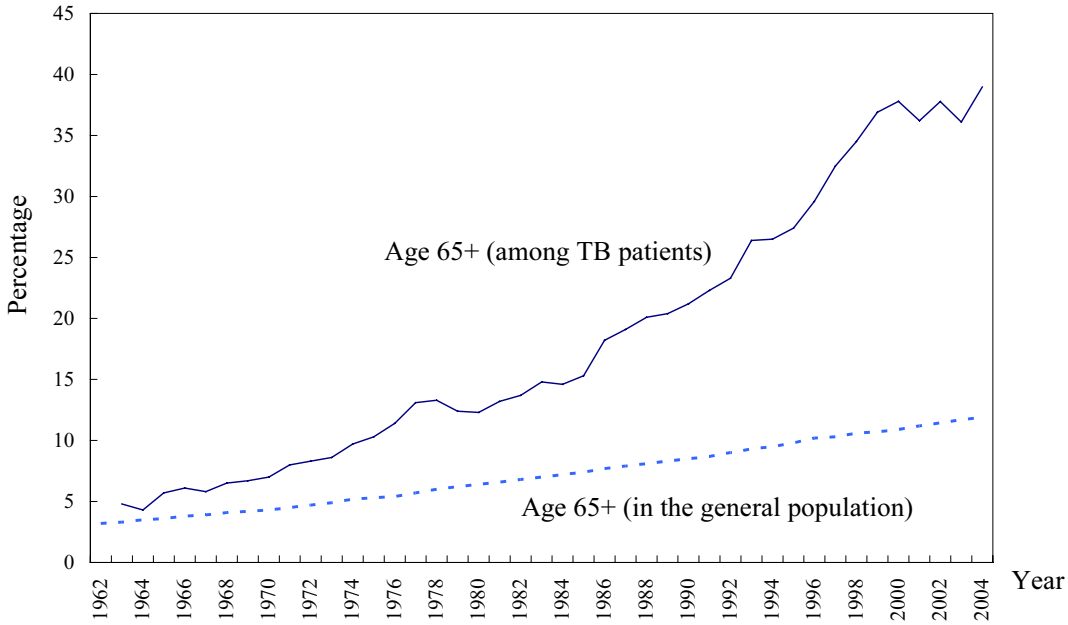


Figure 1.4. Percentage of elderly among tuberculosis patients and in the general population (1962-2004)

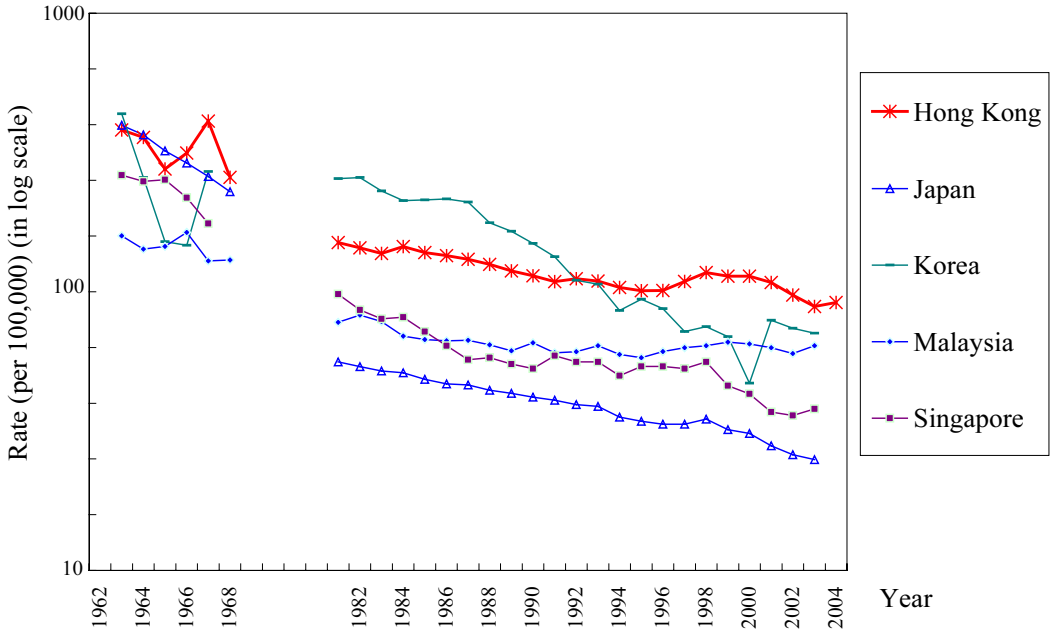


Figure 1.5. Tuberculosis notification rates in some places in the Western Pacific Region

Strengthened Surveillance

The recent fluctuation in TB notification trend has raised some concern about TB resurgence locally. From the rate of 100.9 per 100,000 in 1995, the notification rate increased in three consecutive years to 101.0 in 1996, 109.0 in 1997, and 117.3 in 1998. In terms of actual numbers, there were 7,673 notified TB cases in 1998 as compared to 6,212 cases in 1995, representing an increase of 1,461 cases or 23.5%. In the same period, the population increased only by 6.3%. However, there were also significant changes in the distribution of notification sources (Fig 1.6). While the number of notifications from chest clinics and chest hospitals remained more or less the same, being 5,659 in 1995 and 5,824 in 1998, notifications from the public general hospitals and the private sector more

than tripled from 553 to 1,842 in the same period. Such drastic increase probably reflected a positive change of notification behaviour among these previously minor notification sources, and the additional 1,289 cases could almost account for all the increase in notifications from 1995 to 1998. In fact in recent years, increased awareness of notifiable infectious diseases, work of infection control nurses in public hospitals, as well as regular matching with data from TB laboratories and death certificates for tracing back of under-notified cases, are the likely contributing factors for such change in notification behaviour. Since 1999, the number of cases notified from chest clinics continued to decline, while those from public general hospitals fluctuated between 1,724 and 2,405. Significant under-notification in the past and strengthened surveillance nowadays is probably a significant underlying factor for this observed phenomenon.

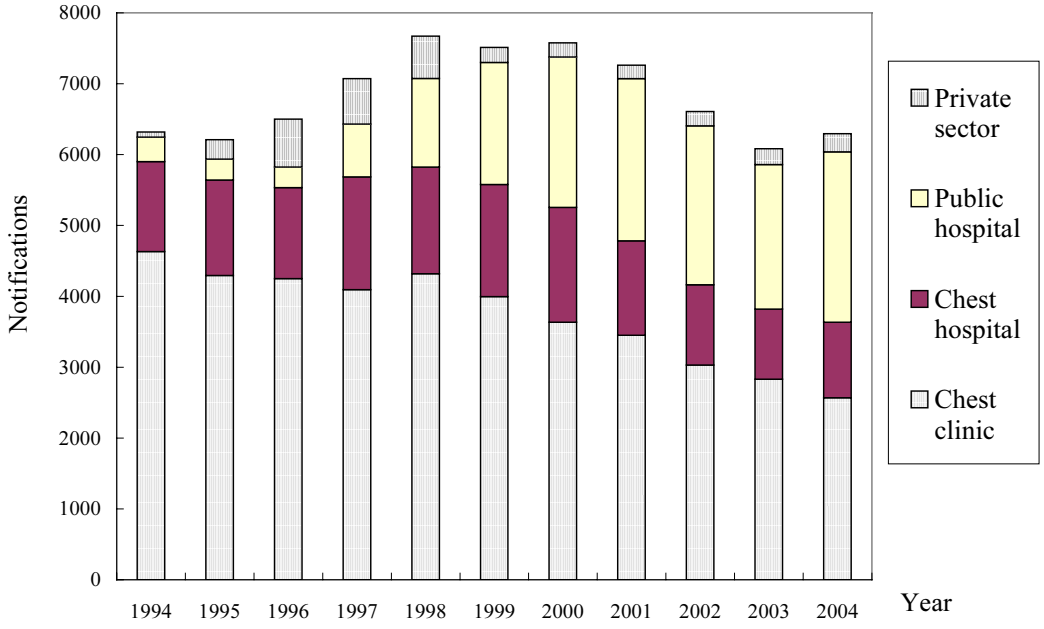


Figure 1.6. Sources of tuberculosis notification (1994-2004)

Ageing of the Tuberculosis Epidemic

Use of the DOTS (directly observed treatment, short course) strategy can effectively contain the transmission of TB in the community. Thus, diseases developing from progressive primary infection (PPI) or exogenous reinfection (ERI) can be effectively reduced (see Chapter 3). On the other hand, however, diseases developing from endogenous reactivation (ERA) is affected to a much lesser extent. Hence, in a place implementing DOTS, the TB epidemic would gradually evolve from one consisting of cases from PPI, ERI and ERA into one consisting of cases developing mainly from ERA with much less from PPI and ERI, so called "ageing of the TB epidemic".[13] In Hong Kong, a recent study showed that recent transmission accounted only for 15% to 20% of cases.[14] Mathematical modeling also showed a significant risk of TB disease through reactivation in the Hong Kong Chinese population particularly among elderly males.[15] The significant proportion of cases from ERA probably accounts to a certain extent for the "stagnant" trend of TB observed recently.

Immigrants and Migration

In the recent decade, less than 200 TB cases each year involved recent immigrants (defined as immigrants within 7 years of arrival) from Mainland China.[16] The estimated rates among these recent immigrants were not higher than that of the general Hong Kong population. In late 1970s and early 1980s, significant numbers of TB cases involved Vietnamese boat people but these are no longer a problem in the recent decade.[16] Overall, these immigrant groups only represented a very small proportion of the total caseload. This is in sharp contrast to the situation in many western

countries. The much smaller differences in disease risk between the indigenous population and the recent immigrant groups locally may largely account for such observation.

On the other hand, there is increase in population movement over the years (Fig 1.7). With such increases in people-to-people contact, it is possible that airborne infections which are transmitted from human to human, like TB, can have a significant chance to continue its propagation in the community. Although restriction fragment length polymorphism (RFLP) surveillance data shows that proportion of cases from recent transmission is not high,[12] we have to be on the alert of this potential problem.

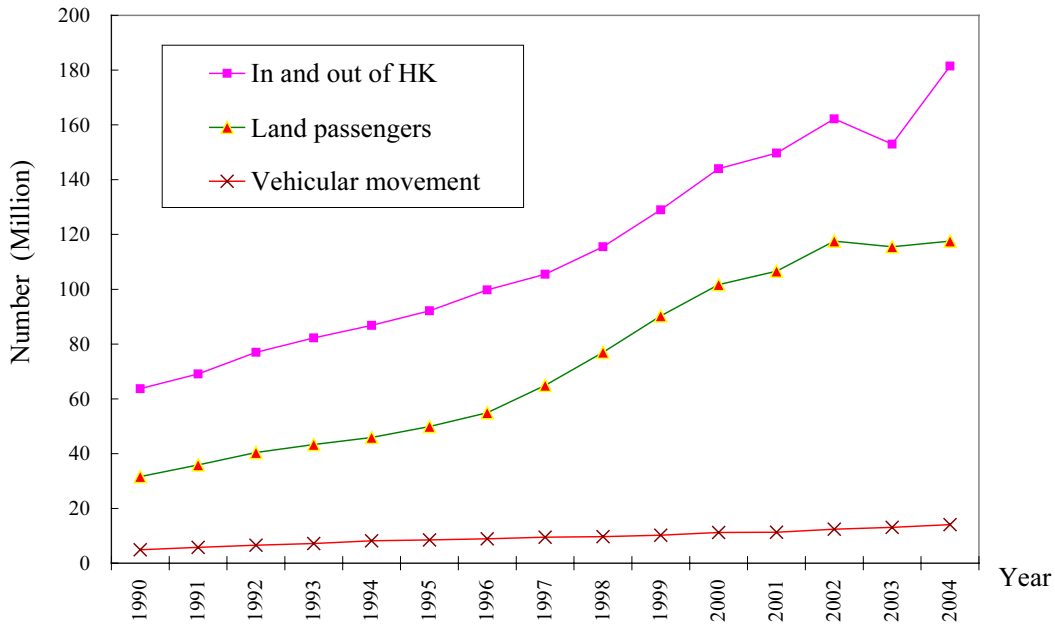


Figure 1.7. Indicators of movement in and out of Hong Kong

Tuberculosis and HIV Co-infection

At present, HIV-related TB cases represent only a minority of the annual TB notification. Unlinked anonymous testing has shown that less than 1% of the TB patients in the chest clinics were HIV seropositive (Fig 1.8). There has been a slow rising trend over the years, probably because of increasing number of HIV-infected persons developing AIDS with the passage of time as the HIV epidemic matures, and the use of highly active anti-retroviral therapy in prolonging their survival and thus allowing a higher chance for development of TB disease.

Drug Resistance

The problem of drug non-adherence has been recognised in Hong Kong in the 1950s with only about one quarter of patients completing anti-TB treatment. Thus, supervised drug treatment was used on a trial basis in the 1960s and then on a service basis since the 1970s. This is now better known as DOT (directly observed treatment). With DOT, the problem of drug resistance can thus be contained. Recent surveillance data shows that the rate of drug resistance to any one of the four first-line drugs and MDR-TB are declining.[17] (Fig 1.9) Currently, the rate of MDR-TB is around 1%.[16]

TB Mortality

TB mortality declined from a peak of 207.9 per 100,000 in 1951 to 3.4 per 100,000 in 2004 (Fig 1.10) and TB is now outside the top ten causes of death. The average age at death increased from 25 years in 1951 to 76 years in 2004. While part of the dramatic decline of TB mortality may be

attributed to decreasing incidence of the disease, effective management of TB patients must have been another major contributing factor. Effective chemotherapy in the form of DOT cured many ill patients, and averted many deaths. Increased awareness by both patients and health care workers could have led to earlier diagnosis, and allowed treatment at an earlier stage. However, delay in seeking care, atypical presentation, poorer drug tolerance, co-existing diseases, and psychosocial problems were likely factors that had contributed to the less favourable outcome among the elderly.

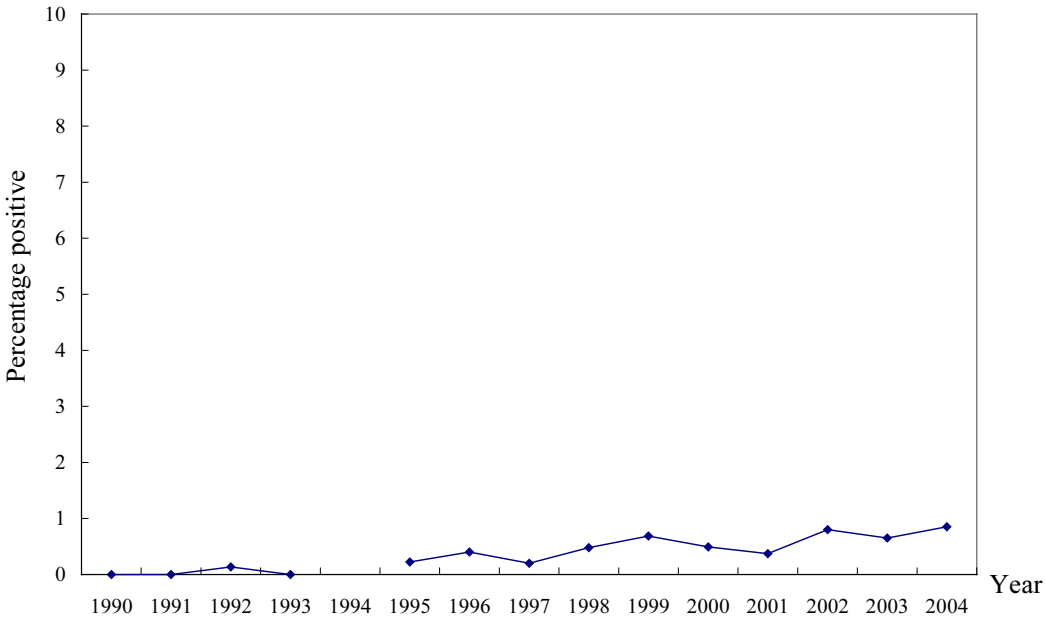


Figure 1.8. HIV seroprevalence among tuberculosis patients from unlinked anonymous urine testing

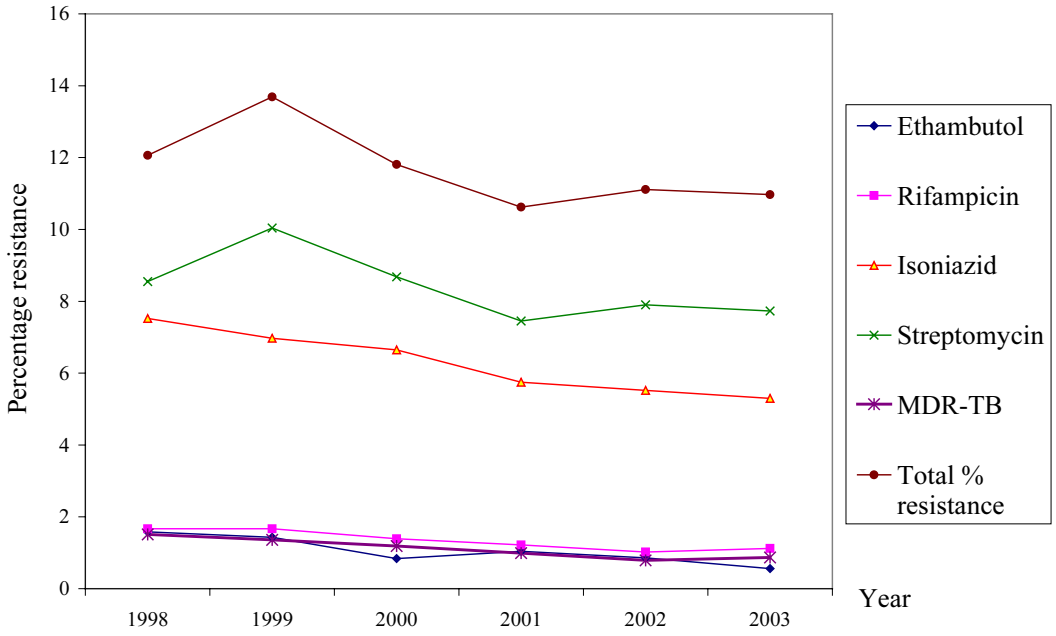


Figure 1.9. Rate of drug resistance among all culture positive cases (1998-2003)

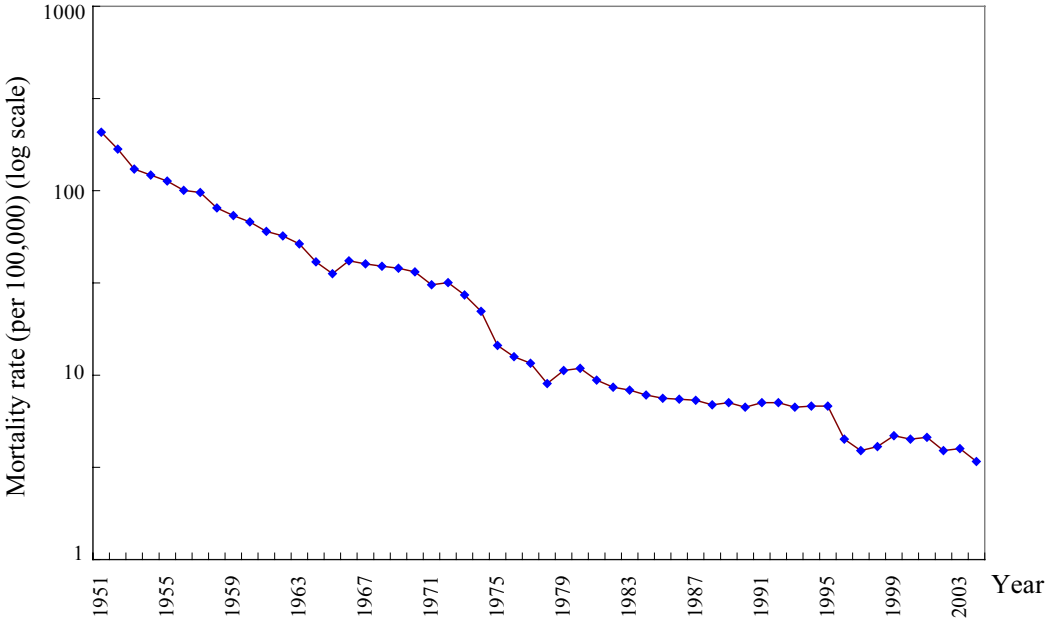


Figure 1.10. Tuberculosis mortality rate (per 100,000) (1951-2004)

Conclusions

TB is a disease of public health importance globally and locally. Although its rate has shown an overall downward trend in the past 40 to 50 years, the rate has become rather stagnant since 1990s. The TB epidemic curve is probably similar to other infectious diseases, although with a much longer time span. Studying its historical development and further researches into factors affecting TB epidemiology would allow better understanding and searching for ways to tackle this important problem.

References

1. Ryan F. Tuberculosis: the greatest story never told. Swift Publishers 1992.
2. Grigg ER. The arcana of tuberculosis. American Review of Tuberculosis and Pulmonary Diseases 1958;78:151-72.
3. Tso HW, Ip WK, Chong WP, Tam CM, Chiang AKS, Lau YL. Association of interferon-gamma and interleukin-10 genes with tuberculosis in Hong Kong Chinese. Genes Immun 2005;6:358-63.
4. Clements CJ. Vaccination – the current status of BCG in Mycobacteria and TB. In: Infectious Disease. Kaufmann and Hahn (eds) 2003 volume 2, pp46-66.
5. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years – Centennial review. Am J Respir Crit Care Med 2005;171:699-706.
6. Government Chest Service, Hong Kong. Annual Report 1967.
7. The Interdepartmental Working Group on Tuberculosis. The prevention and control of tuberculosis in the United Kingdom, September 1998.
8. Centres for Diseases Control. Characteristics of foreign-born Hispanic patients with tuberculosis, eight U.S. counties bordering Mexico, 1995. MMMR 1996;45:47:1032-6.
9. Pozniak A. HIV-associated tuberculosis in the era of HAART. Int J Tuberc Lung Dis 2000;4:993-4.
10. World Health Organisation. Fact sheet N°104 - tuberculosis. Available at http://www.who.int. Accessed 1 September 2005.
11. World Health Organisation Western Pacific Region. Tuberculosis control in South-east Asia and Western Pacific Regions 2005 – a bi-regional report.
12. Leung CCE, Tam CM. Comorbidities among patients with tuberculosis in Hong Kong. Hong Kong Pract 2002;24:170-8.
13. Chang KC, Leung CC, Tam CM. Recent trend of tuberculosis in Hong Kong. Public Health and Epidemiology Bulletin 2002;11:69-75.
14. Chan-Yeung M, Tam CM, Wong H, et al. Molecular and conventional epidemiology of TB in Hong Kong: a population-based prospective study. J Clin Microb 2003;41:2706-8.
15. Vynnycky E, Borgdorff MW, Leung CC, Tam CM, Fine PEM. Limited impact of tuberculosis control in Hong Kong – attributable to high risks of reactivation disease (submitted).
16. Government Chest Service, Hong Kong. Annual Report 2004.
17. Kam KM, Yip CW. Surveillance of Mycobacterium tuberculosis drug resistance in Hong Kong, 1986-1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001;5:815-23.

CHAPTER 2

SURVEILLANCE

CC Leung, CM Tam, CK Chan

Summary points:

1. The systematic collection and analysis of tuberculosis-related data is essential to the planning, implementation, and evaluation of tuberculosis control.
2. A range of methods are available, and all of them have certain limitations in their application in different settings.
3. Notifications and mortality are direct measures of disease impact, while treatment success rates and drug resistance rates are important performance indicators of the tuberculosis control programme.
4. Tuberculosis is a notifiable disease under the Quarantine and Prevention of Disease Ordinance (Cap. 141) and the Occupational Safety and Health Ordinance (Cap. 509).
5. Prompt notification allows effective surveillance of the disease, both in the general community and within occupational settings.

Introduction

The systematic collection and analysis of tuberculosis (TB)-related data is essential to the planning, implementation, and evaluation of TB control. The TB notification system, which allows ongoing monitoring of disease burden and trends, plays a central role in the local TB surveillance system. Other regularly monitored statistics include TB deaths, treatment success rate, and drug resistance.

Tuberculosis – A Notifiable Disease

In Hong Kong, TB is notifiable under two ordinances:

(a) Quarantine and Prevention of Disease Ordinance (Cap. 141)
   - Prevention of the Spread of Infectious Diseases Regulations (Cap. 141B)
     Medical practitioners to report infectious diseases (Reg 4)

(b) Occupational Safety and Health Ordinance (Cap. 509)
   - Medical practitioner to notify occupational disease to Commissioner (Cap. 509 s 15)

Quarantine and Prevention of Disease Ordinance

TB is a notifiable disease in Hong Kong since 1939. Under the Prevention of the Spread of Infectious Diseases Regulations of the Quarantine and Prevention of Disease Ordinance (Cap. 141) in Hong Kong, where any medical practitioner or medical officer has reason to suspect the existence of a case of TB or, in the case of death, that TB existed, he shall forthwith notify the Director of Health. The notification shall be made in accordance with the statutory notification form DH1A(s) (Rev.99), and shall be signed by the medical practitioner. To minimise variations in notification practices, a set of surveillance case definition has been adopted (Appendix 1).

Notification may be made online at CENO On-line (http://www.chp.gov.hk/ceno), or notification forms (Appendix 4) can be obtained from the followings:

- Headquarters of Department of Health (Tel: 29618570; Fax: 28939425)
- Tuberculosis and Chest Service of Department of Health (Tel: 25723487; Fax: 28346627)
- Any chest clinic
- The form can be downloaded from the following websites:
  - http://www.info.gov.hk/dh (homepage of Department of Health)
  - http://www.chp.gov.hk (homepage of Centre for Health Protection)
  - http://www.info.gov.hk/tb_chest (TB website)

Prompt notification and accurate completion of all items on the form allows proper surveillance of the disease in our population, and greatly facilitates the implementation of public health measures like contact tracing and examination.

Under the same Regulation, where a medical practitioner confirms or disproves the existence of TB, concerning which he had notified the Director of Health, he shall forthwith report the said confirmation or disproof to the Director of Health. Hence, in case certain information (e.g. culture results) is not yet available at the time of notification, supplementary information can be sent at a later date. Unconfirmed cases can also be denotified using a denotification form (Appendix 6).

To ensure quality and timeliness of notification data, continuing effort has been invested to promote accurate reporting from both public and private sectors. Data from the laboratories and the death registry are also regularly captured and cross matched with the TB notification registry. Reminders will be sent to relevant institutions or practitioners for notification of un-notified cases.

Despite concerns over access to care, data quality and completeness of routinely collected data, it is possible to estimate the actual incidence of TB through the following formula[1]:

Incidence = notifications / case detection rate (proportion detected)

In Hong Kong and other developed areas with a good health care infrastructure, easy access to health care, and well developed reporting systems, a high case detection rate can be expected, and the incidence may well be approximated by the notification rate. In developing areas with poorly organised health systems, the case detection rate is often an educated guess from the quality of the surveillance system, as it is most difficult to be certain of those who have not been covered.

Occupational Safety and Health Ordinance

Under the Occupational Safety and Health Ordinance, if a medical practitioner finds or suspects that an employee or former employee is or was suffering from an occupational disease specified in Schedule 2 to the Ordinance AND believes that the disease was or may have been attributable to an occupation specified in column 3 of that Schedule, the practitioner must notify the finding or suspicion to the Commissioner for Labour. The notification must be in writing and on a form provided or approved by the Commissioner (Appendix 5) and must be lodged as soon as practicable after the conclusion is formed.

In Schedule 2 (Appendix 2), the specified occupation for TB is any occupation involving close and frequent contact with a source of TB infection that is attributable to employment:

(a) in the medical treatment or nursing of a person or persons suffering from TB, or in a service ancillary to that treatment or nursing; or
(b) in attending to a person suffering from TB, where the need for attendance arises because of the person's physical or mental infirmity; or
(c) as a research worker engaged in research in connection with TB; or
(d) as a laboratory worker, pathologist or post-mortem worker, where the employment involves working with materials that are a source of TB infection; or
(e) in any occupation ancillary to employment in an occupation specified in paragraph (d).

The timely and proper reporting of job-related TB similarly allows proper surveillance of the disease among healthcare and other workers at risk, and greatly facilitates the implementation of appropriate occupational health measures to safeguard their health.

Mortality Statistics

Mortality statistics are regularly collected from death certificates in Hong Kong, In fact, available TB mortality statistics dated back to the beginning of the last century, well before the establishment of the local TB notification registry. In the absence of effective chemotherapy, TB was then a major

killer disease with a case fatality rate of over 50%. Notwithstanding concerns over the accuracy and completeness of such data, it is possible to derive a rough estimate of the historical incidence of the disease through the following formula[1]:

Incidence = deaths / case fatality rate

With the availability of effective chemotherapy, the case fatality rate of TB dropped abruptly. In Hong Kong, increasing proportions of TB patients are elderly with various co-morbidities,[2,3] and many of them died of unrelated causes. The case fatality rate is therefore difficult to measure exactly, especially for those not falling within or having defaulted from, the TB control programme.

Surveys on Disease Prevalence

Attempts have also been made in some countries to measure directly the burden of the disease by periodic prevalence surveys on a representative sample of the population,[4,5] using a combination of symptom surveillance, chest radiograph and sputum examination. If the average duration can be estimated either from the survey or other sources, it is possible to estimate the incidence using the following formula[1]:

Incidence = prevalence / duration of disease

However, a large sample size is required as the estimated local prevalence rate is only in the order of 1 in 1000. Significant logistic problems are involved, and selection bias is most difficult to exclude, especially if the participation rate is low.

Surveys on Infection Prevalence

Tuberculin surveys are also employed in a number of countries to measure the prevalence of infection, usually through clustered sampling in schools. If it is assumed that the annual risk of infection is constant over time and independent of age, the annual risk of infection (ARI) can be estimated by[6]:

$$ARI = 1 - (1 - \text{Infection Prevalence})^{1/Age}$$

An empirical relationship has also been observed between measured ARI and incidence of smear-positive cases[1]:

Incidence of smear-positive cases = ARI * Styblo ratio

From a series of studies, the Styblo ratio was derived to be 1% ARI to 50 smear-positive cases per 100,000 population (range 40-60).[7, 8]

However, such empirically derived ratio may break down, in the presence of rapidly changing incidence rates or HIV infection. Furthermore, the tuberculin test is far from 100% specific. BCG vaccination and exposure to atypical mycobacteria in the environment may lead to a false positive result. While there will be gain in specificity if a high cut-off point (e.g. 15 mm) is adopted, there will be significant loss in sensitivity. With the universal neonatal BCG vaccination in Hong Kong, it will be difficult to estimate the exact prevalence of infection through this approach. Indeed, a recent local study on 21,113 school children aged 6 to 9 years suggested that the conventional methods might have over-estimated the ARI among BCG-vaccinated children by up to three-fold.[9]

Treatment Success Rates

The current emphasis in TB control is to stop TB at the source, i.e. by effective treatment of infectious patients with clinically manifest disease. A TB control programme cannot effectively break the chain of transmission unless it can cure the vast majority (e.g. 85% or above[1]) of these patients. The treatment success rate is therefore an important performance indicator, which is regularly collected by the World Health Organisation (WHO) to monitor the TB control situation all over the world.[1]

A prospective cohort analysis covering all TB patients started on treatment is required to obtain an accurate treatment success rate. A set of TB programme forms have therefore been designed by the TB and Chest Service for prospective monitoring of all notified TB patients in Hong Kong {Appendices 12 and 14}. These serially completed forms are regularly analysed for the evaluation of the local TB control programme and annual reporting to WHO.

Drug Resistance

Drug resistance has been recognised as a major problem since the introduction of anti-TB chemotherapy.[10,11] The current combination "short course" chemotherapy is certainly effective, but it requires six or more months of treatment for completion. Inappropriate regimens or dosages and irregularity or failure of drug taking during this relatively long period will not only jeopardize the patient's cure, but also lead to the emergence of resistant strains, thereby posing a grave risk to the community. Drug resistance is therefore another important performance indicator of a TB control programme.[1,12] The local drug resistance pattern is regularly monitored through laboratory surveillance and the TB programme forms. The relevant data are published in the annual reports of the TB and Chest Service, as well as submitted to WHO.

Conclusions

For planning, implementation and monitoring purposes, it is necessary to measure the burden and trends of the disease. A range of methods are available, all of them have certain limitations in their application in different settings. Notifications and mortality are direct measures of disease impact, while treatment success and drug resistance rates are important performance indicators of the TB control programme. Prompt notification allows effective surveillance of the disease, both in the general community and within the occupational settings. With a quality surveillance programme, public health measures can be planned, implemented, monitored and evaluated to bring the disease under control. Cooperation of all medical practitioners is essential to achieve this goal.

References

1. World Health Organisation. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report 2005. Geneva, Switzerland, WHO/HTM/TB/2005.349.
2. Leung CC, Yew WW, Chan CK, et al. Tuberculosis in older people: a retrospective and comparative study from Hong Kong. J Am Geriatr Soc 2002;50:1219-26.
3. Leung ECC, Tam CM. Comorbidities among patients with tuberculosis in Hong Kong. Hong Kong Pract 2002;24:170-8.
4. China Tuberculosis Control Collaboration. The effect of tuberculosis control in China. Lancet 2004;364:417-22.
5. Hong YP, Kim SJ, Lew WJ, Lee EK, Han YC. The seventh nationwide tuberculosis prevalence survey in Korea, 1995. Int J Tuberc Lung Dis 1998;2:27-36.
6. Arnadottir H, Reider HL, Trebucq A, et al. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. Tuberc Lung Dis 1996;77(Suppl):1-20.
7. Styblo K. The relationship between the risk of tuberculosis infection and the risk of developing infectious tuberculosis. Bull Int Union Tuberc 1985;60:117-9.
8. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
9. Leung CC, Yew WW, Tam CM, et al. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. Thorax. 2005;60:124-9.
10. Medical Research Council. A Medical Research Council Investigation: Streptomycin treatment of pulmonary tuberculosis. BMJ 1948;ii:769-82.
11. Fox W, Wiener A, Mitchison DA, Selkon JB, Sutherland I. The prevalence of drug-resistant tubercle bacilli in untreated patients with pulmonary tuberculosis: A national survey, 1955-56. Tubercle 1957; 38:71-84.
12. WHO/IUATLD. Anti-TB Drug Resistance in the World, Report No. 3, The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1999-2002. Geneva, Switzerland, WHO/HTM/TB/2004.343.

CHAPTER 3

NATURE AND CLINICAL FEATURES OF TUBERCULOSIS

KF Au, LB Tai, DSC Hui

Summary points:

1. Tuberculosis refers to the disease caused by *Mycobacterium tuberculosis complex*.
2. The chances of getting infected upon exposure, and of progression from infection to disease are affected by a number of factors, such as the circumstances of exposure, host immunity, and the virulence of tubercle bacilli.
3. Among those infected, the lifetime risk of progression to disease is about 10% without preventive therapy. Around 50% of the cases of active tuberculosis occur within the first two years after infection.
4. Active tuberculosis may develop from progressive primary infection, exogenous reinfection, or endogenous reactivation
5. Tuberculosis is one of the leading infectious diseases in Hong Kong. Hence, medical practitioners should maintain a high index of clinical suspicion.
6. Local data have shown that the lungs are involved in nearly 90% of patients. About one third of these are sputum smear-positive cases, which carry a higher infectious risk requiring prompt treatment and relevant public health measures.
7. Around 84% of patients present with symptoms in the local setting. Cough and sputum are the commonest symptoms. Passive case finding plays a key role in tuberculosis control.
8. Extrapulmonary involvement is present in around a quarter of tuberculosis patients. Around half of them have both pulmonary and extrapulmonary involvement. Pleura and lymph nodes are the commonest extrapulmonary sites involved.
9. Presentation may be atypical in the elderly. This is important when dealing with an ageing local population. About 44% of tuberculosis patients diagnosed in 2004 were aged 60 or above.

Nature of Tuberculosis

Introduction

"Tuberculosis" (TB) was used in the past to refer to the small, potato-like lesions found inside body tissues affected by this disease.[1] Nowadays, TB refers to the disease caused by the *Mycobacterium tuberculosis complex*, which includes *Mycobacterium tuberculosis* (MTB)*, Mycobacterium bovis, Mycobacterium africanum, and Mycobacterium microti. M. tuberculosis complex* belongs to the genus *Mycobacterium, which* is the only genus of the *Mycobacteriaceae* family.[2] Mycobacteria share the features of acid- and alcohol- fastness on staining. Most species are environmental mycobacteria, which are low-grade pathogens. Some may rarely cause active diseases in diseased lungs. Some are obligate pathogens, as in the case of MTB. The complete genome of MTB has recently been sequenced and this greatly facilitates future research, including studies on its biology, virulence, drug targets, mechanisms of drug resistance, immune reactions, vaccines, and history of evolution in relation to other mycobacterial species.[3]

Transmission

Tuberculosis is transmitted by small droplet nuclei through air. The fact that TB is an airborne infectious disease was established by the Riley's classical experiments using guinea pigs.[4,5] The experiments also demonstrated that patients varied greatly in infectivity, which could be rapidly reduced by effective treatment. From Riley's guinea pig experiments and the observation of the time required for a student nurse working on a TB ward before tuberculin test converted positive in the

prechemotherapy era, it could be estimated that, on average, people have a 50% chance of becoming infected if they spend 8 hours a day for 6 months with an infectious TB patient.[4,5]

An epidemiological study on a navy vessel in 1966 also supported this theory of airborne transmission.[6] Among crew members in two compartments of the navy vessel in which one compartment shared part of the re-circulated air from the other, the chance of being infected were roughly proportional to the amount of contaminated air breathed. The chance was not affected by direct contact with the index case, which occurred only in the first compartment but not in the second compartment. Thus, close personal contact did not greatly increase the likelihood of infection.

Not only are droplet nuclei produced when an infectious person sneezes, sings, or talks, procedures which involve manipulation of infected tissues or specimens in clinical and laboratory settings, such as sputum induction or aerosol treatment, may also give rise to droplet nuclei. These particles can remain in air for a long time particularly in places with poor ventilation. When these particles are inhaled and reach the distal airways, tubercle bacilli may be implanted resulting in infection.

The chance of being infected is affected by the concentration of the organisms in the air, length of exposure, and the immune status of the exposed person. Better understanding of the transmission mechanism may provide a sound theoretical basis for the planning and implementation of effective TB control measures.

Mathematical Modelling of Transmission

In a study of a measles outbreak in an elementary school in 1978, a steady-state mathematical model of transmission of airborne infection was introduced.[7] It was assumed that measles was an airborne disease and the infectious particles were randomly distributed in air. A "quantum" of infection was defined as an infectious dose, which might contain one or more droplet nuclei. Briefly, the equation can be derived as follows:

Iq/Q = equilibrium concentration of quanta in air, where:
q = quanta of airborne infection produced by an infector per minute
I = number of infectors
Q = room ventilation rate with germ-free air in m^3/min

pt = total volume of infected air inhaled, where:
p = pulmonary ventilation rate per susceptible per minute in m^3/min
t = duration of ventilation

Thus,
Iqpt/Q = number of quanta breathed in by the susceptible

Assuming exponential decay in the proportion of uninfected individuals as in a random Poisson process, the probability that a susceptible person will breathe in the quanta and become an infected case is approximately:

$$\mathbf{P} = 1 - e^{-Iqpt/Q}$$

If S is number of susceptible persons exposed and C is the number of newly infected cases,

$$\mathbf{C = S}(1 - e^{-Iqpt/Q})$$

This equation is for a single generation of infection, and is in fact a modification from the Soper mass balance equation[8] for epidemiological investigations of airborne infectious diseases. It may be expanded and further modified for multiple generations of infection.

As TB is spread by droplet nuclei, this model has also been applied to a number of reported episodes of TB transmission.[9,10] The number of infectious doses generated under different scenarios or health care settings could then be estimated. Thus the model is useful in providing quantitative insight into transmission and assessment of the infection risk, which may serve as a guide for modification of environmental factors and implementation of appropriate preventive measures. (See also Chapter 16.)

Pathogenesis of Tuberculosis

Droplet nuclei containing tubercle bacilli may reach the respiratory bronchioles or alveoli after inhalation. Establishment of infection depends on the interplay between the host (e.g. the immune system) and the pathogen (e.g. its virulence). When infection occurs, the tubercle bacilli may spread through the lymphatic system and the blood stream to distant organs before cellular immune response takes place.

The growth of organisms to a number between 10^3 and 10^4 in around 2 to 12 weeks may elicit cellular mediated immune response, in which alveolar macrophages and T-lymphocytes particularly the CD4+ cells have major roles to play.[11,12] After engulfing the tubercle bacilli, alveolar macrophages release various chemokines that can attract more host cells to the site of infection. The macrophages will also present the mycobacterial antigens to the T lymphocytes. This antigen-presenting process is associated with class I and class II MHC-encoded molecules. When the peptide antigens are associated with class I molecules, they are recognised by CD8+ cells, whereas when these antigens are associated with class II molecules, CD4+ cells will be initiated.[13] Various cytokines and interferon-γ are then produced and released.[14] These cytokines are responsible for attracting and activating various host cells to inhibit replication of the tubercle bacilli. Local studies have suggested that cytokines such as interleukin-12 and interferon-γ may play a role in genetic susceptibility to TB.[15,16]

Inflammatory cells are gathered to the site of infection to form concentric rings and giving rise to granuloma formation. The centres of the rings contain debris of the dead macrophages, with a cheesy-white appearance described as caseation. The periphery contains the more competent macrophages. Delayed type hypersensitivity response can be demonstrated by the positive tuberculin test. The test will become reactive within eight weeks of mycobacterial infection.[17]

Most individuals will not develop active disease after infection because the immune processes would contain the multiplication and spread of tubercle bacilli. A positive tuberculin skin test may be the only indication of infection. Among those infected, the lifetime risk of developing TB disease in the absence of preventive therapy is about 10%, and around half of them will develop disease within the first two years after infection.[18,19]

However, patients with compromised immunity are at a higher risk of development of disease. The risk of progression to active TB in those co-infected with TB and human immunodeficiency virus (HIV) is high, with a rate of around 5% to 10% per year.[19-21] Other at risk groups include patients on cytotoxic or corticosteroid therapy, patients with lymphoma, silicosis, diabetes mellitus, alcoholism, malnutrition, post-gastrectomy, renal failure, young infants and the elderly.

Active TB may develop from progressive primary infection, exogenous reinfection, or endogenous reactivation, which may be defined as follows[22]:

- Progressive primary infection: disease occurring within 5 years of infection
- Exogenous reinfection: first disease episode within 5 years of reinfection
- Endogenous reactivation: disease with onset 5 years or more after infection

Disease developing from progressive primary infection is more common in children. On the other hand, postprimary disease, which occurs mainly in adults, is attributed to the latter two mechanisms. However, on an individual basis, it is often difficult to tell whether a patient's active TB is due to reinfection or reactivation.

Multiple Strains of Tuberculosis

Although TB is generally regarded as being due to a single strain, studies have shown that both HIV-negative and HIV-positive patients can be infected with multiple strains of MTB during the same episode of disease.[23,24] Warren et al,[25] after examining sputum specimens of the new and relapse cases of TB by polymerase chain reaction (PCR) method, noted that 19% of all the 186 studied patients were simultaneously infected with Beijing and non-Beijing genotypes. The proportion was higher in retreatment cases (23%) than new cases (17%). This finding could have important implications on the understanding of pathogenesis and development of vaccines against TB.

Clinical Features

Primary Infection

Primary pulmonary tuberculosis is more common in children. It involves the lung and the regional lymph nodes, forming the primary complex. About 85% to 90% of patients with primary complex heal spontaneously, whereas 10% to 15% progress to disease. Infected individuals are mostly asymptomatic and a positive tuberculin skin test may be the only evidence of infection. Some may experience non-specific mild influenza-like symptoms. Presentations may be related to complications of primary TB, which include pneumonitis, lobar collapse, bronchiectasis, and pleural effusion. Some may develop hypersensitivity phenomena such as erythema nodosum or induratum, phlyctenular conjunctivitis, and dactylitis.[26]

Miliary tuberculosis is the result of haematogenous spread of the disease. The lungs, liver, kidneys, bone marrow, central nervous system and other organs may be involved. Patients may have an insidious onset of constitutional symptoms, dry cough and breathlessness. However, children often present more acutely. Chest radiographs typically show diffuse fine micronodular shadows of around 1 to 2 mm in diameter spreading all over the lung fields.

Postprimary Tuberculosis

Postprimary pulmonary tuberculosis

The tubercle bacilli may remain dormant for years. Reactivation may occur when the immunity of the host is diminished. Apical portions of the lungs are the commonest sites of involvement. Symptoms may be constitutional, such as fever, malaise and weight loss, or respiratory, in particular chronic cough and blood-streaked sputum. Physical examination is usually unremarkable although signs related to complications may be found, including those of consolidation, collapse, pleural effusion, and endobronchitis. When the disease involves other organs, other site-specific features may be found.

Extrapulmonary tuberculosis

TB can affect many organs in our body. Clinical features depend on the site of involvement and may include those of pleural effusion as in TB pleuritis; enlarged lymph nodes (particularly in the cervical and mediastinal regions) as in TB lymphadenitis; urinary symptoms, localised swelling of testes and epididymis, infertility, pelvic pain or menstrual disturbance as in genitourinary TB[27]; bone or joint pain, or soft tissue swelling as in patients with skeletal involvement; pain and deformity of the spine, neurological lesions due to spinal TB; features of pericardial effusion or constrictive pericarditis as in cases of TB pericarditis; meningitis and cranial nerve lesions as in patients with central nervous system involvement; and those of peritonitis, diarrhea, weight loss, and abdominal mass as in patients with abdominal involvement.

According to local data, lymph nodes and pleura are the second or third commonest sites of TB infection.[28] Other common extrapulmonary sites include genitourinary tract, bones and joints, gastrointestinal tract, skin, and larynx, etc. There are sex differences in the site of infection. TB lymphadenitis occurs more commonly in women, whereas TB of the pleura occurs more commonly in men.

Cryptic Tuberculosis

This is a form of TB which spreads by the haematogenous route. It is more commonly found in the elderly. This condition is more difficult to diagnose because patients usually present with non-specific symptoms including fever, weight loss and malaise, etc. Findings on chest radiographs are usually atypical. On the other hand, evidence of bone marrow involvement, hepatosplenomegaly, and meningeal involvement may be found.[29]

Profile of TB Patients in Hong Kong

Figures 3.1 to 3.4 and Tables 3.1 to 3.3 show the profile of TB patients in Hong Kong in 2004.[28]

Males and the older age groups constituted higher proportions among TB patients, with 64% being male and 44% being aged 60 or above (Fig 3.1 and 3.2). This relatively high proportion of elderly has a significant bearing in the clinical perspective because they are more likely to have atypical presentations,[30] develop side effects of anti-TB treatment, and have less favorable outcomes. As shown in Table 3.1, the vast majority of TB patients were Chinese and permanent residents, which could be expected from the ethnic composition of the local population. Up to 87% were new cases, without past history of treatment (Table 3.3). More than 80% of patients presented with symptoms (Table 3.2), which is indicative of the dominant role of passive case finding in TB control. The lungs were involved in 88% of cases (Fig 3.3). Around one-third of patients with pulmonary TB were sputum smear-positive which carried a higher infectious risk. On the other hand, more than two-thirds of patients with pulmonary TB were culture positive (Table 3.3). Extrapulmonary involvement was found in 24% overall, including 12% with both pulmonary and extrapulmonary involvement (Fig 3.3). The commonest sites of extrapulmonary involvement were pleura (34%) and lymph nodes (33%) (Fig 3.4).

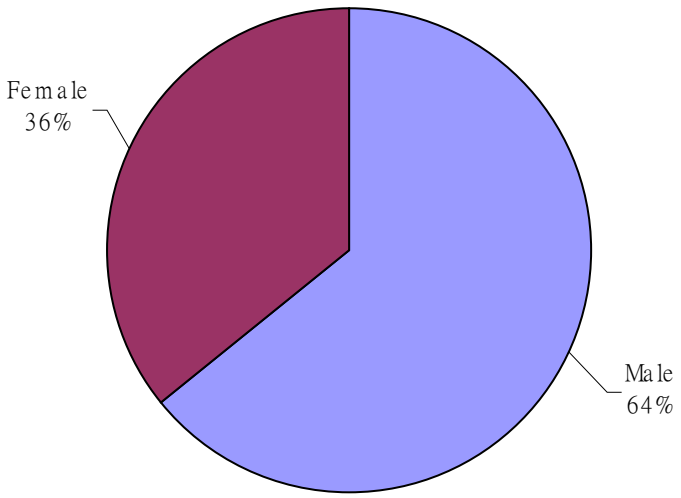


Figure 3.1. Sex distribution of local TB patients in 2004

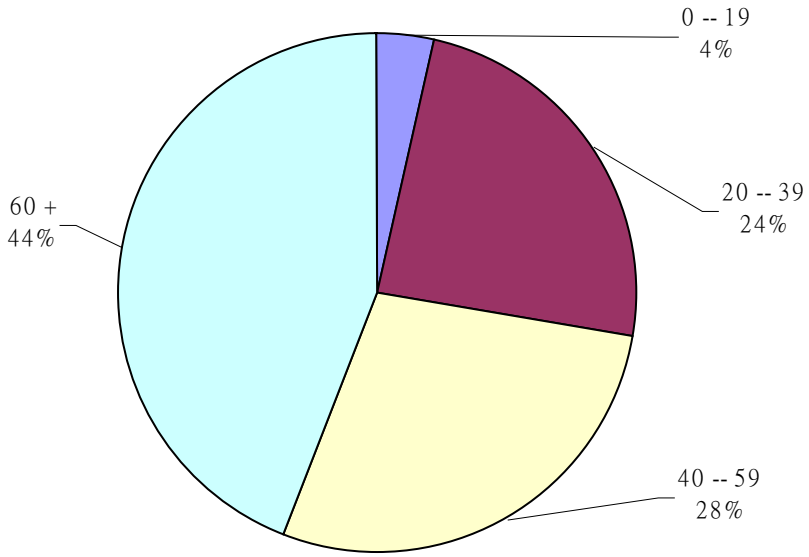


Figure 3.2. Age distribution of local TB patients in 2004

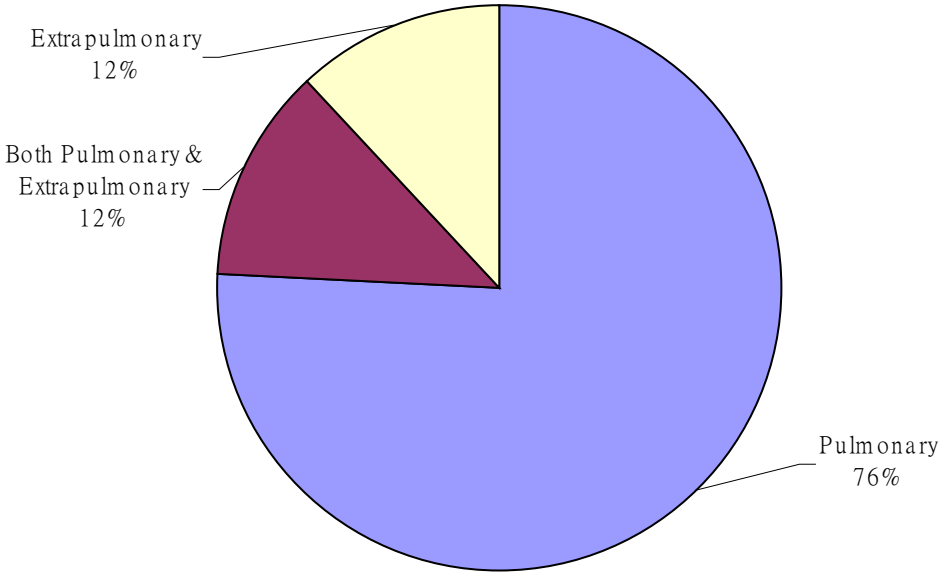


Figure 3.3. Disease classification by sites of involvement in 2004

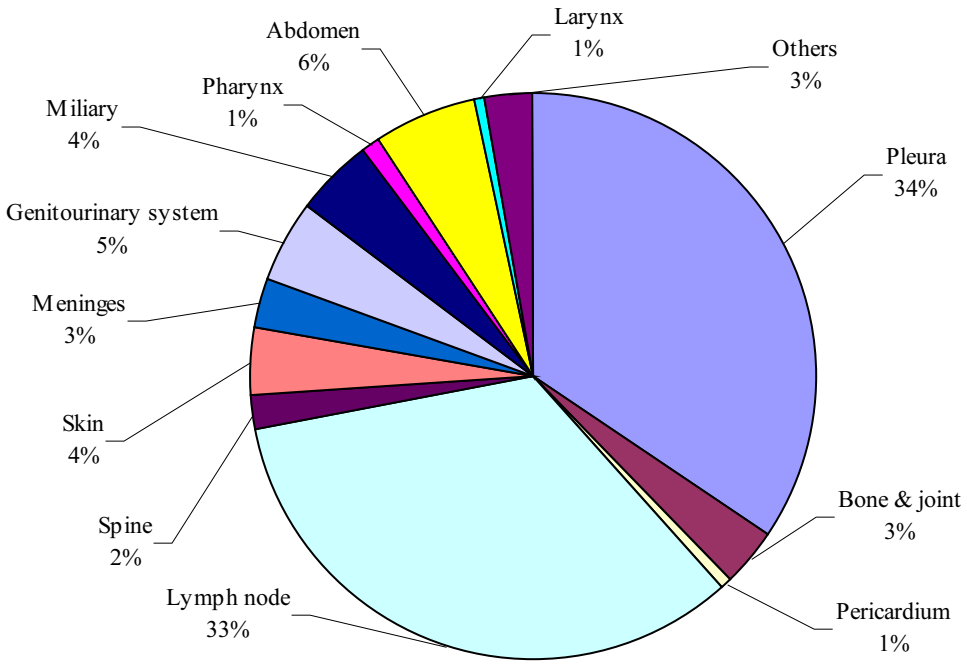


Figure 3.4. Sites of extrapulmonary involvement of TB in 2004

Table 3.1. Basic demographics of tuberculosis patients in 2004 in Hong Kong (in percentages excluding cases without available data)

Categories		**Percentages**
Residential status	Permanent resident	93.4
	Chinese new immigrant	2.8
	Imported worker	2.8
	Tourist – two-way permit	0.5
	Other tourist	0.1
	Vietnamese	0.2
	Illegal immigrants	0.2
Ethnicity	Chinese	94.8
	Other Asian	3.1
	Caucasian	0.3
	Others	1.8
Occupation	Blue collar	45.6
	White collar	15.0
	Medical	0.2
	Nursing	0.5
	Paramedical	0.1
	Support health staff	0.4
	Others	38.1

Conclusions

TB has been a major health threat since the old days. Today, it remains one of the most important infectious diseases not only in developing countries, but also in developed countries and in Hong Kong. As a result, medical practitioners should stay vigilant and maintain a high index of clinical suspicion. Presentations of TB may be atypical in the elderly, the immunocompromised, and in the children. About 44% of TB patients diagnosed in 2004 in Hong Kong were aged 60 years or above. A better understanding of the nature of TB and its transmission dynamics, updating with new

findings from research studies related to the TB genome, in addition to continuous monitoring of clinical profile of TB patients locally, would be of great interest and benefits in TB control.

Table 3.2. Modes of presentation of tuberculosis patients in 2004 in Hong Kong (in percentages excluding cases without available data)

Presentations	Percentages
Symptom	84.4
Contact screening	2.5
Pre-employment check up	1.3
Pre-emigration check up	0.1
Other check up	4.1
Incidental	6.3
Others	1.3

Table 3.3. Disease characteristics among tuberculosis patients in 2004 in Hong Kong (in percentages excluding cases without available data)

		Percentages
Disease characteristics (pulmonary cases only)	Pretreatment smear +ve	35.8
	Pretreatment culture +ve	71.2
	Extent 1 (combined area of lesion less than one lobe)	54.8
	Extent 2 (area less than one lung but more than one lobe)	30.9
	Extent 3 (area more than one lobe)	14.3
	No cavity on chest radiograph	79.8
	Cavity on chest radiograph	20.2
Case category	New cases	87.0
	Relapse	12.1
	Retreatment after default	0.8
	Retreatment after failure	0.1

References:

1. Keers RY. Pulmonary tuberculosis: a journey down the centuries. London: Cassell Ltd., 1978.
2. Grosset J, Truffot-Pernot C, Cambau E. Bacteriology of tuberculosis. In: Tuberculosis - A comprehensive international approach. Reichman LB, Herschfield E (eds). Marcel Dekker. New York 2000, pp157-85.
3. Cole ST, Brosch R, Parkhill J, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 1998;11:393(6685):515-6.
4. Riley RL, Wells W, Mills C. Air Hygiene in tuberculosis: quantitative studies of infectivity and control in a pilot ward. Am Rev Tuberc Pulm Dis 1957;75:420-30.
5. Riley R, Mills C, Nyka w. Aerial dissemination of pulmonary tuberculosis – a two year study of contagion in a tuberculosis ward. Am J Hyg 1959;70:185-96.
6. Houk V et al. The epidemiology of TB in a closed environment. Arc Environ Health 1968;16:26-52.
7. Riley EC, Murphy G, Riley RL. Airborne spread of measles in a suburban elementary school. Am J Epidem 1978;107:421-32.
8. Soper HE. The interpretation of the periodicity of disease prevalence. J Royal Statis Soc 1929;92:34.
9. Nardell E, Keegan J, Cheney S, Etkind S. Airborne infection: theoretical limits of protection achievable by building ventilation. Am Rev Respir Dis 1991;144:302-06.
10. Catanzaro A. Nosocomial tuberculosis. Am Rev Respir Dis 1981;123:559-62.
11. Dannenberg AM. Pathogenesis of pulmonary tuberculosis - host-parasite interactions, cell-mediated immunity, and delayed type hypersensitivity. In: Basic Principles in tuberculosis. D Scholssberg (ed). Springer-Verlag, New York 1992, 3rd ed.
12. Condos R, Rom W N, Liu YM, Schluger NW. Local immune responses correlate with presentation and outcome in tuberculosis. Am J Respir Crit Care Med 1998;157:729-35.
13. Braciale TJ, Morrison LA, Sweetser MT, Sambrook J, Gething MJ, Braciale VL. Antigen presentation pathways to class I and class II MHC-restricted T-lymphocytes. Immunol Rev 1987;98:95-114.
14. Taha RA, Kotsimbos TC, Song YL, Menzies D, Hamid Q. IFN-γ and IL-12 are increased in active compared with inactive tuberculosis. Am J Respir Crit Care Med 1997;155:1135-9.
15. Tso HW, Ip WK, Chong WP, Tam CM, Chiang AK, Lau YL. Association of interferon gamma and interleukin 10 genes with tuberculosis in Hong Kong Chinese. Genes Immun 2005;6:358-63.
16. Tso HW, Lau YL, Tam CM, Wong HS, Chiang AKS. Associations between IL12B polymorphisms and tuberculosis in the Hong Kong Chinese population. J Infect Dis 2004;190:913-9.
17. Menzies RI. Tuberculin skin testing. In: Tuberculosis - A comprehensive international approach. Reichman LB, Herschfield E (eds). Marcel Dekker, New York 2000, pp279-322.

18. Styblo K. Epidemiology of tuberculosis. Royal Nethers Tuberculosis Association Selected Papers. Royal Netherlands Tuberculosis. The Hugue. 1991.
19. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376-95.
20. Selwyn P, Hartel D, Lewis V, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989;320:545-50.
21. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Ann Intern Med 1993;119:185-93.
22. Vynnycky F, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. Epidemiol Infect 1997;119:183-201.
23. Braden CR, Morlock GP, Woodley CL, et al. Simultaneous infection with multiple strains of Mycobacterium tuberculosis. Clin Infect Dis 2001;33:E42-E47.
24. Richardson M, Carroll NM, EngelkeE, et al. Multiple Mycobacterium tuberculosis strains in early cultures from patients in a high-incidence community setting. J Clin Microbiol 2002;40:2750-4.
25. Warren RM, Victor TC, Streicher EM, et al. Patients with active tuberculosis often have different strains in the same sputum specimen. Am J Respir Crit Care Med 2004;169:610-4.
26. Stead WW, Kerby GR, Schlueter DP, Jordah CW. The clinical spectrum of primary tuberculosis in adults. Ann Intern Med 1968;68:731-45.
27. Christensen WI. Genito-urinary tuberculosis: review of 102 cases. Medicine 1974;53:377-90.
28. Hong Kong Tuberculosis and Chest Service. Annual Report 2004 of the Tuberculosis and Chest Service of the Department of Health, HKSAR.
29. Yew WW, Tam CM. Tuberculosis. In: Principles and practice of clinical medicine in Asia – treating the Asian patient. Sung JJY, Wong LKS, Li PKT, Sanderson J, Kwok TCY (eds). Lippincott Williams & Wilkins Asia Ltd, Hong Kong SAR 2002, pp172-84.
30. Leung CC, Yew WW, Chan CK, et al. Tuberculosis in older people: A retrospective and comparative study from Hong Kong. J Am Geri Society 2002;50:1219-26.

CHAPTER 4

DIAGNOSIS

KF Au, KM Kam, PC Wong

Summary points:

1. Timely and accurate diagnosis of tuberculosis is important to allow early detection and prompt initiation of effective treatment.
2. The diagnostic workup aims at establishing the diagnosis of tuberculosis as well as excluding other competing differential diagnoses.
3. Chest radiograph and bacteriology remain to be the basic investigations for cases of suspected tuberculosis.
4. Other methods such as histological examination, biochemical and immunological markers, and newer methods, such as the nucleic acid amplification technique, usually play a supplementary role.
5. Newer diagnostic tools aim at improving the accuracy and timeliness, but their strengths and limitations in different clinical conditions should be considered so that they can be used appropriately.
6. Nucleic acid amplification techniques appear to be one of the most promising new methods. They are faster than culture and more specific than direct smear examination, although they are much more costly.
7. No single test should replace sound clinical judgment.

Introduction

This chapter focuses on the diagnosis of active tuberculosis (TB) disease. Diagnosis and treatment of latent TB infection will be covered in other sections (Chapters 13 and 14). In view of the endemic nature of the disease and its ability to mimic many other respiratory and non-respiratory conditions, a high index of suspicion is called for in our daily clinical practice.

Clinical presentation of TB has been covered in the last chapter. In the local setting, for patients presenting with persistent chest or systemic symptoms, TB is usually considered as one of the differential diagnoses. This is particularly true for those at a higher risk of TB such as patients with compromised immunity. Examples include patients with human immunodeficiency virus (HIV) infection, those on cytotoxic or corticosteroid therapy, patients with lymphoma, silicosis, diabetes, alcoholism, malnutrition, post- gastrectomy or renal failure, as well as young infants and the elderly. The diagnostic workup for a suspected case of TB follows the usual clinical approach and aims at establishing the diagnosis of TB as well as excluding other competing differential diagnoses. Apart from a proper clinical assessment, simple investigations like chest radiograph and sputum for AFB examination may already provide important clues to the diagnosis. A range of other radiological, bacteriological, molecular, biochemical and immunological tools are also available, and clinicians should be aware of their relative merits and limitations, so that the necessary test(s) can be performed for the right condition at the appropriate time.

Radiological Examination

The plain chest radiograph remains one of the most important diagnostic tools for pulmonary TB. It is a relatively simple and affordable examination. The air inside our lung provides a natural radiolucent contrast for visualization of the various intrapulmonary structures. The radiation dose is minimal and examination result is almost instantly available.

In patients with primary TB, the chest radiograph typically shows lung shadows in the middle or

lower lobes with ipsilateral hilar lymphadenopathy. In patients with postprimary TB, radiological abnormalities can usually be found at the apical or posterior segment of the right upper lobe, apical-posterior segment of the left upper lobe, or the apical segments of the lower lobes. Abnormalities include infiltrative shadows, volume loss, cavity formation, fibrosis and calcification. Atypical presentation is common among elderly subjects. In a local report, they were more likely to have extensive disease and lower zone involvement.[1]

In patients with typical clinical presentation and radiological features, it is often not difficult to make a presumptive diagnosis of TB, even in the absence of bacteriological confirmation or histological support. In an area with relatively high TB prevalence, it would be reasonable to start empirical anti-TB treatment basing only on clinico-radiological grounds for individuals at low risk of other diseases. However, accuracy of using radiological features in diagnosis has varied with different experience and epidemiological settings. Close monitoring of the patient is important, and further investigation may be warranted if the clinical or radiological response is not satisfactory or when patients develop significant adverse reactions to anti-tuberculosis treatment.

Other useful imaging techniques include computed tomography and magnetic resonance imaging. Computed tomography is more sensitive than the chest radiograph in detecting small lesions, cavities, miliary disease and lymphadenopathy.[2,3] However, the dose of radiation is much higher (Table 4.1).[4] Magnetic resonance imaging is particularly helpful in the diagnosis of TB bones and joints, as well as intracranial TB.

Table 4.1. Radiation dose of some conventional X-ray examinations and computerised tomography examinations (United Kingdom, Data from the Report to the General Assembly of the United Nations Scientific Committee on the Effect of Atomic Radiation, 1993) (As a reference, the annual effective dose from natural sources is 2.38 mSv globally.) [4]

X-ray examination	Effective dose (mSv)	CT examination	Effective dose (mSv)
Skull	0.15	Head	1.8
Chest	0.05	Chest	8.3
Lumbo-sacral spine	2.2	Cervical spine	2.9
Abdomen	1.4	Thoracic spine	5.8
Pelvis	1.2	Abdomen	7.2
Urography	4.4	Pelvis	7.3
Upper GI tract	3.8		
Lower GI	7.7		

In general, imaging techniques are useful in picking up lesions in various parts of the body, and may also give useful clues to possible underlying pathologies. However, they fall short of providing an exact proof of the aetiology.

Microbiological Tests

Microbiological tests, together with radiological investigations, are the key investigative tools used in the diagnosis of TB. Sputum for acid fast bacilli (AFB) direct smear and culture examination should be performed as part of the initial investigations of choice for patients with suspected pulmonary TB. For some patients with unremarkable chest radiological findings, sputum examination for AFB may still be indicated if there are other suspicious or compatible clinical features.[5] Other clinical samples for microbiological diagnosis include gastric washing, bronchial aspirate, pleural fluid, biopsy specimens of the lung, or non-respiratory specimens like early morning urine, lymph node aspirate, pericardial fluid, cerebrospinal fluid, joint fluid, etc. Although a range of laboratory diagnostic tests are available, the basic tests include strain identification and drug susceptibility test for positive culture isolates apart from direct microscopy and culture.

Direct microscopy for AFB is a simple, inexpensive, rapid and well-tested diagnostic method. A positive sputum smear usually indicates significant infectivity. In fact, sputum microscopy, as a case finding tool, is one of the five key components of the “Directly Observed Treatment, Short Course” (DOTS) strategy advocated by the World Health Organisation (WHO).[6] However, to yield a positive

smear result, it requires 5,000 to 10,000 bacilli per mL of specimen.[7,8] The sensitivity ranges from 22% to 78% depending on clinical presentation, e.g. higher for cavitary disease,[9] and it would not be possible to differentiate the various mycobacterial species.

Culture examination is generally regarded as the gold standard for TB diagnosis. Although conventional cultures usually take a longer time to complete (4-9 weeks), it is more sensitive than direct smear examination because it requires less tubercle bacilli (10 to 100 bacilli per mL of specimen) to become positive.[7,8] Recovery of mycobacteria also allows subsequent identification and drug susceptibility tests to be carried out. Drug susceptibility testing is a key component of the "DOTS-Plus" strategy, and it provides critical guidance in the choice of drugs in drug-resistant TB.[10-11]

With the radiometric broth system, AFB culture tests can be shortened to about two weeks or less for positive cases.[12] The radiometric method is usually semi-automated and involves handling of radioactive materials. A fully automatic non-radiometric system is perhaps more advantageous. One example is the MB/BacT system, which has been shown to be comparable to conventional agar method in accuracy and reliability.[13] High running costs associated with these test formats are the usual considerations that hamper more extensive use.

Apart from the commonly performed AFB direct smear and culture examination, other microbiological tests could also be considered in specific scenarios.

Nucleic acid amplification technique appears to be one of the most promising new methods.[14-16] Polymerase chain reaction (PCR) procedures, which are based on different target sequences, have been described for detection of the various parts of the *Mycobacterium tuberculosis* (MTB) genome.[17,18] It is faster than culture, but sensitivity decreases with smear negative cases. It detects 95% of smear-positive cases with a specificity of 98%, and 48% to 53% of smear-negative culture-positive cases with a specificity of 95%.[19] It is particularly useful in confirming TB in smear-positive cases, pending the availability of culture results. With better techniques, its use has been expanded to other scenarios as well.[20] Studies have shown that its performance in cerebrospinal fluid,[21,22] urine,[23,24] gastric aspirate,[25] liver biopsy and bone marrow specimen[26] are more encouraging compared with current alternatives. However, the benefit of its use in the case of pleural effusions is less conclusive.[27,28] In particular, it cannot differentiate between dead and live tubercle bacilli. The major limitations are variable sensitivity and high cost.

MTB strain typing by DNA fingerprinting (restriction fragment length polymorphism, RFLP) using insertion sequence *IS6110* as the standard probe has been proven to be a powerful molecular tool for epidemiological investigation, especially in outbreak situations.[19]

Rapid detection of drug resistance is particularly useful when there is a high chance of multidrug-resistant TB (MDR-TB) as in the cases of treatment failure or early relapse after treatment completion. Testing for rifampicin mono-resistance by detection of mutations of the MTB *rpo*B gene has been recommended because of its high predictive value for multidrug-resistance and its technological feasibility.[29-31] Direct detection of rifampicin resistant MTB in *IS6110* PCR or PCR-positive respiratory specimens by *rpoB* PCR-DNA sequencing of the 81-bp rifampicin resistance determining region (RRDR) was found to be feasible in a local study.[32]

Histological Diagnosis

Tissue biopsy of the affected organs or sites may provide a rapid confirmatory result which serves to support the diagnosis of TB and to look for other differential diagnoses. It may be the initial investigation of choice when the affected sites are easily accessible for biopsy such as peripheral lymphadenopathy and pleural effusion. It may also be the only definitive diagnostic test for some cases of extrapulmonary TB like bone marrow, and abdominal disease. In patients with lung shadow without conclusive result on preliminary investigations, the lung lesion may also be biopsied through bronchoscopic examination or needle aspirate. Typical histological features include caseating granuloma, aggregation of epitheliod cells, Langhan's giant cells, while presence of acid-fast bacilli using Ziehl-Neelsen staining is confirmatory of the diagnosis. It is desirable that biopsy samples

should also be sent for bacteriological examination and drug susceptibility testing as far as possible, in particular when bacteriological results of other specimens are not available. The benefit of getting a confirmatory diagnosis should be balanced against the potential risks and complications inherent to the biopsy procedures especially in the very old and frail subjects.

Tuberculosis-related Biochemical and Immunological Markers

Diagnosis of TB pleurisy is difficult because of the nonspecific clinical features and the paucibacillary nature. Several biochemical and immunological markers in pleural fluid have been used to aid the diagnosis of TB. Studies have shown that adenosine deaminase (ADA) and interferon-gamma (INF-γ) have good sensitivities and specificities.[33,34] In a local retrospective study, Chen et al analysed 210 patients with exudative pleural effusion and used a cut-off value of ADA >55.8 U/L for diagnosing TB pleural effusion.[35] The sensitivity, specificity, positive predictive and negative predictive values were rather promising, with values of 87.3%, 91.8%, 82.1% and 94.4% respectively. Other mycobacterial markers have also been used in diagnosing TB meningitis cases which often pose difficulty in different presentation scenarios.

One study[36] applied fuzzy-logic analysis to assign patients with pleural effusion to the underlying diseases including TB, bronchial carcinoma, congestive heart failure and pneumonia with 80% accuracy using interleukin (IL)-6 and IL-15 measurement. This analysis was based on the complex interactions of various local and circulating cells as well as numerous soluble parameters like interleukins in pleural effusions caused by highly different underlying diseases. It demonstrated the potential role of fuzzy-logic-based procedures to characterise and distinguish effusions of unknown origin.

Tests for Tuberculosis Infection:

It is not always possible to obtain a firm diagnosis of TB in patients presenting with either chronic fever or nonspecific lesion in the lung or elsewhere, especially among young children for whom bacteriological confirmation is often an exception. As disease should only develop among those who have been infected, knowledge of the infection status of the patient would, in theory at least, assist in the differential diagnosis.

Tuberculin skin test (TST) has been the basic test for diagnosing TB infection since decades ago. However, a positive result could also be caused by BCG vaccination or exposure to non-tuberculous mycobacterial infection. In places with a wide coverage of BCG vaccination such as in Hong Kong, a positive TST should therefore be interpreted with caution. Newer techniques involving T-cell based gamma-interferon assay after stimulation with antigens present mainly in MTB are likely to be more specific. Notwithstanding this, only a small proportion of infected individuals will ever develop disease. In those areas with a high background prevalence of infection, a positive test for infection is probably of little help in confirming whether or not a disease in question is tuberculosis in origin.

False negative results have well been reported among patients with bacteriologically confirmed active TB. Therefore a negative TST does not exclude MTB infection or disease. A relatively high sensitivity has been reported for some of the T-cell based gamma-interferon assays.[37] While this might suggest a better negative predictive value, further evaluation is required to establish their exact diagnostic role in this aspect. Diagnosis of latent TB infection would be discussed in further detail in another section. (See Chapters 13 and 14.)

Empirical Trial of Anti-tuberculosis Drugs

Despite the full range of investigation tools available, there are occasions where the diagnosis of TB remains elusive after exhaustive investigations and/ or when further invasive investigations are precluded by the patient's clinical condition. Empirical trial of a course of anti-TB drugs may be justified in such circumstances, especially if the patient has failed to respond to antibiotics against a broad spectrum of other pathogens. Although some of the anti-TB drugs, e.g. rifampicin and streptomycin, also possess activity against the usual bacterial pathogens, the clinical context in which they are used seldom leaves room for confusion. An initial trial for a few days of isoniazid and

ethambutol may also be considered in patients with pyrexia of unknown cause for which TB is strongly suspected. While it is reassuring if there is definite clinical and/ or radiological response after initiation of anti-TB treatment, paradoxical reactions or adverse drug reactions are not uncommon. Careful monitoring and ongoing reassessment are therefore mandatory. It is also important to ensure adequate treatment of any other comorbid conditions such as diabetes mellitus, heart failure, bronchial asthma, HIV, etc. Poorly controlled concomitant illnesses may masquerade as failure of anti-tuberculosis treatment or disease progression.

Conclusions

Prompt treatment of active tuberculosis is the cornerstone in TB control. This relies heavily on accurate and timely diagnosis. As a result, development of better tests is important. Nowadays, chest radiographic examination and bacteriology remain to be the basic investigations for suspected cases of TB, while newer diagnostic methods mainly play a supplementary role. Competing differential diagnoses other than TB should also be looked for during the workup for cases of suspected TB. Histology involving tissue biopsy with or without surgery may be required in certain settings.

Among the newer methods, nucleic acid amplification seems to be a more promising one and it is getting more commonly used. Economic analysis should be considered particularly when these new, and often expensive, techniques are to be used on a larger scale. The use of such techniques may have to be studied in various clinical settings so that they can be optimally employed in the right situation, at the right time, and achieving best cost benefit. No single test should replace sound clinical judgment.

References

1. Leung CC, Yew WW, Chan CK, et al. Tuberculosis in older people: A retrospective and comparative study from Hong Kong. J Am Geri Society 2002;50:1219-26.
2. Im JG, Itoh H, Shim YS. Pulmonary tuberculosis: CT findings-early active disease and sequential change with antituberculosis therapy. Radiology 1993;186:653-60.
3. Lee KS, Hwand JW, Chung MP, Kim H, Kwon OJ. Utility of CT in the evaluation of pulmonary tuberculosis in patients without AIDS. Chest 1996;110:977-84.
4. Cheng KM, Chan CN. Radiation protection in diagnostic radiology. Public Health and Epidemiology Bulletin 1997;6:17-21.
5. Marciniuk DD, McNab BD, Martin T, Hoeppner VH. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Chest 1999;115;445-52.
6. World Health Organization. WHO tuberculosis programme: framework for effective tuberculosis control, Geneva, 1994, WHO/TB/94.175.
7. Hobby GL, Holman AP, Iseman MD, Jones J. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 1973;4:94-104.
8. Yeager HJ, Lacy J, Smith L, LeMaistre C. Quantititaive studies of mycobacterial population in sputum and saliva. Am Rev Respir Dis 1967;95:998-1004.
9. Lobue PA. Diagnosis of tuberculosis. In: Tuberculosis: A comprehensive international approach. Reichman LB, Herschfield E (eds). Marcel Dekker, New York 2000, pp341-75.
10. Farmer PE, Kim JY. Community-based approaches to the control of multidrug-resistant tuberculosis: introducing “DOTS-plus”. Br Med J 1998;317:671-4.
11. World Health Organization, Report: basis for the development of an evidence-based case-management strategy for MDR-TB within the WHO’s DOTS strategy, Geneva, 1999, WHO/TB/99.260.
12. Siddiqi SH, Hwangbo CC, Silcox V, Good RC, Snider DEJr, Middlebrook G. Rapid radiometric methods to detect and differentiate Mycobacterium tuberculosis/ M bovis from other Mycobacterial species. Am Rev Respir Dis 1984;130:634-40.
13. Yew WW, Tong CW, Lui KS, Leung KF, Chau CH, Wang EP. Comparison of MB/BacT system and agar proportion method in drug susceptibility testing of Mycobacterium tuberculosis. Diag Microbiol Infect Dis 2001; 39:229-32.
14. Eisenach KD, Sifford AD, Cave MD, Bates JH, Crawford JT. Detection of Mycobacterium tuberculosis in sputum samples using a polymerase chain reaction. Am Rev Respir Dis 1991;144:1160-3.
15. Clarridge JE, Shawar RM, Shinnick TM, Plikaytis BB. Large scale use of polymerase chain reaction for detection of Mycobacterium tuberculosis in a routine mycobacteriology laboratory. J Clin Microbiol 1993;31:2049-56.
16. Querol JM, Farga MA, Granda D, Gimeno C, Garcia-de-Lomas J. The utility of polymerase chain reaction in the diagnosis of pulmonary tuberculosis. Chest 1995;107:1631-5.
17. Brisson-Noel A, Lecossier D, Nassif X, et al. Rapid diagnosis of tuberculosis by amplification of mycobacterial DNA in clinical samples. Lancet 1991;338:364-6.
18. Cousins DV, Wilton SD, Francis BR, Gow BL. Use of polymerase chain reaction for rapid diagnosis of tuberculosis. J Clin Microbiol 1992;30:255-8.

19. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376-95.
20. Della-Latta P, Whittier S. Comprehensive evaluation of performance, laboratory application, and clinical usefulness of two direct amplification technologies for the detection of Mycobacterium tuberculosis complex. Am J Clin Pathol 1998;110:301-10.
21. Kox LF, Kuijper S, Kolk AH. Early diagnosis of tuberculosis meningitis by polymerase chain reaction. Neurology 1995;45:2228-32.
22. Pfyffer GE, Kissling P, Jahn EM, Welscher HM, Salfinger M, Weber R. Diagnostic performance of amplified Mycobacterium tuberculosis direct test with cerebrospinal fluid, other non-respiratory, and respiratory specimens. J Clin Microbiol 1996;34:834-41.
23. van Vollenhoven P, Heyns CF, de Beer PM, Whitaker P, van Helden PD, Victor T. Polymerase chain reaction in the diagnosis of urinary tract tuberculosis. Urolog Res 1996;24:107-11.
24. Fontana D, Pozzi E, Porpiglia F, et al. Rapid identification of Mycobacterium tuberculosis complex on urine samples by Gen-Probe amplification test. Urol Res 1997;25:391-4.
25. Delacourt C, Poveda JD, Chureau C, et al. Use of polymerase chain reaction for improved diagnosis of tuberculosis in children. J Pediatr 1995;126:703-9.
26. Akcan Y, Tuncer S, Hayran M, Sungur A, Unal S. PCR on disseminated tuberculosis in bone marrow and liver biopsy specimens: correlation to histopathological and clinical diagnosis. Scand J Infect Dis 1997;29:271-4.
27. Vlaspolder F, Singer P, Roggeveen C. Diagnostic value of an amplification method Gen-Probe compared with that of culture for diagnosis of tuberculosis. J Clin Microbiol 1995;33:2699-703.
28. Querol JM, Minguez J, Garcia-Sanchez E, Farga MA, Gimeno C, Garcia-de-Lomas J. Rapid diagnosis of pleural tuberculosis by polymerase chain reaction. Am J Respir Crit Care Med 1995;152:1977-81.
29. World Health Organization. Global project on anti-tuberculosis drug resistance surveillance. Third report 2004, WHO/HTM/TB/2004.343.
30. Schluger NW. Changing approaches to the diagnosis of tuberculosis. Am J Respir Crit Care Med 2001;164:2020-4.
31. Hellyer TJ, DesJardin LE, Teieira L, Perkins MD, Cave MD, Eisenach KD. Detection of viable Mycobacterium tuberculosis by reverse transcriptase-strand displacement amplification of mRNA, J Clin Microbiol 1999;37:518-23.
32. Yam WC, Tam CM, Leung CC, et al. Direct detection of rifampin-resistant mycobacterium tuberculosis in respiratory specimens by PCR-DNA sequencing. J Clin Microbiol 2004;42:4438-43.
33. Villegas MV, Labrada LA, Saravia NG. Evaluation of polymerase chain reaction, adenosine deaminase, and interferon-gamma in pleural fluid for the differential diagnosis of pleural tuberculosis. Chest 2000;118:1355-64.
34. Greco S, Girardi E, Masciangelo R, Capoccetta GB, Saltini C. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculosis pleurisy: a meta-analysis. Int J Tuberc Lung Dis 2003;7:777-86.
35. Chen ML, Yu WC, Lam CW, Au KM, Kong FY, Chan AY. Diagnostic value of pleural fluid adenosine deaminase activity in tuberculosis pleurisy. Clin Chim Acta 2004;341:101-7.
36. Chomej P, Bauer K, Bitterlich N, et al. Differential diagnosis of pleural effusions by fuzzy-logic-based analysis of cytokines. Respir Med 2004;98:308–17.
37. Lalvani A, Pathan AA, Durkan H, et al. Enhanced contact tracing and spatial tracking of Mycobacterium tuberculosis infection by enumeration of antigen-specific T cells. Lancet 2001;23:2017-21.

CHAPTER 5

TUBERCULOSIS REFERENCE LABORATORY OF THE PUBLIC HEALTH LABORATORY SERVICES BRANCH, CENTRE FOR HEALTH PROTECTION, DEPARTMENT OF HEALTH - AN INTRODUCTION OF ITS WORK

CW Yip, MY Chan, WS Wong, KM Kam

Summary points:

1. The Tuberculosis Reference Laboratory (The Laboratory) provides quality laboratory services for the clinical management of tuberculosis and other mycobacterial diseases.
2. The Laboratory is a specially designed Biosafety Level III Laboratory for the safe handling of *Mycobacterium tuberculosis* and other Class 3 pathogens.
3. A range of laboratory tests including smear, culture, culture identification, drug susceptibility tests, molecular diagnosis, drug serum level and *M. tuberculosis* typing are provided.
4. Direct sputum smear microscopy is very useful for rapid detection of infectious tuberculosis cases.
5. Nucleic acid amplification test is provided for rapid confirmation of *M. tuberculosis* when the result of direct smear is positive. This test is still not yet sensitive enough for excluding *M. tuberculosis* in smear-negative cases.
6. Culture is used to provide a definitive laboratory diagnosis of tuberculosis and other mycobacterial infections. A turn-around-time of 3 to 8 weeks is required. However, with pre-arrangement and agreement, rapid culture using liquid medium with a shorter turn-around-time can be performed.
7. The Laboratory also provides a panel of identification tests including conventional biochemical and molecular tests, chromatographic analysis and DNA sequencing for mycobacterial species identification.
8. Drug susceptibility tests on first-line anti-tuberculosis drugs and other antimicrobial agents against *M. tuberculosis* and non-tuberculous mycobacteria are also performed.
9. Other tests such as urine isoniazid metabolite, rifampicin plasma level and *M. tuberculosis* fingerprint typing are also available.

Introduction

The Tuberculosis (TB) Reference Laboratory (the Laboratory) of the Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health supports the TB control program in Hong Kong. It provides a range of laboratory services for clinical management of TB and other mycobacterial infections, as well as organising and participating in TB surveillance and epidemiological studies. The Laboratory is presently receiving patients' specimens, from Government Chest Clinics, private laboratories and practitioners for detection of acid fast bacilli (AFB) by microscopy examination and mycobacterial culture. Positive mycobacterial cultures are received from all public hospital laboratories under the Hospital Authority for mycobacterial identification and drug susceptibility tests. These services are also open for laboratories in private hospitals, as well as other private laboratories.

The Laboratory is one of the twenty Supranational Reference Laboratories (SRL) within the World Health Organisation (WHO)/ International Union Against Tuberculosis and Lung Diseases (IUATLD) TB Reference Laboratories Network. In order to ensure high quality of TB laboratory testing, the Laboratory organises as well as participates in a number of TB laboratory quality assurance

programmes. In collaboration with Hong Kong Institute of Medical Laboratory Sciences, it has organised an “AFB smear Quality Assurance Programme” for clinical bacteriology laboratories in Hong Kong. Moreover, as member of the WHO SRL network, the Laboratory also organises "Proficiency on Anti-tuberculosis Drugs Susceptibility Test Programme" to various provinces of Mainland China. The Laboratory also participates in the External Quality Assurance Programme organised by the United Kingdom National External Quality Assessment Service (NEQAS) for mycobacteria smear and culture, and the World Health Organisation Supranational Reference Laboratory Network for mycobacteria drug susceptibilities testing.

In order to ensure laboratory safety during laboratory work on *M. tuberculosis* (MTB), all potentially bio-hazardous procedures are carried out in specially designed Biosafety Level III Laboratories in the Public Health Laboratory Centre. Apart from design in building architecture, equipment with appropriate biosafety devices are used in carrying out the necessary TB laboratory works. In addition, personal protective equipment and biosafety training is provided to all laboratory staff working in the Laboratory to ensure adequate safety and protection to staff. Regular talks or seminars on laboratory safety issues have also been conducted to medical and health care professionals. In case of special laboratory safety issues, medical microbiologists can always be approached for further discussions.

Following is a list of services presently provided by the Laboratory. In general, these can be classified into eight major categories:

1. Direct microscopy for the detection of AFB;
2. Direct detection of MTB from sputum by nucleic acid amplification method;
3. Primary isolation of mycobacteria from various clinical specimens;
4. Positive mycobacterial culture identification;
5. Drug susceptibility tests for both MTB and Mycobacteria other than TB (MOTT);
6. Urine isoniazid metabolite tests;
7. Rifampicin in plasma level determination;
8. MTB strain typing for outbreak investigation.

Since each laboratory test has its inherent limitation, turn-around-time (TAT), as well as examination cost, medical microbiologists in the TB laboratory are willing to discuss with clients on their specific circumstance and requirements, in order to provide the most appropriate tests for best patient management.

Brief Description on the Available Laboratory Services

1. Direct Microscopy for the Detection of Acid-fast Bacilli

Direct microscopy is used for detection of infectious cases by rapid diagnosis of TB and other mycobacterial diseases, as a relatively long period of time is required for mycobacteria to be detected by bacteriological culture.[1] Positive smears reflect higher bacterial load, and thus increased likelihood of spreading TB. Results from direct smear microscopy can be available within 24 hours. Clinically, it is important to detect presence of mycobacteria as rapidly as possible for appropriate patient care and implementation of public health measures. Moreover, direct microscopy on successive specimens is used to monitor outcome of chemotherapy for smear positive patients by observing 'smear conversion'.

In a strict sense, this test only detects presence of AFB in patient’s specimens. Although a positive smear result in general indicates the presence of MTB, definite diagnosis cannot be reached without examining the clinical picture, +/- confirmation by culture or MTB nucleic acid amplification methods.

In the TB Reference Laboratory, fluorochrome-staining method has been found to be sensitive and is used routinely for the detection of AFB. Acid-fast mycobacteria resist decolourisation by acid-alcohol after primary staining with basic fuchsin, owing to the high lipid (mycolic acid) content in the cell walls. With this staining procedure, a minimum concentration of 5,000 to 10,000 bacilli per mL of specimen is usually required for the detection of positive smear. Various studies have

shown that the overall sensitivity of the direct smear ranges from 22% to 43%, when compared with culture. When sputum smear examinations are performed on 3 appropriately collected separate specimens, the sensitivity can approach that of culture examination. Despite the rapidity and high specificity of direct smear for detection of mycobacteria, this test cannot be used to differentiate the various mycobacterial species.

For patients with unexpected smear examination results, further investigation has to be done, in particular to examine for significant clinical manifestations. For some members of the *Actinomycetes* family e.g. *Nocardia* or *Rhodococcus*, these may also appear as acid-fast when using the fluorescence staining method. Under these circumstances, the smears have to be reconfirmed by the classical Ziehl-Neelsen staining method. Specialised microscopists are available in the Laboratory for discretion of these difficult cases.

2. Direct Detection of *Mycobacterium Tuberculosis* from Sputum by Nucleic Acid Amplification Method

Due to the inherent slow growth of MTB *in vitro*, a period of 4 to 9 weeks is usually required to obtain a definite bacteriological diagnosis by culture examination. In this connection, the Laboratory provides another option for TB diagnosis by using a nucleic acid amplification (NAA) assay to detect the presence of MTB specific mRNA fragments and identify MTB directly from smear-positive clinical respiratory specimen. This Food and Drug Agency (FDA), U.S.A., approved test has a sensitivity of >95%, specificity of >98%, and results can be obtained within 2 days. This NAA assay is particularly useful when rapid differentiation between MTB infection and non-tuberculous mycobacteria infection is required, especially for AIDS patients. This test may also be performed if an unexpected smear-positive result was obtained from a patient with clinically incompatible picture, as a positive smear may only be due to presence of saprophytic AFB in the specimen.

From results of published studies[2] as well as local TB laboratory experience, sensitivity of this NAA assay against smear-negative specimen is only about 50%, despite the rapidity of the test. Presently, only limited data is available to guide the use and interpretation of this test for non-respiratory source specimens. This low sensitivity limits the use of this test for excluding MTB infection, and may give a false sense of security when an initial negative result is reported. As with any NAA test, there are inherent risks of specimen contamination as well as amplification inhibition. Special precautions have to be observed both in the method of specimen collection as well as in the Laboratory. Coupled with the high cost of this test, special arrangement with the Laboratory has to be made before sending in specimens for this NAA assay for laboratory diagnosis.

3. Primary Isolation of Mycobacteria from Clinical Specimen

To confirm a definitive laboratory diagnosis of TB or other mycobacterial infections, isolation of definite pathogen e.g. MTB, or repeated isolation of opportunistic pathogens from clinical specimens are necessary. Due to slow growth rates of most clinically encountered mycobacteria (including MTB) as well as presence of normal microbial flora in the upper respiratory tract, differential killing (alkaline decontamination) on the normal microflora in sputum specimens is conducted before inoculation to optimise yield of mycobacterial culture. Due to slow growth and effects of differential killing on mycobacteria, 4 to 9 weeks are usually required for conventional cultures to complete.[3]

Because a long incubation period is required for mycobacteria culture, contamination due to growth of other bacteria and fungi is almost inevitable. In general, a level of contamination of not more than 5% should be expected. In this connection, two to three consecutive specimens collected at different times may be useful to maximize the chance of mycobacterial isolation.

Bacterial flora which are resident in the upper respiratory tract, such as *Pseudomonas* species, may be particularly more resistant to alkaline decontamination, and overgrow the mycobacterial culture. With repeated contaminated reports that require investigations, special arrangement with medical microbiologists can be made to look into the reasons of contamination, and specific procedures may be designed to minimise the chance of further contamination from same patient.

Apart from using conventional solid (Löwenstein-Jensen) culture medium as the major culturing tool, the Laboratory also employs a rapid liquid culture system (MGIT) for specimens of non-pulmonary and non-urinary origins, and for specimens under special request by the chest physician. This test yields a definitive negative result after six weeks' incubation, although about 90% of positive mycobacterial cultures can be obtained within three weeks. Since the cost of test is relatively high, this is not in routine laboratory service. For individual laboratory referrals, special arrangement and agreement with medical microbiologists is necessary before ordering this test.

4. Positive Culture Identification

All positive mycobacterial cultures are identified to confirm presence of pathogen. In the Laboratory, mycobacteria isolates will always be identified to species level if possible. A number of laboratory methods for identification of mycobacteria are available in the Laboratory. These include conventional biochemical tests, analysis of mycobacterial fatty acids or mycolic acids profiles by chromatography, and mycobacterial genetic investigation through the use of nucleic acid probes, restriction fragment analysis of DNA amplification products, and DNA sequencing.

For rapid molecular identification test of MTB, heat stock protein (HSP) gene[4] as target has been used by the Laboratory. A TAT of three working days can be expected for more than 90% of cases. For other atypical mycobacteria, such as *M. avium intracellulare* complex*, M. fortuitum* and *M. chelonae*, TAT is about one to two weeks. For the identification of other mycobacteria, the TAT varies much from case to case according to the progress and stages of expected examination times of the tests.

Since the amount of growth from mycobacteria isolates limits the performance of most conventional biochemical identification tests,[3] additional time is required for subculturing isolates to obtain sufficient amounts for these subsequent tests. With cases having only limited growth on the culture medium, a further two to three weeks is required to complete the tests. Clients can check the progress of the test by contacting the Laboratory.

For rare or difficult mycobacterial species, it is quite often that their identities cannot be determined by a few simple tests. In order to tackle these, a whole panel of tests may be required, including chromatographic[5] and DNA sequencing methods.[6] Under these circumstances, additional efforts and time is required for performing the tests and subculturing the mycobacterial strains. As with experiences in most reference TB laboratories, there will be still around 5% of total isolates that could not be identified to species level, despite using all available means.[7]

Since the Laboratory has to process about 500 mycobacterial identification cases every week, work has to be done in batches which may result in a longer TAT. For urgent case, clients can contact the Laboratory for special arrangements and necessities of rapid mycobacterial identification.

5. Drug Susceptibility Tests

With the emergence of drug resistant MTB isolates, drug susceptibility tests (DST) for MTB has become a very important tool for revealing the causes of treatment failure, and providing a guide on the choice of anti-TB drugs in drug resistant cases. The Laboratory performs DST against all clinical MTB isolates for the four first-line anti-TB drugs (streptomycin, isoniazid, rifampicin and ethambutol) using standardised methodology.[8,9] When the isolate is found to be resistant to rifampicin, or any two drugs other than rifampicin, DST on second-line anti-TB drugs (ethionamide, pyrazinamide, kanamycin, capreomycin, cycloserine, ofloxacin and amikacin) will proceed with an interim report to the attending physician on the DST results of the first-line anti-TB drugs.

For MTB isolates from retreatment, suspected relapse or failure cases, DST on ethionamide, amikacin and ofloxacin are included in the first place. Further tests on kanamycin, capreomycin, cycloserine and pyrazinamide are also added when required. Since DST require four weeks incubation, DST report is usually available within five to six weeks after receipt of the specimen (positive culture).

For clinically difficult cases, such as multidrug-resistant TB (MDR-TB), where anti-TB drugs other than those listed above are intended for use, clients are encouraged to discuss with the Laboratory on possibility of performing these special DST. However, in these cases, methods that are not yet standardised sometimes have to be employed. This approach limits the usefulness of the tests and rendering much difficulty in interpretation of test results.

The Laboratory is using a well calibrated, standardised absolute concentration method to perform the DST to first-line anti-TB drugs. Proficiency exercises of DST have been conducted within the Global WHO/ IUATLD Supranational TB Laboratory Network.

DST can also be done in broth medium for those MTB isolates obtained from rapid broth culture (MGIT) method. For these cases, results can be ready within two to three weeks. Although this method can provide faster test results, only tests for the four first-line anti-TB drugs (streptomycin, isoniazid, rifampicin and ethambutol) are presently available.

Apart from MTB, the Laboratory also conducts DST on atypical mycobacteria using National Committee for Clinical Laboratory Standards (NCCLS, USA) microbroth dilution methods for amikacin, levofloxacin, clarithromycin, cefoxitin and doxycycline against *M. fortuitum*, *M. chelonae* and *M. abscessus*.[10] These are done routinely for those isolated from sterile sites or from wound. On a case-by-case basis, NCCLS susceptibility test on ethambutol, ofloxacin and rifampicin against *M. kansasii* and *M. marinum* can also be conducted. For DST on other anti-mycobacterial agents or tests against mycobacterium species not mentioned above, medical microbiologists can be consulted for further discussion on the availability and the limitations of these tests under different scenarios.

6. Urine isoniazid metabolite test

This is a chemical spot test that is used to detect isoniazid metabolite in patient's urine.[11] This test facilitates the measurement and monitoring of isoniazid drug uptake by TB patients. Moreover, a surprise urine test, which makes use of detection of isoniazid metabolite as a marker for drug compliance, can be requested for assessing the regularity with which anti-TB drugs prescribed for self-administration are actually ingested. Test results can usually be available within a week.

7. Rifampicin in plasma level determination

For patients with complications during chemotherapy, investigations on different patient's pharmacokinetic parameter may be useful to elucidate the possible cause of unfavourable treatment outcome. The Laboratory provides this service to determine the rifampicin plasma level using liquid chromatography-mass spectrometry technology. In order to have a rough estimation on the peak plasma level, as well as the half life of metabolising rifampicin, EDTA-blood samples are required to be taken at 2 hours and 4 hours after the administration of drug. Test results will usually be available within a week. Special arrangement with the Laboratory is required for ordering this test.

8. MTB strain typing for outbreak investigation.

Epidemiological study is essential in the prevention and control of TB. In recent years, DNA fingerprinting (restriction fragment length polymorphism, RFLP) using insertion sequence *IS6110* as standard probe internationally, has proven to be a powerful laboratory tool for molecular epidemiological investigations.[12] In the Laboratory, when positive MTB cultures are available from suspected TB outbreak cases, DNA fingerprinting analysis can be conducted for confirming epidemiological relationships. For detailed arrangements of requirements, chest physicians and epidemiologists are requested to contact the Laboratory for further information.

Conclusions

The TB Reference Laboratory plays an essential role in supporting the local TB control programme. The Laboratory serves clinicians in both public and private sectors. In addition, it participates in and organises a number of surveillance and laboratory quality assurance programmes. When necessary, the Laboratory may be contacted for further information or arrangement for some of the special tests.

Reference

1. Collins CH, Grange JM and Yates MD. Organization and Practice in Tuberculosis Bacteriology. Butterworth & Co. Ltd, London 1985.
2. American Thoracic Society Workshop. Rapid diagnostic tests for tuberculosis. What is the appropriate use? Am J Respir Crit Care Med 1997;155:1804-14.
3. Kent PT, Kubica GP. 1985. A guide for the Level III laboratory. Centers for Disease Control, Atlanta, GA.
4. Wong DA, Yip CW, Cheung TL, Kam KM. Simple and rational approach to the identification of *Mycobacterium tuberculosis, Mycobacterium avium* complex species, and other commonly isolated mycobacteria. J Clin Microbiol 2001;39:3768-71.
5. Nonald NM. Mycobacteriology, section 3 *In* Isenberg HD (ed). Clinical microbiology procedure handbook, Am Soc Microbiol 1994;6:469-73.
6. Edwards U, Rogall T, Blocker H, Emde M, Bottger EC. Isolation and direct complete nucleotide determination of entire genes. Characterisation of a gene coding for 16S ribosomal RNA. Nucleic Acids Research 1989;17:7843-53.
7. Tortoli, E, Bartoloni A, Bottger EC, et al. Burden of unidentifiable mycobacteria in a reference laboratory. J Clin Microbiol 2001;39:4058-65.
8. Canetti G, Fox W, Khomenko A, et al. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organisation 1969;41:21-43.
9. Kam KM, Yip CW. Surveillance of *Mycobacterium tuberculosis* drug resistance in Hong Kong, 1986-1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001;5:815-23.
10. The National Committee for Clinical Laboratory Standards. 2003. Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. M24-A Vol.23 No.18.
11. Ellard GA, Greenfield C. A sensitive urine-test method for monitoring the ingestion of isoniazid. J Clin Pathol 1977;30:84-7.
12. Van Embden JDA, Cave MD, Crawford JT, et al. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: Recommendations for a standardized methodology. J Clin Microbiol 1993;31:406-9.

CHAPTER 6

TUBERCULOSIS CONTROL MEASURES

CC Leung, CM Tam, CK Chan

Summary points:

1. The objectives of tuberculosis control are to reduce morbidity and mortality, stop new infections, and prevent progression from infection to disease.
2. The core components of the local tuberculosis control programme include case finding, effective chemotherapy, treatment of latent tuberculosis infection, BCG vaccination and health education.
3. Passive case finding, i.e., picking up the disease in those symptomatic patients coming forward for treatment, has been shown to be more cost effective in most control programmes. Active screening is being carried out mainly for highly selected risk groups, such as close contacts of tuberculosis patients.
4. Effective treatment of infectious tuberculosis patients is the most important component for tuberculosis control. The use of directly observed treatment, short course (DOTS) is strongly recommended by the World Health Organisation in the control of tuberculosis.
5. With the imperfect diagnostic and treatment tools for latent tuberculosis infection, targeted screening and treatment of latent tuberculosis infection is currently offered mainly to household contacts under 35, silicotic patients and HIV-infected subjects.
6. Neonatal BCG vaccination coverage helps to protect the local children against serious forms of tuberculosis. In the absence of evidence supporting any additional protective efficacy offered by revaccination, the school revaccination programme has been stopped in 2000.
7. Health education efforts are being directed at the public at large, selected high risk groups and health care professionals to promote the awareness of tuberculosis.
8. Implementation of these control measures has brought about major reduction in the tuberculosis morbidity and mortality in the past decades. Continuing evaluation, research and development are required to meet the new challenges ahead.

Introduction

The objectives of tuberculosis (TB) control are to reduce morbidity and mortality, stop new infections, and prevent progression from infection to disease. The core components of the local TB control programme include case finding, effective chemotherapy, treatment of latent TB infection (LTBI), BCG vaccination, and health education.

Case Finding

Mass Screening

In a series of studies conducted between 1960 and 1973, it was shown that even in places with active case finding programmes, about 60% of sputum smear-positive patients were discovered because of their symptoms.[1,2] Only 20% of new cases were found through indiscriminate mass radiography alone.[1] This is explained by the relative rapidity with which infectious cases develop, faster than repeat screening can be accomplished. Mass chest X-ray screening has been abandoned in many places including Hong Kong in the mid-1970's upon WHO's recommendations because of its low cost-effectiveness.[3] A more recent evaluation of the national TB programme in India also concluded that X-ray and smear microscopy should not be used indiscriminately as case finding tools in mass case finding programmes, because their predictive values of positivity were likely to be very low at the prevalence rates of 200 to 800 per

100,000 in that community.[4] Periodic chest radiography are generally considered unnecessary and expensive.[5]

Active Screening among High Risk Groups

While mass screening of asymptomatic individuals is no longer advocated, active screening of selected high risk groups are practised in low incidence countries. Two major groups may be targeted for screening activities, firstly persons with a high risk of TB in need of curative treatment; and secondly, persons at high risk of developing TB later who may benefit from preventive intervention.[6] Target groups may include immigrants and refugees from high incidence countries,[7,8] inner-city marginalised populations,[9] inmates of correctional facilities[10,11] and other groups as determined by local epidemiology. Given the incomplete knowledge on high TB risk groups, and limitation of existing diagnostic tools, active case finding may not be very cost effective in many developing countries.[12]

Currently in Hong Kong, active screening is being carried out mainly for highly selected groups, such as close contacts of TB patients (See Chapter 12). Even among the household contacts, a commonly recognised high risk group, the yield of active TB is only in the order of 1% (Table 6.1). The yield of infectious bacteriologically positive cases is even much lower. It is therefore prudent to exercise due caution in introducing any large scale active case finding programme, as resources so invested may have much better alternative uses.

Table 6.1. Results of chest radiograph screening for household contacts (2004)

Categories	**Smear +ve index**		**Smear –ve index**		**Total**	
	Number	**%**	**Number**	**%**	**Number**	**%**
Number of contacts examined	4799	100.0	10312	100.0	15111	100.0
Results						
(a) No significant findings	4111	85.7	8972	87.0	13083	86.6
(b) Diseases other than TB	417	8.7	779	7.6	1196	7.9
(c) Inactive respiratory TB	187	3.9	399	3.9	586	3.9
(d) Active TB (radiological)	**33**	**0.7**	**56**	**0.5**	**89**	**0.6**
(e) Active TB (bacteriological)	**10**	**0.2**	**8**	**0.1**	**18**	**0.1**
(f) Active TB (incomplete)	**6**	**0.1**	**8**	**0.1**	**14**	**0.1**
(g) Non-respiratory TB	**0**	**0.0**	**3**	**0.0**	**3**	**0.0**
(h) Unknown	35	0.7	87	0.8	122	0.8

Although screening of immigrants is commonly practised in low incidence countries, there is probably little role for such screening in Hong Kong as a result of the following two observations:
1. very low proportion of cases are attributable to recent immigrants;
2. absence of increased risk for recent Chinese immigrants.

A local study also showed a low yield in the chest radiograph screening of HIV-infected patients.[13] As for screening of other groups such as elderly in institutions, and prison inmates, the diagnostic tool to be employed, the role of treatment of LTBI, and the question of cost effectiveness must be carefully addressed before such screening can be applied on a service basis.

Passive Case Finding

Passive case finding, i.e., picking up the disease in those symptomatic patients coming forward for treatment (symptom motivation), has been shown to be more cost effective in most control programmes and accounts for over 90% of the detected TB cases. It has been shown in a number of studies that smear-positive patients were the main infectious sources and over 90% of these patients have symptoms,

predominantly cough.[1,2] It has also been shown that examination of symptomatic patients give a much higher yield than screening of asymptomatic individuals.[4] The WHO TB control strategy therefore stresses on case detection through passive case finding, i.e. detection of TB cases among persons presenting themselves to a health worker with symptoms suspicious of TB.[3] In high incidence countries, especially where resources are limited in comparison with the size of TB problem, passive case finding must remain the primary strategy in detecting infectious new TB cases. Passive case finding has been the mainstay of the local case finding activities. A walk-in approach has been employed by the chest clinics. Free diagnostic and treatment services are offered at multiple convenient sites by the 18 chest clinics.

Effective Chemotherapy

The most effective preventive measure for the control of TB is to stop it at the source. The source of TB spread is infectious TB patients. Effective treatment of infectious TB patients is therefore the most important component for TB control. Non-adherence with treatment is the commonest cause of treatment failure, and is common with the long course of treatment necessary for TB. Therefore, the use of directly observed treatment, short course (DOTS) is strongly recommended by the World Health Organisation (WHO) in the control of TB. DOTS has five key components[14]:

(i) Government commitment to ensuring sustained, comprehensive TB control activities.
(ii) Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
(iii) Standardised short-course chemotherapy using regimens of six to eight months, for at least all confirmed smear-positive cases. Good case management includes directly observed treatment during the intensive phase for all new sputum smear-positive cases, the continuation phase of rifampicin-containing regimens and the whole re-treatment regimen.
(iv) A regular, uninterrupted drug supply of all essential anti-tuberculosis drugs.
(v) A standardised recording and reporting system that allows assessment of case finding and treatment results for each patient and of the TB control programme performance overall.

Hong Kong was among the first to pioneer with directly observed treatment (also known as “supervised treatment”) in the 1960/1970’s, largely in response to low treatment completion rate and mounting resistance at that time (see also Chapter 11). The short course treatment regimen was introduced in 1979. A highly efficacious regimen comprising six months of treatment was used. This consisted of four drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol) in the initial phase, followed by two drugs (isoniazid and rifampicin) in the subsequent continuation phase. As a result of these measures, the majority of TB patients managed to complete the full course of treatment. Resistance to anti-TB drugs started to fall.[15] The success of these early trials, undertaken with the British Medical Research Council in Hong Kong and other places, contributed to the foundation of the current WHO recommendation. The cost for providing DOTS is justifiable in view of a higher cost being saved by avoiding the need to manage many patients with destroyed lungs, treatment failures, disease relapses and the spreading epidemic of multidrug-resistant TB that have been witnessed in certain communities.

DOTS may not work on its own as exemplified by some recent studies.[16-18] Community acceptance, a committed team of staff and measures to promote adherence by convenient location, convenient hours, education, counselling, rapid defaulter identification, exhaustive defaulter tracing, and incentives and enablers are all essential to allow the system to work. Even with our existing arrangement, there remain a significant percentage of treatment defaulters at a rate of around 5%. As defaulters pose a potential persistent source of infection in the community, continuing effort is called for to further reduce this in the years to come.

Treatment of Latent Tuberculosis Infection (LTBI)

It is estimated that two billion people worldwide have been latently infected with TB.[19] Although the risk is highest in the first two years after infection, the risk persists for their lifetime. In contrast with the DOTS strategy, improved diagnosis and treatment of LTBI has the potential to tackle the large pool of

infected individuals across successive birth cohorts, and thereby to bring the disease under more rapid control.

Traditional treatment of LTBI has typically involved the use of isoniazid for 6 to 12 months. With the reported efficacy of a 2-month course of rifampicin plus pyrazinamide in the treatment of LTBI among the HIV-infected individuals, there was revived enthusiasm in adopting such an approach. The American Thoracic Society (ATS) and the United States Centres for Disease Control and Prevention (CDC) issued a joint statement in 2000 entitled "Targeted tuberculin testing and treatment of latent tuberculosis infection" to guide clinicians in the care of people with LTBI.[20] Emphasis was duly put on directing tuberculin testing to populations at risk instead of offering broad screening, more treatment options, including short course rifampicin-based regimens, and simplified monitoring of treatment that emphasises clinical evaluation more than laboratory examination. However, subsequent field surveillance[21-23] and clinical trials suggested that the two month regimen of rifampicin and pyrazinamide is associated with a high incidence of hepatotoxicity.[24,25] The revised ATS/CDC recommendations now advise that this regimen should generally not be offered to persons with LTBI.[23]

Imperfect diagnostic tool, long duration of treatment and potential serious side effects are inherent difficulties in the current approach to treatment of LTBI. Problem of motivation in symptomless people, adverse social factors among risk groups, and the huge infected pool render it almost impossible to apply such an approach on a wide service scale in most high incidence areas. However, even in these areas, identifying those at increased risk of progression to active disease, improved screening, diagnosis, and treatment of LTBI are still called for.

Treatment of LTBI has not been very widely practised in Hong Kong, partly because of the difficulty in interpreting a positive tuberculin response within a community with very wide BCG coverage, and partly because of the potential problems of drug adherence and drug reaction with prolonged course of treatment. However, in the Government TB & Chest Service (TB&CS), treatment of LTBI or chemoprophylaxis is regularly offered to all infant close contacts of smear-positive patients, and also to similar contacts aged under 35 if the tuberculin response is 15 mm or greater, or if there is documented tuberculin conversion (see Chapter 14). Treatment of LTBI is also offered to tuberculin-positive HIV-infected individuals and tuberculin-positive silicotic patients (see Chapter 14).

BCG vaccination

The practice of BCG vaccination varies widely in different parts of the world (see Chapter 15). Some countries do not give BCG vaccination regularly, while others vaccinate all infants at birth. The efficacy of BCG vaccination in newborns is well recognised and the topic has been reviewed by Colditz et al recently.[26] It is particularly useful in the protection against disseminated TB such as TB meningitis and miliary TB.[27,28] However, the efficacy of BCG revaccination in older individuals is in doubt.[29-31]

In Hong Kong, BCG vaccination was first introduced in April 1952 as an organised campaign by the government with technical and material assistance from the UNICEF (United Nations International Children's Emergency Fund) and the WHO. Over the years, the BCG vaccination programmes have been modified according to the local situation, availability of up-to-date scientific information, and international recommendations. For the past few decades, the BCG team of the TB&CS offered the vaccination to two main target groups: the newborns and the primary school students.

The coverage for newborn babies has been persistently over 98% since 1980 and this has contributed significantly to the low rate of TB among the young age group locally (Fig 6.1). On the other hand, a statement was issued by WHO in 1995 stating that there is no proven value for BCG revaccination and it is not recommended. Hence, a review of the local BCG revaccination programme for primary school children has been carried out. As the data did not suggest any additional protective efficacy offered by the revaccination,[32,33] the programme has been stopped in the school year starting from September 2000.

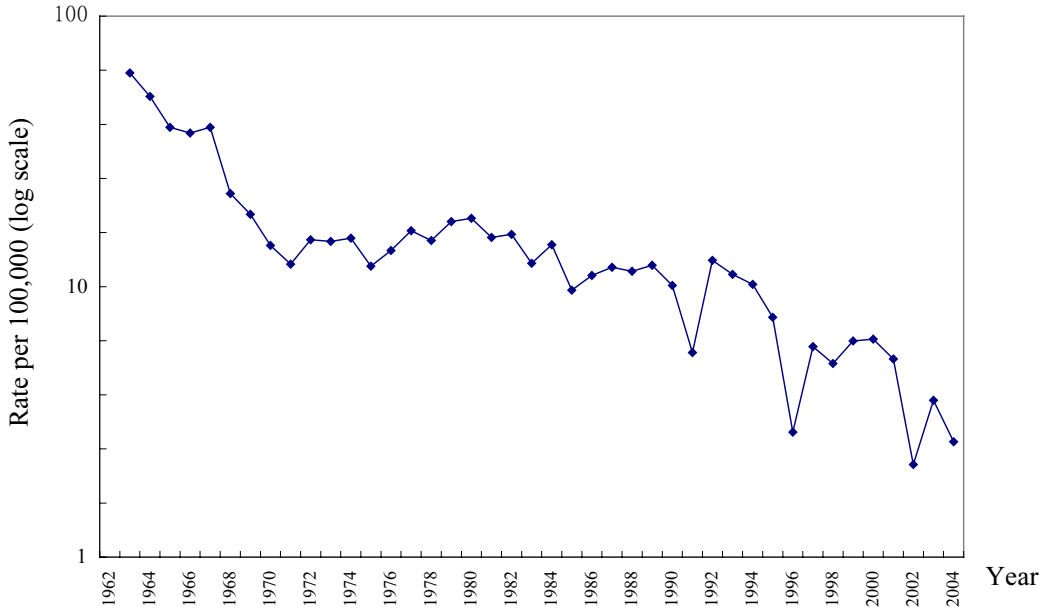


Figure 6.1. Tuberculosis notification rate among children under 5

Hence, the current policy is to vaccinate newborn babies, as well as children residing in Hong Kong and aged under 15 without any prior BCG vaccination. Repeated doses of BCG vaccination are in general not recommended in any individuals.

Health education

Although some groups may be at greater risk of developing TB, no one is completely free from risk. This clearly applies to Hong Kong where TB is prevalent. Therefore, a population approach has to be adopted in health education, in addition to activities focusing on potential risk groups.

Health education of the public is crucial to promote passive case finding. Messages relayed to the public include nature of the disease, symptoms suspicious of TB, available local services for TB, treatment, preventive and rehabilitative measures. Clearing of common misunderstandings also helps to reduce the stigma and consequential discrimination, which is a critical barrier to access of care.

Announcements of public interest in TV and radio have been launched to encourage those with chronic cough and other symptoms suggestive of TB to come forward for examination. In collaboration with the media and professional associations, educational programmes on TB also appear from time to time on TV and radio. The World TB Day on March 24 each year offers good opportunity for TB exhibition, health talk and other awareness promoting activities. In addition, health talks are organised from time to time in schools, elderly homes, homes for the handicapped, and other institutions. Posters, pamphlets and leaflets are other tools frequently employed for public health education. CD-ROMs on control of infectious diseases (including TB) for schools have been developed by the Department of Health (DH). In addition, development of CD-ROMs targeting at the general public has been carried out in collaboration by the Hong Kong Tuberculosis, Chest and Heart Diseases Association and TB&CS.

Smoking has been found to be positively associated with TB in terms of infection,[34-36] disease[37-41] and death.[42-45] A strong dose-response relationship was found between the number of cigarettes smoked per day and the risk of developing active TB, and stopping smoking substantially reduced the risk.[41] More aggressive lung involvement and potentially greater infectivity were also found among ever smokers.[40]

Thus, it is desirable that anti-smoking messages be incorporated into the health education programmes for TB. Smoking cessation activities are actively promoted to assist those addicted to quit within the TB&CS. Opportunistic intervention is likely to be more effective in the health care settings, as most of the clients are coming forward with symptoms.

Promoting awareness of TB is equally important among health care workers. In a study undertaken by Medical Research Council in Kenya, 90% of TB suspects attended a health care facility for an average of more than 5 times, yet 65% had neither chest radiographic or sputum examination done.[46] TB shares symptoms with many common respiratory conditions. Unless the attending doctor or health worker is alert of the possibility of TB, and order appropriate investigations, TB patients coming forward with symptoms will remain unidentified. Continuing medical education is also essential to ensure that the essential public health functions like notification, contact screening, and DOT are clearly understood, and TB patients are given timely and effective treatment. Therefore, TB articles are published in professional journals and the Epidemiology Bulletin of DH from time to time. In collaboration with other organisations, seminars on TB are also provided for doctors and other health care workers. A TB website has been developed targeting at both health care professionals and the public. A CD-ROM on TB has also been developed and sent to all doctors in Hong Kong. This manual represents another step in the same direction.

Conclusions

Case finding, effective chemotherapy, treatment of LTBI, BCG vaccination and health education are the core components of the local TB control strategy. Implementation of these control measures has brought about major reduction in the TB morbidity and mortality in the past decades. However, with the changing demography, increasing prevalence of chronic degenerative disease, high population density, and rapid population movement, there are new challenges to meet. Continuous evaluation and refinement of the existing measures are called for. As TB remains a global problem, it is often useful to draw reference from updated information elsewhere.[47] Greater investment in research and development is also desirable in order to bring along new initiatives in the frontiers of our long battle against this important human pathogen.

References

1. Meijer J, Barnett GD, Kubik A, Styblo K. Identification of sources of infection. Bull Int Union Tuberc 1971;45:5-50.
2. Toman K. Mass radiography in tuberculosis control. WHO Chronicle 1976;30:51-7.
3. World Health Organisation. WHO Expert Committee on Tuberculosis, Ninth Report. WHO Technical Report Series 552, 1974.
4. Balasangameshwara VH et al. Validity of case-finding tools in national tuberculosis programme. Tuberc Lung Dis 1993;74:52-8.
5. Mangura BT, Reichman LB. Periodic chest radiography: unnecessary, expensive, but still pervasive. Lancet 1999;353:319-20.
6. Rieder HL, Zellweger JP, Raviglione MC, Keizer ST, Migliori GB. Tuberculosis control in Europe and international migration, Report of a European Task Force. Eur Respir J 1994;7:1545-53.
7. Rieder HL, Cauthen GM, Kelly GD, Bloch AB, Snider DE Jr. Tuberculosis in the United States. JAMA 1989;262:385-9.
8. Joint Tuberculosis Committee of the British Thoracic Society. Control and Prevention of Tuberculosis in the United Kingdom: Code of Practice 1994. Thorax 1994;49:1193-200.
9. Friedman LN et al. Tuberculosis screening in alcoholics and drug addicts. Am Rev Respir Dis 1987;136:1188-92.
10. Anderson KM et al. Tuberculosis screening in Washington State male correctional facilities. Chest 1986;89:817-21.
11. Leung CC, Chan CK, Tam CM, et al. Chest radiograph screening for tuberculosis in a Hong Kong prison. Int J Tuberc Lung Dis 2005;9:627-32.
12. World Health Organisation. WHO Tuberculosis Programme, Framework for Effective Tuberculosis Control. WHO/TB/94.179.
13. Ho TTY, Wong KH, Lee SS. Low yield of chest radiography in screening for active pulmonary tuberculosis in HIV-infected patients in Hong Kong. Int J STD AIDS 1999;10:409-12.
14. World Health Organisation Western Pacific Region. Tuberculosis control in South-east Asia and Western Pacific Regions 2005 – a bi-regional report.
15. Kam KM, Yip CW. Surveillance of Mycobacterium tuberculosis drug resistance in Hong Kong, 1986-1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001;5:815-23.
16. Zwarenstein M, Schoeman JH, Vundule C, et al. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. Lancet 1998;352:1340–3.

17. Walley JD, Khan MA, Newell JN, et al. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. Lancet 2001;357:664–9.
18. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomized controlled trial of lay health worker as direct observers for treatment of tuberculosis. Int J Tuberc Lung Dis 2000;4:550-4.
19. Dye C, Scheele S, Donlin P, et al. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
20. Centres for Diseases Control. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49, No. RR-6.
21. Centers for Disease Control and Prevention/ American Thoracic Society: Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/ CDC recommendations – United States, 2001. MMWR 2001;50:733-735.
22. Stout JE, Engemann JJ, Cheng AC, Fortenberry ER, Hamilton CD. Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. Am J Respir Crit Care Med 2003;167:824-7.
23. Centers for Disease Control and Prevention/ American Thoracic Society. Update: Adverse event data and revised American Thoracic Society/ CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection – United States, 2003. MMWR 2003;52:735-739.
24. Jasmer RM, SaukkonenJJ, Blumberg HM, et al. Short-course rifampicin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002;137:640-47.
25. Leung CC, Law WS, Chang KC. et al. Initial experience of a randomized controlled trial on the treatment of latent tuberculosis infection among silicotic subjects in Hong Kong: two months of rifampin and pyrazinamide versus six months of isoniazid. Chest 2003;124:2112-8.
26. Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of Bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analysis of the published literature. Pediatrics 1995;96:29-35.
27. Schwoebel V, Hubert B, Grosset J. Tuberculous meningitis in France in 1990: characteristics and impact of BCG vaccination. Tuberc Lung Dis 1994;75:44-8.
28. Camargos PAM, Guimaraes MD, Antunes CMF. Risk assessment for acquiring meningitis tuberculosis among children not vaccinated with BCG: A case control study. Int J Epidemiol 1988;17:193-7.
29. Springett VH, Sutherland I. A re-examination of the variations in the efficacy of BCG vacination against tuberculosis in clinical trials. Tuberc Lung Dis 1994;75:227-33.
30. Tala-Heikkila MM TJ, Tala EOJ. Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence. Am J Respir Crit Care Med 1998;157:1324-7.
31. Karonga Prevention Trial Group. Randomized controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet 1996;348:17-24.
32. World Health Organisation. Global Tuberculosis Program and Global Program on Vaccines: Statement on BCG revaccination for the prevention of tuberculosis. WHO Wkly Epidem Rec 1995;70:229-36.
33. Leung CC, Tam CM, Chan SL, et al. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. Int J Tuberc Lung Dis 2001;5:717-23.
34. Anderson RH, Sy FS, Thompson S, Addy C. Cigarette smoking and tuberculin skin test conversion among incarcerated adults. Am J Prev Med 1997;13:175-9.
35. Solsona J, Cayla JA, Nadal J, et al. Screening for tuberculosis upon admission to shelters and free-meal services. Eur J Epidemiol 2001;17:123-8.
36. Plant AJ, Watkins RE, Gushulak B, et al. Predictors of tuberculin reactivity among prospective Vietnamese migrants: the effect of smoking. Epidemiol Infect 2002;128:37-45.
37. Yu GP, Hsieh CC, Peng J. Risk factors associated with the prevalence of pulmonary tuberculosis among sanitary workers in Shanghai. Tubercle 1988; 69:105-12.
38. Chang KC, Leung CC, Tam CM. Tuberculosis risk factors in a silicotic cohort in Hong Kong. Int J Tuberc Lung Dis 2001;5:177-84.
39. Kolappan C, Gopi PG, Tobacco smoking and pulmonary tuberculosis. Thorax 2002;57:964-6.
40. Leung CC, Yew WW, Chan CK, et al. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003;7:980-6.
41. Leung CC, Li Teresa, Lam TH, et al. Smoking and tuberculosis among the elderly in Hong Kong. Am J Respir Crit Care Med 2004;170:1027-33.
42. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors BMJ 1994;309:901-11.
43. Liu BQ, Peto R, Chen ZM, et al. Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. BMJ 1998;317:1411-22.
44. Lam TH, Ho SY, Hedley AJ, Mak KH, Peto R. Mortality and smoking in Hong Kong: case-control study of all adult deaths in 1998. BMJ 2001;323:361.
45. Gajalakshmi V, Peto R, Kanaka TS, Jha P. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43000 adult male deaths and 35000 controls. Lancet 2003;362:507-15.
46. Aluoch JA, Edwards EA, Stott H, Fox W, Sutherland I. A fourth study of case-finding methods for pulmonary tuberculosis in Kenya. Trans R Soc Trop Med Hyg 1982;79:679-91.
47. American Thoracic Society/ Centres for Disease Control and Prevention/ Infectious Diseases Society of America: Controlling tuberculosis in the United States. Am J Respir Crit Care Med 2005;172:1169-227.

CHAPTER 7

GUIDELINES ON TREATMENT

CM Tam, CC Leung, WW Yew

Summary points:

1. In the treatment of tuberculosis, the attending physician has the responsibility to ensure successful treatment till completion, in collaboration with the public health programme and in consultation with experts in the field, wherever appropriate.
2. As far as possible, all anti-tuberculosis drugs should be administered using directly observed treatment.
3. Apart from drug treatment, appropriate public health measures should be taken, including notification, contact tracing, and health education.
4. Adjunctive measures such as short courses of corticosteroids may be useful in specific circumstances.
5. The standard regimen for treatment of new cases of pulmonary tuberculosis consists of 6 months treatment, with four drugs in the initial phase including isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin, followed by two drugs in the continuation phase including isoniazid and rifampicin.
6. In the presence of risk factors like cavitation on the initial chest radiograph and persistence of sputum culture positivity at 2 month, the total duration of treatment may have to be extended.
7. For retreatment cases, the recommendation is a 9-month standard regimen starting with five drugs including isonazid, rifampicin, pyrazinamide, ethambutol and streptomycin for the initial 3 to 4 months, followed by isoniazid and rifampicin in the continuation phase.
8. Multidrug-resistant tuberculosis requires individually tailored treatment regimens as guided by drug susceptibility testing, and the duration of treatment is generally much longer. Fluoroquinolones are generally useful agents.
9. Recommendations for extrapulmonary tuberculosis are based on relatively limited data.
10. Treatment of tuberculosis under specific circumstances including coexisting medical conditions, pregnancy, old age, liver and renal function impairment are discussed.

Introduction

Tuberculosis (TB) is endemic in Hong Kong. As TB can mimic other respiratory tract infections or affect organ systems other than the lungs, doctors practising in various specialties may from time to time encounter patients with this disease. Hence, continuous updating of professional knowledge in this disease would be useful in the clinical management and disease control. In fact, as TB is a communicable disease with public health significance, and the main control strategy lies in effective treatment, it has to be noted that **the attending physician has the responsibility to ensure successful treatment as far as possible**, in collaboration with the public health programme wherever appropriate.[1]

It is desirable for TB patients to be managed by or in consultation with doctors experienced in this field. Proper pretreatment assessment and careful monitoring during treatment are necessary. While a treatment protocol is mandatory for programme purpose, flexibility as tailored to individual patient's clinical status is often needed. Drug adherence is crucial for treatment success and prevention of development of drug resistance. As far as possible, all anti-TB drugs should be administered using "directly observed treatment" (DOT).[1-3]

At the start of treatment, the chance of emergence of drug resistance is highest as the size of viable bacterial population is largest. Hence, more drugs are used during the initial phase of treatment. During the subsequent continuation phase, fewer drugs may be used as the risk would be smaller.[4]

Apart from administering anti-TB drugs, adjunctive measures such as short courses of corticosteroids can be useful in managing TB pericarditis, advanced stages of TB meningitis, certain cases of TB lymphadenitis, TB pleural effusion, TB pyrexia, genitourinary TB, and some other forms of extrapulmonary TB.[5,6] A systematic review also found benefits in use of systemic corticosteroids in selected patients with advanced pulmonary TB.[7] Furthermore, corticosteroids may also be used to suppress severe hypersensitivity reactions to anti-TB drugs.

Public health measures should also be taken. All cases of TB must be notified to the Department of Health using notification form DH1A(s)(Rev.99) in accordance with the Quarantine and Prevention of Disease Ordinance. Proper completion of all items in the form is essential to provide comprehensive data on the surveillance of the disease. (See also Chapter 2.)

Local guidelines on the recommended regimens for treatment of different categories of TB have been promulgated.[8] These recommendations are elaborated in the following sections, with clinical situations broadly classified into several categories. As accrual of new scientific data is always ongoing, periodic updating of such information will be required.

Section I: Pulmonary Tuberculosis

Category A: Uncomplicated Tuberculosis

Category A1: New cases
Recommendation* 2HRZ+(E or S) / 4 HR

---

* *Notations used for TB treatment regimens in this chapter:*
Drugs: *E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide*
Duration: *This is shown by the figures (in months) in front of the drug combinations. The slash "/" is used to separate different phases of treatment.*
Frequency: *This is shown by the subscripts attached to the individual drugs (i.e. subscript "3" indicates thrice weekly administration) and absence of subscript indicates daily administration.*

Four drugs – isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin – are recommended for the initial 2-month phase of treatment,[1-3] as the rate of initial resistance to isoniazid is more than 4% in Hong Kong. Two drugs – isoniazid and rifampicin – are recommended for the 4-month continuation phase,[1-3] which makes a total treatment duration of 6 months.

The drugs may be given on a daily or thrice-weekly basis in both the initial and the continuation phases.[2] Studies have shown that daily administration for 2 months followed by thrice-weekly treatment for 4 months can be equally efficacious.[1,2,9] The adverse reactions and recommended dosages are listed in Appendices 7 and 8. The existing service programme in the chest clinics is intermittently administered chemotherapy throughout the 6 months[10,11] and is suitable for patients who are receiving ambulatory treatment right from the start of therapy. This regimen can also be considered for those inpatients who have uncomplicated TB and are soon ready for discharge to chest clinics for continuation of ambulatory chemotherapy.

For patients with extensive disease, the 2-month initial phase may be extended to 3 or 4 months, depending on clinical, bacteriological, and radiological responses, while the total duration of treatment may still remain at 6 months. An occasional patient may need prolongation of therapy to beyond 6 months. If there is a suspicion of drug-resistant TB (e.g. in contacts of patients with drug-resistant TB), the initial phase of treatment may be similarly extended, pending the conventional drug susceptibility test (ST) results, if rapid susceptibility studies are not available. In fact, in the updated statement from ATS/CDC/IDSA, extended treatment is recommended for patients with drug-susceptible pulmonary TB who have risk factors like cavitation on the initial chest radiograph and persistent sputum culture positivity at two months.[1] This recommendation is supported by studies examining risk factors for relapse after treatment.[12-14]

Category A2: Retreatment cases
Recommendation 3(4)HRZES / 6(5)HR±E

Five drugs – isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin – are recommended for the initial 3 to 4 months,[2] depending on the timing of the availability of ST results, the rate of smear conversion, extent of disease, and probability of drug resistance. Isoniazid and rifampicin (also with ethambutol if the disease is extensive or the ST pattern is unknown) are recommended for the continuation phase; the total treatment duration is 9 months. If the ST results that are available subsequently are unfavourable, the above regimen may need to be modified (see Category B).

Category B: Drug-resistant Tuberculosis

Comparative less supporting data are available for categorical recommendation of regimens for the treatment of drug-resistant TB.[15] It is important to avoid the "addition phenomenon"[16] – namely, adding a single drug to a failing regimen. Otherwise, acquired resistance to the newly added drug may develop. Instead, add at least two, three, or more drugs to which the organisms are known to be susceptible, or which have not already been taken by the patient. To assist in the management of drug-resistant TB, the following regimens are suggested for reference.

Category B1: Resistance to isoniazid alone
Recommendations[9,17-20]

(1) If the ST pattern is known before starting treatment:
(a) **2 SRZE / 7 RZE** *or*
(b) **12 RZE**

(2) If ST results are reported during treatment of new cases (as in category A1):
During treatment, the ST results may become available during the continuation phase when using the drug combination of isoniazid with rifampicin. If resistance to isoniazid is noted, the treatment regimen should be changed to the daily administration of rifampicin, pyrazinamide, and ethambutol as follows:
2HRZ + (E or S) / (1-2) HR ± E / (9-8) RZE
Apart from these regimens, clinical trials have also shown that other regimens, such as **6HRZ + (E or S)** are useful in isoniazid-resistant disease. Regimens such as **2HRZS / 4H_3R_3** and **2$H_3R_3Z_3S_3$ / 2$H_3R_3S_3$ / 2H_3R_3** are also acceptable regimens and have a relapse rate of ≤10%.
Some TB workers noted that in the continuation phase with an isoniazid/ rifampicin regimen, rifampicin is the only effective drug against persisters, as shown by the similarity of response by patients with initially isoniazid-resistant or sensitive strains under such circumstances.[21]

(3) If ST results are reported during retreatment, the following regimen is recommended:
(3-4) HRZES / (9-8) RZE

Category B2: Resistance to rifampicin alone (rare)
Recommendations[22]

(1) If the ST pattern is known before starting treatment, the following regimen can be given for a total duration of 18 months, or 12 months after sputum culture conversion to negative:
(a) **(3-4) HZES / (15-14) HZE** *or*
(b) **18 HZE**
Some authorities recommend adding a fluoroquinolone to shorten the duration of therapy to 9 to 12 months.[1]

(2) If ST results are reported during treatment for new cases, the following can be given for a total duration of 18 months, or 12 months after negative culture:
2HRZ + (E or S) / (1-2) HR ± E / (15-14) HZE
However, if before changing to a combination of isoniazid, pyrazinamide, and ethambutol, additional acquired resistance to isoniazid is also suspected or the treatment response is unsatisfactory (e.g. if the sputum remains positive for acid-fast bacilli), isoniazid, pyrazinamide,

and ethambutol with streptomycin (or other drugs) can be given in the third phase, until the new ST results are available.

(3) If the ST results are reported during retreatment, the following can be given for a total duration of 18 months, or 12 months after negative culture:
(3-4) HRZES / (15-14) HZE

Category C: Multidrug-resistant Tuberculosis

For the treatment of multidrug-resistant TB (MDR-TB) – that is, TB caused by bacilli that are resistant to at least isoniazid and rifampicin in vitro, a combination of drugs to which the organism is, or is likely to be, susceptible should be used. Drugs that have not been used to treat the patient before are preferred, and so are bactericidal drugs to bacteriostatic drugs. Treatment usually comprises 5 or 6 drugs for the initial 6 months, followed by 3 or 4 drugs subsequently.[16] The inclusion of an injectable agent for the initial months and a fluoroquinolone all through are generally recommended. Daily regime should be used, except perhaps for the injectables. Drugs showing in vitro resistance are generally excluded, with the possible exception of use of isoniazid in cases of low level resistance. The possibility of cross resistance between drugs should be noted.[1,23]

Apart from first-line anti-TB drugs (ethambutol and pyrazinamide), other drugs available include the fluoroquinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (kanamycin or amikacin), prothionamide/ ethionamide, cycloserine, para-aminosalicylic acid, and clofazimine. (Appendices 7 and 8) These drugs vary in terms of anti-TB activity, convenience of administration, potential toxicity and cross resistance.

The optimum duration of therapy for MDR-TB has not yet been clearly identified. Some authorities recommend a total duration of at least 18 months after culture negativity.[16] However, local experience suggests that, with adequate multidrug-treatment regimens, and the inclusion of fluoroquinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 15 months, or one year after sputum culture conversion.[24] A longer duration may however be required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, or extensive drug resistance or extensive radiographic disease.

Treatment should be conducted in specialised centres.[16] It is essential to monitor the clinical, radiological, and most importantly bacteriological progress.[24] Caution is to be exercised in the use of second-line drugs, as they are often associated with significant side effects.[16,24] (See also Chapter 18.)

Section II: Extrapulmonary Tuberculosis

As there have been few large scale studies on the treatment of extrapulmonary TB, consensus is often lacking, especially in relation to the duration of treatment. The following regimens are recommended as reference to assist in the management of extrapulmonary TB. These recommendations are based on limited current evidence and local experience, and may have to be further modified when more data is available. Generally speaking, the initial phase should be advisably given on a daily basis. Adjunctive corticosteroid therapy can be useful as previously alluded.

Category A: Tuberculous Meningitis (Including Central Nervous System Tuberculoma)
Recommendation[1,3,25,26] **3 HRZE ± S / 9 HR ± E**

Depending on computed tomography findings and treatment response, some authorities may further prolong the total duration of treatment for central nervous system tuberculoma. Extended treatment may also be considered for those presenting at an advanced stage (e.g. stage III) of TB meningitis. On pharmacokinetic consideration in relation to cerebrospinal fluid penetration, there may be a role of giving pyrazinamide for more than 3 months, especially in those cases where the earlier response is not entirely satisfactory. The use of corticosteroids in adolescents and adults as an adjunctive treatment has been found to improve survival but probably not preventing severe disability.[27] Nonetheless, early recognition, diagnosis and prompt treatment are important factors in reducing mortality and morbidity,[28] although the prognosis is likely to be poor in cases associated with

multidrug-resistant organisms.[29,30]

Category B: Miliary Tuberculosis [1,3]
Recommendation 3 HRZ + (E or S) / 9 HR ± E

Category C: Tuberculosis of Bone and Joint [1,3]
Recommendation 2 HRZ + (E or S) / 10 HR

The total duration of treatment may be reduced to 6 or 9 months in the case of TB of the spine or in other settings with mild disease, although a recent study doubted the adequacy of 6 months treatment.[31]

Category D: Tuberculous Lymphadenitis [1,3,32]
Recommendations

(1) For peripheral disease which commonly involves the cervical region and where there are only solitary/ few affected lymph nodes together with normal chest radiograph, the same treatment as stipulated in Section I, Category A1 should be given for a total duration of 6 months.

(2) Other situations are treated using the same regimen as in Section I, Category A1, but with the continuation phase extended such that the total duration of treatment is 9 months. One such situation is peripheral cervical lymphadenopathy with the same setting as (1) above but involving many, enlarged lymph nodes, or supraclavicular lymph nodes (with or without the chest radiograph showing active TB). Another such situation is mediastinal lymphadenopathy as detected by computed tomography or plain chest radiograph, and confirmed histologically.

It has to be noted that the clinical response of TB lymph nodes during treatment may be quite unpredictable, sometimes with paradoxical increases in size probably due to immunological reactions. Residual nodes may still be palpable after completing the full course of treatment

Category E: Tuberculous Pericarditis, Peritonitis, and Genitourinary Tuberculosis

The recommendation is the same as in Section I, Category A1[1,3,33,34], but the continuation phase is extended such that the total duration of treatment becomes 9 months. For some cases that involve limited gut and genitourinary disease, 6 months of treatment may be adequate. One study on tuberculous pericarditis has shown that 3 SHRZ / 3 HR is highly effective.[33]

Section III: Pulmonary Tuberculosis Associated with Medical Diseases or Special settings

Category A: Diabetes Mellitus

The recommendation is the same as in Section I, Category A1, but the continuation phase is extended such that the total duration of treatment becomes 9 months.

Category B: Immunocompromised Patients

The recommendation is the same as in Section I, Category A1, but the continuation phase is extended such that the total duration of treatment becomes 9 months. For patients infected with HIV (human immunodeficiency virus), the total duration of treatment should be 9 months,[35,36] or at least 4 months after culture conversion to negative. However, the treatment may have to be modified if the patient is also on concurrent anti-retroviral medications (e.g., highly active anti-retroviral therapy (HAART)). Possible constituent agents for anti-retroviral therapy (ART) include NARTI (nucleoside analogue reverse transcriptase inhibitor), NNRTI (non-nucleoside reverse transcriptase inhibitor), and PI (protease inhibitor). There are significant drug-drug interactions between the rifamycins (rifampicin and rifabutin) and the PI and NNRTI anti-retrovirals, predominantly relating to metabolism involving cytochrome P-450 isoenzymes. Thus, in the HIV-TB co-infected patient, of paramount importance is appropriate, adequate treatment of TB, while decisions regarding ART must also be made. Possible options include:

- anti-TB treatment with rifamycin-based (rifampicin or rifabutin) regimens, while ART can be deferred either to the time of completion of anti-TB treatment, or completion of initial phase of anti-TB treatment;
- anti-TB treatment with rifamycin-based regimens, plus ART with appropriate modification of dosages of the rifamycins/ anti-retroviral agents;
- anti-TB treatment with non-rifamycin-based regimens, plus ART.

There are pros and cons for each option, e.g., using non-rifamycin-based regimens to avoid drug-drug interactions but at the cost of necessitating extended treatment duration. The best approach should be tailored to the circumstances of each individual case. As new anti-retroviral agents come up in the market from time to time, the interested reader should check the local availability of the ART agents and updated recommendations on their use including drug-drug interactions with the necessary dosage modifications.[37] It has to be noted that paradoxical reactions or immune-reconstitution syndrome occur at a higher frequency during anti-TB treatment in HIV-infected TB patients, especially when they are also receiving ART.[38] Treatment with corticosteroids may be indicated in such circumstances.[39]

For retreatment and drug-resistant cases in immunocompromised subjects, the regimens are essentially similar to those immunocompetent patients except that a longer duration of treatment is required. Universal precaution and infection control measures should be strictly observed if drugs are to be given by injection.

Category C: Pregnancy

Basically, rifampicin, isoniazid, ethambutol, and pyrazinamide can still be used, although the manufacturers of rifampicin advise caution during pregnancy. Pyridoxine is sometimes recommended for pregnant women receiving isoniazid. Streptomycin should be avoided because of ototoxicity to the foetus. The safety profiles of the second-line drugs and ofloxacin have not been ascertained and thus these drugs should also be avoided. The taking of anti-tuberculous drugs is by itself not an absolute contra-indication to breast feeding.[1-3,40] The infectiousness of the mother, however, must be considered. The interested reader can refer to the detailed guidelines from World Health Organisation.[41]

Category D: Children

The treatment regimens are essentially similar to those for adults,[1,3,40] except that ethambutol should generally be avoided in children until they are at least 6 years old[3,40] and capable of reporting symptomatic visual changes accurately. The drug dosages need to be calculated according to the body weight and may have to be adjusted, especially during the period of adolescent growth spurt.

Category E: Silico-tuberculosis

A longer duration of treatment is required for patients with silico-tuberculosis. The recommendations[42,43] are as follows:

(1) new cases
  (a) **8 $H_3R_3Z_3$ + (E_3 or S_3)** *or*
  (b) **2 HRZ + (E or S) / 7 HR**

(2) retreatment cases
  (a) **3 $H_3R_3Z_3E_3S_3$ / 5 $H_3R_3Z_3$ + (E_3 or S_3)** *or*
  (b) **3 HRZES / 6 HR±E**

The former regimen, (a) is likely associated with a higher success rate but the tolerance is questionable (≥20% intolerance especially to streptomycin and/ or pyrazinamide).

Category F: Geriatric Tuberculosis

Basically, the treatment of tuberculosis in the elderly should not differ markedly from that in the younger population. However, due regard must be paid to the physiological, psychological and social changes as well as the increased prevalence of co-morbidity that may be associated with aging. As the risk of hepatotoxicity is much higher[44] especially in those with malnourishment, some individual tailoring of dosage, say by using isoniazid 200 mg instead of 300 mg once daily and pyrazinamide 1 g instead of 1.5 g once daily may appear warranted. Pyridoxine supplement should also be considered for those with poor nutritional intake or at increased risk of neuropathy. When the drug susceptibility pattern of the cultured bacilli is known to be favourable, use of rifampicin and isoniazid together may prove sufficient[45] for diseases with limited bacillary load. A total duration of 9 months is required for co-administration of these two drugs. Use of ethambutol can be problematic in many old patients with poor baseline visual function and/ or difficulty in assessing visual acuity.

Category G: Liver Dysfunction

Transient changes in bilirubin and alanine transaminase levels are relatively common during anti-tuberculosis chemotherapy and do not signify true hepatotoxicity. Drug-induced hepatitis which occurs more commonly in patients with compromised liver reserve such as in chronic hepatitis B and C infection and alcoholic liver disease[1,46,47] necessitates cessation of therapy. Although it is somewhat controversial whether routine monitoring of liver function tests is required in patients receiving anti-tuberculosis drugs, those at risk should be managed with vigilance both clinically and biochemically.

When the disease is mild or has improved markedly, one can wait until the liver chemistry has normalised before retrial of the conventional anti-tuberculosis drugs, by gradual re-institution. Whenever possible, isoniazid and rifampicin should be included in the regimen, so that treatment duration will not be unduly prolonged.

In the face of extensive disease when delay in therapy might be detrimental to the patient's health, ofloxacin can be used together with streptomycin and ethambutol as an interim regimen for treatment.[48] This has been found to be safe and efficacious for the majority of such patients. Incorporation of ofloxacin as a component of a definitive regimen should only be considered when the patient cannot tolerate the co-administration of rifampicin and isoniazid. The optimum dosage of ofloxacin is unknown. Current experience shows that 500 to 600 mg once daily can be tolerated by most patients in this setting. For levofloxacin, the dosage of 400 mg, or perhaps 500 mg, once daily may be employed, pending accumulation of more experience. The fluoroquinolones' dosages should be tailored to age, body weight, renal function, extent of disease, and the number of accompanying drugs. The optimum duration of ofloxacin plus either rifampicin or isoniazid together with ethambutol as a definitive therapeutic regimen is unknown, and probably should be at least 1 year. (See also Chapter 9.)

Category H: Renal Impairment

The development of anti-tuberculosis drug-related renal impairment necessitates the withdrawal of the drug(s). Examples include streptomycin and rifampicin. In general, isoniazid, rifampicin and pyrazinamide can be used in normal dosages in the face of renal impairment.[2,3,40] In severe renal impairment, the dosage of isoniazid should be reduced to 200 mg once daily and pyridoxine supplementation is needed to prevent the development of peripheral neuropathy. Streptomycin and aminoglycosides should be avoided[2,3,40] or must have dosages adjusted in the presence of renal impairment. Ethambutol is also predominantly removed by the kidney. Dosage reduction is also mandatory.[1-3,40,49] In patients with creatinine clearances of 50 to 100 mL/min, ethambutol at 25 to 30 mg/kg thrice weekly can be given; for patients with creatinine clearances of 10 to 50 mL/min, 15 to 25 mg/kg thrice weekly should be given. With lower creatinine clearance (<10 mL/min), a dosage of 15 mg/kg thrice weekly has been suggested. (See also Chapter 10.) Therapeutic drug monitoring of streptomycin and ethambutol concentrations in serum may help to optimise therapy and minimize toxicity. Ofloxacin and ciprofloxacin are also dependent on renal clearance and dosage reduction in the presence of renal impairment must be made accordingly.

Isoniazid has previously been shown to be significantly removed by haemodialysis,[50] but a study showed that the median isoniazid recovery in the dialysate was only 9.2%, suggesting that hepatic metabolism remains the primary mechanism of clearing isoniazid.[51] Rifampicin is not significantly removed by haemodialysis.[50-52] Both of them may be given in their usual daily dosage.[51,53] Haemodialysis removal of pyrazinamide is significant.[51] Its primary metabolite, pyrazinoic acid, has been shown to accumulate in patients with renal failure. It is still not clear whether dosage reduction or spacing is required for patients on haemodialysis and receiving pyrazinamide.[51,52] A dosage of 25 to 30 mg/kg thrice per week has been recommended by some authorities,[51] whereas 40 mg/kg thrice per week has been recommended by others.[53] Ethambutol can still be given at a dosage of 15 to 25 mg/kg thrice per week.[40,51,53] Regarding the timing of administration of drugs, some authorities have recommended dosing 6 to 24 hours prior to haemodialysis,[53] while others have recommended post-dialysis treatment.[51] (See also Chapter 10.)

Section IV: Use of Fixed-dose Combination Tablets

Use of fixed-dose combination tablets (FDC) can provide a number of advantages. These include reduced chance of development of acquired drug resistance, simplification in prescribing effective regimens by physicians, improvement in patient adherence and lessened risk of inappropriate use of rifampicin.[1-3,40] However, there are also possible disadvantages such as compromised efficacy due to preparations with suboptimum bioavailability, higher cost and lack of flexibility in dosing.[2] More experience is required to recommend widespread use of FDC under programme setting.[40] Current and future preparations include combinations of rifampicin, isoniazid, pyrazinamide and ethambutol in various ways. However, the presently available combinations in Hong Kong include only rifater (R + H + Z) and rifinah (R + H).

Conclusions

Overall, directly observed treatment remains the mainstay of anti-tuberculosis chemotherapy. A 6-month standard combination regimen with four drugs in the initial phase is recommended for uncomplicated new cases of pulmonary tuberculosis. In the presence of cavitation on the initial chest radiograph and when the sputum culture remains positive at the time when 2 months of treatment is completed, it is recommended that the total duration of treatment should be extended. For retreatment cases, the recommendation is a 9-month standard regimen starting with 5 drugs. Multidrug-resistant tuberculosis requires individually tailored treatment regimens as guided by drug susceptibility testing. Recommendations for extrapulmonary tuberculosis are based on relatively limited data. Shorter regimens may be acceptable in some situations when better evidences accrue. A longer duration of treatment is generally required for patients with diabetes mellitus, silicosis and immunocompromisation. During pregnancy, streptomycin should be avoided and the safety of most second-line agents has not yet been ascertained. Potentially hepatotoxic agents should be used with caution in patients with liver dysfunction. The renal route of elimination of streptomycin, ethambutol and some second-line agents necessitates caution and dosage reduction in case of renal impairment.

Current anti-TB treatment relies on first-line drugs that were developed in the 1950s and 1960s. Regimens are relatively complex, lengthy, and drug administration are labour intensive. The Global Alliance For TB Drug Development of the World Health Organisation has been formed with the goal to stimulate, support, and ensure the reemergence of a global TB drug development pipeline. A scientific blueprint for this purpose was designed.[54] A number of compounds and drug candidates have now been included in the TB drug development pipeline.[55] Hopefully, better new drugs can come into use in the near future.

References

1. American Thoracic Society/ Centers for Disease Control and Prevention/ Infectious Diseases Society of America: Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
2. World Health Organization. Treatment of tuberculosis - guidelines for national programmes 3rd edition. WHO/CDS/TB/2003.313. WHO, Geneva, 2003.
3. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax 1998;53:536-48.

4. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years – Centennial review. Am J Respir Crit Care Med 2005;171:699-706.
5. Alzeer AH, FitzGerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. Tuber Lung Dis 1993;74:6-11.
6. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: A critical reappraisal of the literature. Clin Infect Dis 1997;25:872-87.
7. Smego RA, Ahmed N. A systematic review of the adjunctive use of systemic corticosteroids for pulmonary tuberculosis. Int J Tuberc Lung Dis 2003;7:208-13.
8. Tuberculosis Control Coordinating Committee of Department of Health and Tuberculosis Subcommittee of Hospital Authority. Chemotherapy of tuberculosis in Hong Kong – update in 2001. Annual Report 2001 of the TB & Chest Service of Department of Health, HKSAR.
9. Singapore Tuberculosis Service / British Medical Research Council. Five-year follow-up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1988;137:1147-50.
10. Chan SL, Wong PC, Tam CM. 4-, 5- and 6-month regimens containing isoniazid, rifampicin, pyrazinamide and streptomycin for treatment of pulmonary tuberculosis under programme conditions in Hong Kong. Tuber Lung Dis 1994;75:245-50.
11. Tam CM, Chan SL, Lam CW et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. Am J Respir Crit Care Med 1998;157:1726-33.
12. Vernon AA, Iademarco MF. In the treatment of TB, you get what you pay for. Am Rev Respir Crit Care Med 2004; 170:1040-2.
13. Tam CM, Chan SL, Kam KM, Goodall RL, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Final report at 5 years: prognostic value of various measures. Int J Tuberc Lung Dis 2002;6:3-10.
14. Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. Am J Respir Crit Care Med 2004;170:1124-30.
15. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986;133:423-30.
16. Crofton J, Chaulet P, Maher D. Guidelines for the management of drug-resistant tuberculosis WHO/TB/96.210 (Rev 1) World Health Organization, Geneva 1997.
17. Hong Kong Chest Service/ British Medical Research Council. Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Am Rev Respir Dis 1987;136:1339-42.
18. Hong Kong Chest Service/ British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide - results at 30 months. Am Rev Respir Dis 1991;143:700-6.
19. Davidson PT. Drug resistance and the selection of therapy for tuberculosis. Am Rev Respir Dis 1987;136:255-7.
20. Babu Swai O, Aluoch JA, Githui WA et al. Controlled clinical trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. Tubercle 1988;69:5-14.
21. Mitchison DA. Role of individual drugs in the chemotherapy of tuberculosis. Int J Tuberc Lung Dis 2000;4:796-806.
22. Barnes PF, Bloch AB, Davidson PT, Snider DE Jr. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 1991;324:1644-50.
23. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474-81.
24. Yew WW, Chan CK, Chau CH et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/ levofloxacin-containing regimens. Chest 2000;117:744-51.
25. Humphries M. The management of tuberculous meningitis [editorial]. Thorax 1992;47:577-81.
26. Ellard GA, Humphries MJ, Allen BW. Cerebrospinal fluid drug concentration and the treatment of tuberculous meningitis. Am Rev Respir Dis 1993;148:650-5.
27. Thwaites GE, Bang ND, Dung NH, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741-51.
28. Lau KK, Yu TS, Chan CK, et al. A registry of tuberculous meningitis in Hong Kong. Int J Tuberc Lung Dis 2005 (accepted).
29. Thwaites GE, Lan NT, Dung NH, et al. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192:79-88.
30. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. Lancet Neurol 2005;4:160-70.
31. Ramachandran S, Clifton IJ, Collyns TA, Watson JP, Pearson SB. The treatment of spinal tuberculosis: a retrospective study. Int J Tuberc Lung Dis 2005;9:541-4.
32. Yuen AP, Wong SH, Tam CM, Chan SL, Wei WI, Lau SK. Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. Otolaryngol Head Neck Surg 1997;116:189-92.
33. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as an adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 1987, ii:1418-22.
34. Balasubramanian R, Nagarajan M, Balambal R et al. Randomized controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. Int J Tuberc Lung Dis 1997;1:44-51.
35. Scientific Committee of the Advisory Council on AIDS, Hong Kong. Prevention and management of tuberculosis in HIV infected patients in Hong Kong - an information paper. April 1995. Hong Kong: Scientific Committee of the Advisory Council on AIDS, 1995.
36. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 1999;340:367-73.

37. CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. MMWR 2004 Version 1.20.04. Accessible at http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm.
38. Wendel KA, Sterling TR. HIV and paradoxical worsening of tuberculosis. The Hopkins HIV Report 2001;13(5):8.
39. Wendel KA, Alwood KS, Gachuchi R, et al. Paradoxical worsening of tuberculosis in HIV-infected persons. Chest 2001;120:193-7.
40. ERS, WHO, IUATLD (Europe Region) Task Force. Tuberculosis management in Europe: Recommendations of a task force of the European Respiratory Society, the World Health Organization and the International Union against Tuberculosis and Lung Disease (Europe Region). Eur Respir J 1999;14:978-92.
41. WHO (Division of Child Health Development). Breastfeeding and maternal tuberculosis. 1998;23:1-4. Available at: http://www.who.int/child-adolescent_health/publications/NUTRITION/Up_23.htm. Accessed on 1 July 2005.
42. Lin TP, Suo J, Lee CN, Lee JJ, Yang SP. Short-course chemotherapy of pulmonary tuberculosis in pneumoconiotic patients. Am Rev Respir Dis 1987;136:808-10.
43. Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. Am Rev Respir Dis 1991;143:262-7.
44. Gronhagen-Riska C, Hellstrom PE, Froseth B. Predisposing factors in hepatitis induced by isoniazid-rifampin treatment of tuberculosis. Am Rev Respir Dis 1978;118:461-6.
45. Stead WW. Tuberculosis among elderly persons, as observed among nursing home residents. Int J Tuberc Lung Dis 1998;2:S64-S70.
46. Ungo JR, Jones D, Ashkin D et al. Antituberculosis drug-induced hepatotoxicity: The role of Hepatitis C and the human immunodeficiency virus. Am J Respir Crit Care Med 1998;157:1871-6.
47. Wong WM, Wu PC, Yuen MF et al. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. Hepatology 2000;31:201-6.
48. Yew WW, Lee J, Wong PC, Kwan SYL. Tolerance of ofloxacin in treatment of pulmonary tuberculosis in presence of hepatic dysfunction. Int J Clin Pharm Res 1992;XII:173-8.
49. Ministry of Health. Guidelines for tuberculosis control in New Zealand 2003. Wellington: Ministry of Health.
50. Andrew OT, Schoenfeld PY, Hopewell PC, Humphreys MH. Tuberculosis in patients with end-stage renal disease. Am J Med 1980;68:59-65.
51. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide and ethambutol. Am J Respir Crit Care Med 1999;159:1580-4.
52. Swan SK, Bennett WM. Use of drugs in patients with renal failure. In: Diseases of the kidney. Schrier RW, Gottschalk CW (eds). 6th Edition, Volume 3, 1997, New York Little Brown pp2968-3011.
53. Ellard GA. Chemotherapy of tuberculosis for patients with renal impairment. Nephron 1993;64:169-181.
54. Global Alliance For Tuberculosis Drug Development. Scientific Blueprint For Tuberculosis Drug Development 2001. Available at http://www.tballiance.org. Accessed on 1 July 2005.
55. Global Alliance For Tuberculosis Drug Development. Annual Report 2003/04. Available at http://www.tballiance.org. Accessed on 1 July 2005.

CHAPTER 8

DEALING WITH ADVERSE DRUG EVENTS IN A PATIENT TAKING ANTI-TUBERCULOSIS TREATMENT

KC Chang, CC Leung, CK Chan

Summary points:

1. Adverse drug events occur at a considerable frequency in patients taking anti-tuberculosis treatment. Most are mild and self-limiting but some may be severe and life-threatening.
2. Prevention and early management take priority. Patients and their family members should be educated on common and important adverse events, and be reminded to report symptoms promptly.
3. A pragmatic approach for managing adverse drug events includes recognition, assessment of severity and risk, deciding on continuation or suspension of treatment, and sequential re-introduction of drugs.
4. Recognition of adverse drug events requires meticulous attention to risk factors, progress, and clinical findings.
5. The decision to continue or suspend treatment hinges on risk assessment, which is done clinically and aided by blood tests as appropriate.
6. Mild drug allergy and non-hepatitis gastrointestinal upset can often be managed symptomatically without interrupting treatment.
7. While dose-dependent adverse events can be managed by adjusting dosage or dosing frequency, never give suboptimal treatment such as split doses.
8. If treatment is continued, monitor the patient carefully by clinical assessment and/ or biochemical tests. If treatment is suspended, resume treatment as soon as adverse drug events have subsided.
9. Drug reintroduction involves one or both of two distinct processes: challenge and desensitisation. Challenge aims at identifying the offending agent; desensitisation tackles hypersensitivity reactions.
10. To reduce the risk of acquiring drug resistance, it is essential to avoid monotherapy for any significant duration. Attempts should be made to establish an effective regimen within a reasonably short period.

Introduction

Despite the effectiveness of the modern six-month short course combination regimen in the treatment of tuberculosis (TB), adverse drug events are encountered at a considerable frequency, especially among the elderly and patients with various comorbidities or concomitant medications. Most of these adverse events are mild and self-limiting, but some are severe and life-threatening. Patients experiencing such effects are also more likely to default.[1] With the changing demographic and clinical profile of our patients, careful management is therefore called for.

Prevention is Always the Best

Proper clinical assessment is important before starting anti-TB treatment. Baseline blood and visual tests help to identify risk factors,[2] and also provide a basis for comparison in case of problems. While hypersensitivity reactions and idiosyncratic toxicity are often difficult to predict, dose-related adverse events are preventable by proper prescription with due attention to underlying risk factors[3] (Table 8.1). It is also essential to educate patients and their family members on common and important adverse drug events[3] (see Appendix 8). They should be reminded to report symptoms promptly so that appropriate actions can be taken early. Directly observed treatment facilitates early detection of adverse drug events.[3] Periodic biochemical monitoring is recommended for patients at risk of adverse drug events.[2]

Table 8.1. Risk factors for adverse drug events complicating anti-tuberculosis treatment

Risk factor	Reasons
Ageing	Changes in drug metabolism and excretion
Malnutrition	Fatty liver reduces hepatocyte glutathione and hence neutralisation of toxic metabolites originating from drug acetylation; hypoalbuminaemia increases the unbound drug fraction.
Pregnancy	Fatty liver; hypoalbuminaemia; adverse effects on fetus (examples: aminoglycoside impairs hearing of newborns; quinolones cause growth cartilage abnormalities; ethionamide is potentially teratogenic)
Liver or kidney dysfunction	Anti-TB drugs can cause liver or kidney toxicity. Chronic hepatitis status (notably hepatitis B or C), and chronic liver diseases (notably alcoholic liver diseases), predispose to drug-induced hepatitis.
Treatment with other drugs	Cytochrome P450 has been frequently associated with the production of hepatotoxic reactive metabolites.
Disseminated or advanced TB	Probably a consequence of malnutrition or liver deterioration
Previous anti-TB treatment	Increased risk of hypersensitivity reactions; history of adverse events may recur.
Atopy	Linked to a family history of adverse anti-tuberculosis drug reactions
HIV infection	The risk of adverse reactions increases with the degree of host immunosuppression.

A Problem-oriented Approach

Owing to substantial individual variations and difficulty in predicting adverse drug events, most of the following recommendations are based on expert reviews rather than controlled trials.[2-5] As untreated TB carries a high mortality as well as public health hazard, it is desirable to avoid unnecessary drug interruption or suboptimal treatment, which may lead to treatment failure and/ or emergence of resistance. On the other hand, timely removal of the offending drug in presence of adverse drug events is crucial for safety. To strike a balance of these two conflicting goals, a pragmatic approach may comprise several steps: recognition, assessment of severity and risk, deciding on treatment continuation versus suspension, and sequential reintroduction of drugs.

Recognition of Adverse Drug Events

Not all adverse events in the course of anti-TB treatment are drug-induced. For example, fungal infection and scabies may be mistaken for drug rash, thrombocytopenia due to hypersplenism for rifampicin-induced thrombocytopenia, and senile purpura for thrombocytopenic purpura. Meticulous attention to the patient's past health, the time course of the events, careful examination and clinical acumen are necessary to identify what has actually happened.

When an adverse drug event is identified, it would be useful to review the drug history. One or more drugs may be responsible. While we may be able to ascribe relatively specific drug adverse events to certain drugs (see Appendix 8), it is often difficult to pinpoint the exact offending agent in the first encounter with gastrointestinal intolerance, hypersensitivity reaction or hepatitis. Adverse events may also occur as a result of interaction between rifampicin and concomitant medications[2] (Table 8.2). Rifampicin is a potent inducer of cytochrome P450 (CYP), which is a complex family of metabolic enzymes. The enzyme-inducing activity of rifampicin may last for two to four weeks after its suspension. Rifabutin, a less potent enzyme inducer, is often used to substitute for rifampicin when antiretroviral therapy is co-administered.[6] However, being a partial substrate for CYP 3A, rifabutin may accumulate and predispose to uveitis in the presence of CYP 3A inhibitors.

Assessment of Severity and Risk

Severity of adverse events is assessed clinically and aided by blood tests as appropriate. In general, mild adverse events are either limited in distribution or associated with mild derangement in blood

tests. An important reference is the patient's baseline condition (including underlying diseases). The onset and time course of treatment intolerance are also of direct relevance. Owing to potential risks, some adverse events are always considered severe, for example, thrombocytopenic purpura, retrobulbar neuritis, and convulsion.

Table 8.2. Some common and important drug interactions with rifamycins and fluroquinolones

Major categories	Classified examples
Drugs with concentrations reduced by rifampicin	a. Nine subgroups with "anti-" as prefix: Anticoagulants: warfarin Anticonvulsants: phenytoin, lamotrigine Antibiotics: erythromycin, clarithromycin, doxycycline Antifungals: azoles such as itraconazole, voriconazole Antimalarials: atovaquone, mefloquine Antidepressants: nortriptyline Antiarrhythmic agents: quinidine, tocainide, propafenone Antihypertensive agents: ACEI and AII-RA (e.g. enalapril, losartan) beta-blockers (e.g. propranolol, metoprolol) calcium channel blockers (e.g. nifedipine, diltiazem, verapamil) Antiretroviral agents: Protease inhibitors (e.g. indinavir, ritonavir, saquinavir) NNRTI: delavirdine, nevirapine, efavirenz b. Anxiolytics: diazepam c. Bronchodilators: theophylline d. Cardiac glycosides: digitoxin e. Hormonal agents: combined and progestogen-only pills, tamoxifen, levothyroxine f. Hypoglycaemics (sulphonylurea): tolbutamide, chlorpropamide g. Immunosuppressants: corticosteroids, cyclosporin, tacrolimus h. Lipid-lowering drugs: simvastatin, fluvastatin i. Narcotics: methadone
Drugs that increase rifabutin concentrations	Antibiotics: clarithromycin Antifungals: fluconazole Protease inhibitors: ritonavir
Drugs that reduce rifabutin concentrations	NNRTI: efavirenz
Drugs that reduce absorption of fluoroquinolones	Drugs containing divalent cations such as calcium, iron, and zinc: Antacids Vitamins Sucralfate Didanosine (chewable)

Notes: NNRTI: nonnucleoside reverse transcriptase inhibitor
ACEI: angiotensin converting enzyme inhibitor
AII-RA: angiotensin-II receptor antagonist

Continuation versus Suspension of Treatment

The decision to continue or suspend treatment hinges on risk assessment. In general, mild adverse events can be managed symptomatically without treatment interruption, while others require treatment suspension.[2,3] Table 8.3 summarises actions that may be taken for tackling some common adverse drug events.[2,7]

Table 8.3. Management of common adverse drug events

Adverse events	Recommended actions
Gastrointestinal upset	1. Exclude hepatitis with blood tests. In general, symptoms are assumed to be unrelated to hepatitis if alanine aminotransferase (ALT) is less than 3 times the upper limit of normal or total bilirubin is less than 2 times the upper limit of normal. 2. Administer drugs with food. 3. If necessary, an anti-emetic may be prescribed for relief of symptoms. Avoid antacids if possible because they may reduce absorption of isoniazid and rifampicin.[3] 4. Consider daily regimens if symptoms are related to the bulk of medications in intermittent regimens. Fixed-dose combination tablets may help. 5. Avoid split doses as they may result in suboptimal drug levels. 6. Medication at bedtime may help if treatment is self-administered.
Non-petechial rash	1. Exclude other causes. 2. Mild cases: symptomatic relief with antihistamines and/ or topical steroid; watch out for progression and /or mucosal involvement. 3. Moderate to severe rash: suspend treatment; give anti-histamines, prescribe systemic steroids in life-threatening situations[5]; reintroduce drugs later with caution (see text).
Drug fever	1. Exclude superinfection or worsening of TB. 2. Suspend treatment. Reintroduce drugs later sequentially to identify offending agents. 3. Oral steroids may help (see text).
Hepatotoxicity	1. Identify underlying risk factors. 2. Withhold treatment if ALT exceeds 3 times the upper limit of normal or total bilirubin exceeds 2 times the upper limit of normal. 3. When hepatitis is suspected clinically, treatment may be withheld before blood test results are available. 4. Reintroduce drugs when ALT returns to normal or baseline (see text). 5. In case of treatment need, earlier reintroduction may be considered when ALT is less than 2 times the upper limit of normal. A non-hepatotoxic interim regimen (based on streptomycin, ethambutol and a fluoroquinolone) may also be employed.

If treatment is continued, the patient should be monitored carefully by clinical assessment and/ or biochemical tests. While dosages may be adjusted for dose-dependent adverse effects, split doses should be avoided as they may lead to suboptimal drug levels. Suspension of treatment may be necessary in case of progressive worsening of the adverse events or failure to respond to supportive measures. If it is necessary to withhold first-line drugs, interim treatment with second-line drugs may be required when TB is severe or disease progresses after treatment suspension.[3]

Sequential Reintroduction of Drugs

Although it may be necessary to suspend drugs for up to four weeks in severe cases of adverse drug events, prolonged interruption of treatment may jeopardize the chance of cure or extend the overall treatment duration. Attempts should therefore be made to resume treatment as soon as adverse drug events have subsided.

As it is usually difficult to pinpoint the exact offending agent for the initial adverse events, it is often necessary to reintroduce the original drugs sequentially to identify the culprit. However, drugs that may have caused severe toxic reactions should not be reintroduced as far as possible.[3] Attempts

should be made to establish an effective regimen within a reasonably short period. To avoid the emergence of drug resistance, it is essential to avoid monotherapy of any significant duration (for example, over 1 week[3]). Drugs previously not used or unlikely to cause similar effects may be added if necessary.

Drug challenge aims at identifying the culprit drug in the shortest possible time. Slightly different approaches are adopted for hypersensitivity reactions and drug-induced hepatitis because hypersensitivity reactions usually occur within two to three days of challenge while drug-induced hepatitis often takes one week or more to develop.[2]

Challenge after hypersensitivity reactions is done by reintroducing drugs one by one every two to three days in the order of increasing risk of hypersensitivity reactions, for example, rifampicin, isoniazid, pyrazinamide, and then ethambutol or streptomycin.[2] A starting dose around one-sixth of full dose is recommended (in the belief that it may cause a lesser reaction). This is followed by rapid escalation to full dose.[5] The offending drug is removed should reaction recur. Drugs are added on sequentially until an effective regimen is established.

Challenge after hepatitis is usually done in the presence of at least two other drugs (for example, streptomycin, ethambutol, and levofloxacin) to reduce the risk of acquiring drug resistance. Potential culprits are added in full dose sequentially and cumulatively in the order of increasing risk of hepatitis, for example, rifampicin, isoniazid, and pyrazinamide.[2] Liver function tests are monitored about one week after challenge. Closer monitoring may be required for major hepatotoxicity. Apart from clinical features and risk factors for hepatitis, the maximal serum alanine aminotransferase (ALT) level may serve as a useful guide to the severity of hepatotoxicity (see Chapter 9). When hepatitis occurs with ALT less than five times the upper limit of normal (ULN), challenge may be shortened by reintroducing isoniazid and rifampicin together. If ALT exceeds five times ULN, it is prudent to reintroduce potential culprits one by one weekly. When ALT exceeds ten times ULN, pyrazinamide is often omitted if both isoniazid and rifampicin can be successfully reintroduced.

Desensitisation is sometimes attempted with progressively increasing doses to overcome hypersensitivity reactions. As desensitisation may take more than one week, it is preferably done in the presence of two to three other drugs. Each increment may be around one-tenth[5] or less of full dose. If a mild reaction occurs, symptomatic treatment will be provided with antihistamine and/ or topical steroid. The same dose will be maintained until the rash subsides. The procedure can be shortened by giving the concerned drug twice daily.[5] Some experts recommend giving prednisone (1-2 mg/kg body weight per day) for 3 days before desensitisation and continuing the steroids for up to 2 weeks before gradual tapering.[3] A case series reported the use of prednisone ranging from 20 mg to 80 mg daily during desensitisation.[8] Giving oral corticosteroids twice daily may control drug fever more effectively than a bigger overall dose given once daily.[9] The result of desensitization is not always predictable, and caution should be exercised against the risk of a severe reaction. The threshold for desensitisation is lowered if an optimal regimen cannot be established with alternative drugs.

Conclusions

Although there are rules of thumb for managing adverse drug events in the course of anti-TB treatment, it is difficult to standardise the management for every case.[3] Adverse drug events are preferably managed by, or in consultation with, physicians with adequate experience in the field.[3] Readers are also encouraged to refer to local guidelines for further information.[7,10]

References

1. Chang KC, Leung CC, Tam CM, et al. Risk factors for defaulting from anti-tuberculosis treatment under directly observed treatment in Hong Kong. Int J Tuberc Lung Dis 2004;8:1492-8.
2. American Thoracic Society/ Centers for Disease Control and Prevention/ Infectious Diseases Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603–62.
3. Caminero JA. A tuberculosis guide for specialist physicians. Paris, France: IUATLD, 2004.

4. World Health Organization. Treatment of tuberculosis: guidelines for national programmes, 3rd ed. WHO/CDS/TB/2003.313. Geneva, Switzerland: WHO, 2003.
5. Crofton J, Horne N, Miller F. Clinical tuberculosis. London and Basingstoke: Macmillan Education Ltd; 1992.
6. CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2004 Version 1.20.04. Accessible at http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm.
7. Monitoring for hepatotoxicity during antituberculosis treatment - general recommendations (2002). Accessible at http://www.info.gov.hk/tb_chest/contents/c57.htm.
8. Thompson JE. The management of hypersensitivity reactions to antituberculosis drugs. Med J Aust 1969;2:1058–63.
9. Chung KF, Snashall PD. Suppression of prolonged fever during treatment of pulmonary tuberculosis: importance of using twice versus single daily dose of prednisolone. Postgrad Med J 1983;59:373–5.
10. Preventive measures against drug-induced ocular toxicity during antituberculosis treatment (2002). Accessible at http://www.info.gov.hk/tb_chest/contents/c57.htm.

CHAPTER 9

MONITORING FOR HEPATOTOXICITY DURING ANTI-TUBERCULOSIS TREATMENT

CK Chan, YC Chan, WC Yu

Summary points:

1. Anti-tuberculosis drug-induced hepatotoxicity occurs in a small but significant proportion of patients receiving anti-tuberculosis treatment.
2. Patients with pre-existing liver diseases are at higher risk of developing drug-induced hepatitis during the course of anti-tuberculosis treatment.
3. A baseline clinical and laboratory evaluation, including liver function and hepatitis B surface antigen, should be performed before the start of anti-tuberculosis treatment.
4. Patients should be taught to recognise symptoms of hepatitis and to report them promptly.
5. All patients should be assessed clinically for symptoms and signs of hepatitis during medical consultations in the course of anti-tuberculosis treatment.
6. Patients with risk factors for hepatotoxicity e.g. those with pre-existing liver diseases, the alcoholics, the elderly and the malnourished should have their liver function monitored regularly.
7. Transient changes in liver enzymes are relatively common during anti-tuberculosis treatment and do not signify true hepatotoxicity.
8. Withhold potentially hepatotoxic anti-tuberculosis drugs when there are significant symptoms suggestive of hepatitis or the alanine transaminase level rises to three times or above the upper limit of normal or when the bilirubin level rises to two times or above the upper limit of normal.
9. The timing of resumption of anti-tuberculosis treatment should depend on the severity of liver impairment and the rate of tuberculosis disease progression. A regimen with less hepatotoxic drugs may have to be tried first.

Background

Treatment of tuberculosis (TB) involves several drugs given in combination for six or more months. An updated set of guidelines on the treatment of TB has been published by a working group of the Tuberculosis Control Coordinating Committee/ Tuberculosis & Chest Subcommittee of the Department of Health and the Hospital Authority (TBCCC/TBSC).[1] Anti-TB drug-induced hepatotoxicity occurs in a small but significant proportion of patients receiving anti-TB treatment, and may compromise treatment regimens for TB and can cause significant morbidity.[2,3] In view of the concern about the risk of drug-induced hepatotoxicity, this chapter has been written to address the issue in greater depth.

Prevalence

The incidence of anti-TB drug-induced hepatitis varies, depending on the different definitions of drug-induced hepatitis, different settings and the different characteristics of patient studied.[2,3] The incidence of anti-TB drug-induced hepatitis was reported to be 5.3% under general programme conditions in Singapore in a recent report by Teleman et al.[4] A local study quoted a significant rate at 12% of clinically symptomatic hepatic dysfunction among 1,181 hospital patients who received rifampicin, isoniazid with or without pyrazinamide and other drugs.[5] Hepatic dysfunction is more common among the elderly than younger subjects in another local study (17.7% versus 9.2%) (Table 9.1).[6] A more recent study in Hong Kong showed that among patients treated with anti-TB drugs, the incidences of liver dysfunction and symptomatic hepatitis were rather high especially among Hepatitis B carriers (Table 9.2).[7] Although the definitions employed for hepatitic reactions are different, the rates of liver dysfunction found in the local studies are likely higher than those reported elsewhere.[2,3]

Table 9.1. Rates of liver dysfunction among elderly and young patients from a local study[6]

	Age ≥ 65 (n = 457)	Age < 65 (n = 413)
Peak ALT < 3 times baseline	19 (4.2%)	11 (2.7%)
Peak ALT 3-5 times baseline	33 (7.2%)	10 (2.4%)
Peak ALT > 5 times baseline	29 (6.3%)	17 (4.1%)
Total	81 (17.7%)	38 (9.2%)

Table 9.2. Rates of liver dysfunction and symptomatic hepatitis among patients given anti-tuberculosis drugs, among Hepatitis B carriers as compared with non-carriers, and among Hepatitis B carriers not given anti-tuberculosis drugs[7]

	HBV carriers given anti-TB drugs	Non-carriers given anti-TB drugs	HBV carriers not given anti-TB drugs
Total number	43	276	86
Liver dysfunction *	15 (34.9%)	26 (9.4%)	7 (8.1%)
Symptomatic hepatitis #	7 (16.3%)	13 (4.7%)	1 (1.2%)

* *Liver dysfunction is defined as an increase in ALT levels to 1.5 times above the upper limit of normal on at least 2 consecutive occasions within 4 weeks. For patients with increased pretreatment ALT, the elevation in ALT had to be greater than 1.5 times the baseline level.*

\# *Symptomatic hepatitis is defined as the presence of malaise, nausea, vomiting, lethargy and/or right upper quadrant discomfort together with the presence of liver dysfunction irrespective of the severity of the biochemical abnormality.*

High Risk Groups

While the occurrence of drug-induced hepatitis is difficult to predict, it has been observed that certain patients are at higher risk of developing drug-induced hepatitis during the course of anti-TB treatment. These include patients with pre-existing liver diseases, particularly those associated with chronic viral infection due to Hepatitis B, Hepatitis C, and HIV, the alcoholics, the elderly and the malnourished.[7-10]

The influence of the hepatotoxic risk factors on the severity of anti-TB drug-induced hepatitis has not been studied systematically. In a recent study by Fernandez-Villar A et al,[11] the incidence of anti-TB drug induced hepatitis (serum transaminase >3 times upper limit of normal) was 18.2% in the risk factor group and 5.8% in the non-risk factor group. Severe hepatitis (transaminase >10 times upper limit of normal) occurred in 6.9% of the risk factor group and in 0.4% of the group without risk factors. The results suggest that anti-TB drug-induced hepatitis is significantly more frequent and more severe in patients with hepatotoxicity risk factors.[11]

It is noteworthy that sometimes mildly elevated pretreatment liver enzymes may be encountered among TB patients without any other evidence of liver disease. When these patients are given the full treatment regimen, their enzyme levels are often observed to revert to normal and this phenomenon is presumably related to the resolution of hepatic TB microgranulomas.[1]

Monitoring of Liver Function

The exact role of regular monitoring of liver function tests in patients receiving anti-TB drugs remains controversial. Certain guidelines only emphasize the need of clinical monitoring without mentioning regular biochemical monitoring,[12,13] while a number of authorities recommend routine biochemical monitoring among the high risk groups.[14-16]

Furthermore, opinions on the frequency and duration of biochemical monitoring differ. Transient changes in alanine transaminase and bilirubin levels are relatively common during anti-TB chemotherapy and do not signify true hepatotoxicity. However, progressive rise in alanine transaminase and bilirubin levels is much more ominous. Existing data do not allow reliable prediction of the exact clinical course of asymptomatic patients with moderate degree of biochemical derangement. While more frequent testing may be more likely to pick up those cases with rapid progression, cost-effectiveness and patient acceptance are practical issues among those without clinical symptoms.

A consensus statement has been prepared by a working group of the TBCCC/TBSC on clinical and biochemical monitoring of hepatotoxicity during anti-TB treatment in the local setting.[17] For all patients undergoing treatment with potentially hepatotoxic anti-TB drugs, health education should be provided to alert them of the symptoms suggestive of hepatitis, which include loss of appetite, nausea, vomiting, fever, and jaundice. They should be advised to report such symptoms promptly to the nursing or medical staff should these arise. Liver function tests should be checked before the start of anti-TB treatment. In view of the high Hepatitis B carrier rate and the high incidence of drug-induced hepatic dysfunction among them locally, it is also desirable to check the HBsAg status of patients who need to receive anti-TB treatment. In a sample survey conducted by the TB & Chest Service of the Department of Health in 2005, the HBsAg seropositive rate among TB patients treated at chest clinics was around 10% (unpublished data) (Table 9.3). Patients at risk of developing drug-induced hepatitis, e.g. those with pre-existing liver diseases, the alcoholics, the elderly and the malnourished should be identified at the beginning of the treatment course.

Table 9.3. HBsAg seropositivity rates among tuberculosis patients treated at chest clinics during a 2-month period from March 2005 to May 2005

Sex/Age group	HBsAg status			HBsAg seropositivity rate*	Total
	Positive	Negative	Unknown		
Male					
0-19	1	11	3	8.3%	15
20-39	6	73	4	7.6%	83
40-59	28	114	5	19.7%	147
≥ 60	17	192	15	8.1%	224
Female					
0-19	0	19	0	0%	19
20-39	5	84	6	5.6%	95
40-59	6	56	3	9.7%	65
≥ 60	6	66	2	8.3%	74
Total	69	615	38	10.1%	722

* *HBsAg seropositivity rate = number of HBsAg positive patients/ (number of HBsAg positive patients + number of HBsAg negative patients)*

During medical consultations in the course of anti-TB treatment, all patients should be assessed clinically for symptoms and signs suggestive of hepatitis. Directly observed treatment (DOT), apart from ensuring treatment adherence, allows health care workers to monitor the patients closely for such symptoms and signs. Patients developing symptoms suspicious of hepatitis should have liver function tests repeated. For those with risk factors for hepatotoxicity, it would be desirable to monitor liver function tests once every two weeks during the initial two months of treatment, or more frequently as clinically indicated.

It should be noted that biochemical monitoring is not a replacement for close clinical monitoring. Clinical heterogeneity dictates that each case should be assessed individually with the monitoring procedures tailored accordingly. More frequent and intensive biochemical monitoring may be indicated in situations where the patient's condition or the liver enzyme levels change rapidly.

When to Withhold/ Modify Anti-tuberculosis Treatment

Opinions differ as at what cut-off level of liver dysfunction should modification of treatment regimen be initiated. For the alanine transaminase level, some recommend stopping the hepatotoxic drugs when it increases to three times or above that of normal,[15,16,18-20] while others recommend five times.[13,14,21] The recommendations regarding the level of bilirubin are also not uniform.[21] The local recommendation is to withhold potentially hepatotoxic anti-TB drugs in patients without hepatitis symptoms when the alanine transaminase level rises to three times or above the upper limit of normal or when the bilirubin level rises to two times or above the upper limit of normal. In the case of clinical suspicion of significant hepatitic reactions, the anti-TB drugs may have to be stopped even before the availability of the test results.[17]

Re-challenging Anti-tuberculosis Drugs

If significant drug-induced hepatitis develops, careful balance of all factors is required to decide on when and how to resume treatment. In case of doubt, experts in the field should be consulted. It should be noted that patients with active TB disease would develop detrimental consequences if the TB is left untreated, particularly if the disease is extensive. Hence, the decision on when to resume treatment with anti-TB drugs should be made not only by the time the liver function tests reverting to the normal or pretreatment level, but also on the rate of TB disease progression and the disease severity. Often a regimen with less hepatotoxic drugs or a combination of drugs without potential hepatotoxicity may have to be tried first, with the more potent but potentially hepatotoxic drugs added subsequently one after the other (Table 9.4). The recurrence rate of hepatotoxicity is higher in the reintroduction of a full regimen including pyrazinamide, which causes more hepatoxicity than gradual reintroduction of a regimen without pyrazinamide.[22] Quinolones such as ofloxacin and levofloxacin have anti-tuberculosis activity and exclusive renal clearance. These drugs may be used along with other drugs in the treatment of tuberculosis in presence of hepatic dysfunction, either during the interim phase to await recovery of liver function, or as definitive therapy.[23] It is generally desirable to include both isoniazid and rifampicin in the final regimen whenever possible, so that the duration of treatment does not need to be excessively prolonged. Resumption of treatment utilizing the original full drug regimen may rarely be possible. During resumption of the treatment, the liver chemistry should be closely monitored, and the frequency of monitoring usually depends on the severity of the liver dysfunction that has had occurred, the drugs on trial and also the presence of any underlying liver disease. It has to be noted that the cause of that hepatitis, apart from being drug-induced, could be due to alternatives such as viral infections, or induction by other drugs or herbs used at the same time.

Although there has been substantial progress in the treatment of certain liver diseases, like chronic viral hepatitis, the implications of these advances on the treatment of tuberculosis have not yet been fully clarified. The above guidelines and recommendations need to be reviewed periodically with the availability of future updates in scientific data and medical literature, as well as further accumulation of local experience.

Table 9.4. Anti-tuberculosis drugs and potential for hepatotoxicity

Potentially hepatotoxic drugs	Drugs with much lower or little potential for hepatotoxicity
Isoniazid Rifampicin, Rifabutin Pyrazinamide Ethionamide, Prothionamide Para-aminosalicylic acid	Streptomycin, Kanamycin, Amikacin, Capreomycin Ethambutol Ofloxacin, Levofloxacin, Ciprofloxacin Cycloserine

Monitoring for Hepatotoxicity During Treatment of Latent Tuberculosis Infection

The standard for safety monitoring is clearly higher if the anti-TB drugs are given for the treatment of latent TB infection (LTBI) than that for the treatment of active disease.[24] In year 2001, a number of fatal cases of drug-induced hepatitis were reported during the course of treatment of LTBI with rifampicin and pyrazinamide since the publication of the guidelines for the treatment of LTBI by ATS/CDC.[25] Although the absence of data on the denominator precludes an accurate assessment of the risk, an updated statement has been promulgated recommending more vigilant measures in liver function and clinical monitoring.[21] CDC published yet another paper more recently and recommended clinicians to use alternative regimens for the treatment of LTBI.[26] The recommendations against the use of rifampicin and pyrazinamide for the treatment of LTBI do not apply to the appropriate use of these drugs in multidrug regimens for the treatment of persons with active TB disease. In these circumstances, the risk for morbidity and mortality from TB disease is substantially greater than with LTBI. Rifampicin and pyrazinamide are essential components of recommended CDC regimens that render patients non-infectious rapidly and are effective in curing patients with drug susceptible *M. tuberculosis* strains within 6 months.[26]

Conclusions

Hepatotoxicity is one of the most important adverse effects of anti-TB drugs. It can cause significant morbidity, and even mortality. Frequent clinical monitoring for symptoms and signs of hepatitis is essential during the course of anti-TB treatment. Patients with risk factors for hepatotoxicity should have their liver function monitored regularly. Timely detection and temporary withdrawal of the offending drug is important in the successful management of anti-TB drug-induced hepatotoxicity. The decision on when and how to resume anti-TB treatment can be difficult if significant drug-induced hepatotoxicity develops. The opinion of the TB experts should be sought in case of doubt.

References

1. Chemotherapy of tuberculosis in Hong Kong – update in 2001. A consensus statement of the Tuberculosis Control Coordinating Committee of the Department of Health and the Tuberculosis & Chest Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Annual Report of the Tuberculosis & Chest Service, Department of Health, 2001.
2. Ormerod LP, Skinner C, Wales JM (on behalf of Joint Tuberculosis Committee of the British Thoracic Society). Hepatotoxicity of antituberculosis drugs. Thorax 1996;51:111-3.
3. Murray JF, Nadel JA. Textbook of Respiratory Medicine. WB Saunders Company 2000 3rd ed. P. 1067.
4. Teleman MD, Chee B, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002;6:699-705.
5. Yew WW, Chau CH, Leung S. Anti-tuberculosis drugs and liver toxicity (Letter). Eur Respir J 1996;9:389-90.
6. Leung CC, Yew WW, Chan CK et al. Tuberculosis in older people: a retrospective and comparative study from Hong Kong. J Am Geriatr Soc 2002;50:1219-26.
7. Wong WM, Wu PC, Yuen MF, et al. Anti-tuberculosis drug-related liver dysfunction in chronic hepatitis B infection. Hepatology 2000;31:201-6.
8. Ungo JR, Jones D, Askin D, et al. Anti-tuberculosis drug-induced hepatotoxicity. The role of hepatitis C and the human immunodeficiency virus. Am J Respir Crit Care Med 1998;157:1871-6.
9. Pande JN, Singh SPN, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from anti-tuberculosis drugs: a case-control study. Thorax 1996;51:132-6.
10. Lee BH, Koh WJ, Choi MS et al. Inactive hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy. Chest 2005;127:1304-11.
11. Fernandez-Villar A, Sopena B, Fernandez-Villar J et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8:1499-505.
12. World Health Organisation. Treatment of TB: guidelines for national programmes 1997. WHO/TB/97.220.
13. Task Force of ERS, WHO and the Europe Region of IUATLD. TB management in Europe. Eur Respir J 1999;14:978-92.
14. BTS. Chemotherapy and management of tuberculosis in the UK: recommendations 1998. Thorax 1998;53:536-48.
15. Rom WN, Garay SM. Tuberculosis. Little, Brown & Company, 1996 1st ed. p.830-2.
16. Thompson NP, Caplin ME, Hamilton MI, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. Eur Respir J 1995;8:1384-8.
17. Monitoring for hepatotoxicity during anti-tuberculosis treatment – general recommendations. A consensus statement of the Tuberculosis Control Coordinating Committee of the Department of Health and the Tuberculosis & Chest Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Annual Report of the Tuberculosis & Chest Service, Department of Health, 2002.
18. Mitchell I, Wendon J, Fitt S, Williams R. Anti-tuberculous therapy and acute liver failure. Lancet 1995;345:555-6.
19. O'Brien. The treatment of tuberculosis. In: Tuberculosis – a comprehensive international approach. Reichman LB, Hershfield ES (eds). Marcel Dekker Inc. 1993. p.224.
20. O'Brien RJ. Hepatotoxic reactions to anti-tuberculosis drugs: adjustments to therapeutic regimens. JAMA 1991;265:3323.
21. ATS/CDC. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent TB infection, and revisions in ATS/CDC recommendations – US, 2001. MMWR 2001;50:733-5.
22. Tahaoglu K, Atac G, Sevim T et al. The management of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2001;5: 65-9.
23. Yew WW, Lee J, Wong PC, Kwan SY. Tolerance of ofloxacin in the treatment of pulmonary tuberculosis in presence of hepatic dysfunction. Int J Clin Pharmacol Res 1992;12:173-8.
24. Burman WJ, Reves RR. Hepatotoxicity from rifapmin plus pyrazinamide. Am J Respir Crit Care Med 2001;164:1112-3.
25. ATS/CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49:RR-6.
26. ATS/CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection – United States, 2003. MMWR 2003;52:735-9.

CHAPTER 10

OCULAR TOXICITY AND ANTI-TUBERCULOSIS TREATMENT

KC Chang, WW Yew, KS Chan

Summary points:

1. Given proper prescription, ocular toxicity during anti-tuberculosis treatment occurs uncommonly as a result of retrobulbar neuritis caused by ethambutol, or rarely as optic neuritis caused by isoniazid.
2. The major indications for ethambutol are (1) a relatively high risk of initial resistance to isoniazid; (2) drug-induced hepatitis; (3) multidrug-resistant tuberculosis; and (4) administering isoniazid, rifampicin and pyrazinamide in an intermittent regimen.
3. The major relative contraindications for ethambutol are (1) inability to report symptoms; (2) lacking reasonable vision for carrying out activities of daily living independently; and (3) renal impairment. Avoid ethambutol as far as practicable in the presence of either one of the first two contraindications.
4. Congenital colour weakness or blindness *per se* is not a major contraindication for ethambutol.
5. Ocular toxicity during anti-tuberculosis treatment is preventable. The most important measures against ocular toxicity are judicious prescription, appropriate dosage, prompt self-reporting of symptoms, and baseline assessment with preference for reasonable vision.
6. Judicious prescription with appropriate dosage is important. Retrobulbar neuritis is dose-related. The recommended dosage of ethambutol for patients with normal renal function is 15 mg/kg daily or 30 mg/kg thrice weekly.
7. When renal insufficiency is the only relative contraindication, ethambutol may be used safely in a thrice-weekly regimen with isoniazid, rifampicin and pyrazinamide after appropriate adjustment of dosages. We recommend the following doses for ethambutol given thrice weekly with isoniazid, rifampicin and pyrazinamide: 25 to 30 mg/kg when creatinine clearance equals 50 to 100 mL/min; 15 to 25 mg/kg when creatinine clearance equals 10 to 50 mL/min; and 15 mg/kg when creatinine clearance is less than 10 mL/min.
8. Suspicion of ocular toxicity during treatment indicates a semi-urgent ophthalmological assessment. Ethambutol should be stopped immediately and not given again when there are signs of ocular toxicity complicating its use.
9. In the event of severe optic neuritis or failure of improvement of vision within six weeks after stopping ethambutol, it may also be necessary to stop isoniazid.

Introduction

The major cause of ocular toxicity during anti-tuberculosis (anti-TB) treatment is ethambutol, which causes retrobulbar neuritis.[1–4] The risk of ocular toxicity is dose-related, ranging from less than 1% at the dosage of 15 mg/kg daily, to 3.4% to 5.3% at 25 to 30 mg/kg daily, and 18.6% to 31.4% above 35 mg/kg daily after receiving treatment for more than two months.[5-7] A much less common cause of drug-induced ocular toxicity is isoniazid, which may rarely cause optic neuritis.[8]

This chapter focuses on ethambutol as it is the single most important cause of ocular toxicity during anti-tuberculosis treatment. We will first describe the clinical manifestation, pathology and pathogenesis of ocular toxicity caused by ethambutol. Then we will summarize the indications and contraindications for ethambutol, discuss measures against ocular toxicity, and provide some suggestions for prescribing ethambutol in typical clinical scenarios.

Clinical Manifestation, Pathology and Pathogenesis

The ocular manifestations of ethambutol were first described by Carr and Henkind in 1962.[9] There are two types of retrobulbar neuritis: central (axial) toxicity that involves the central fibres, and peripheral (periaxial) toxicity that affects the peripheral fibres of the optic nerve.[5,6] In most instances, the optic disc appears normal. Central toxicity is more common than peripheral toxicity, which is rare under the recommended dosages.[5] Symptoms and signs of central toxicity include visual blurring, impaired visual acuity on physical examination, central scotoma and loss of perception of red-green colour. Peripheral toxicity may cause few visual symptoms but there is peripheral constriction of visual fields on physical examination. Retrobulbar neuritis is dose-related. It is generally reversible after rapid withdrawal of ethambutol.[6] A small follow-up study showed the condition was partially reversible in most patients aged below 60 years but caused irreversible damage in most of the older population.[10]

The exact pathogenesis of ethambutol-induced retrobulbar neuritis is not known. It may be related to the chelation of zinc by ethambutol. In animal studies, it has been shown that ethambutol depletes zinc from the optic nerves.[11] It has also been reported that patients receiving ethambutol with lower plasma zinc level have a higher risk of optic neuropathy.[12] Although unusual idiosyncratic hypersensitivity with irreversible blindness occurring after receiving six days of ethambutol at 15 mg/kg daily has also been described,[13] the most common scenario of retrobulbar neuritis is inappropriate dosage.

Indications for Ethambutol

Despite the potential complication of ocular toxicity, ethambutol is currently one of the first-line anti-TB drugs [2–4] because its effectiveness often outweighs the risk.

Ethambutol is effective for preventing treatment failure in intermittent regimens, although it is less so for preventing relapse.[14] It is virtually non-hepatotoxic.[4,15] Thus ethambutol is recommended for use in combination with other suitable anti-TB drugs in the following scenarios: (1) when clinical and epidemiological circumstances suggest an increased probability of isonaizid resistance,[4] such as when the prevalence of isoniazid resistance rate exceeds 4%,[2,16,17] especially when the bacillary load is high; (2) when standard anti-TB treatment is complicated by drug-induced hepatitis; and (3) multidrug-resistant TB. It is also advisable to add a fourth drug, which may be streptomycin or ethambutol, to reduce the rate of bacteriological failure during intermittent chemotherapy with isonaizid, rifampicin and pyrazinamide.[18]

Contraindications for Ethambutol

The three major, albeit relative, contraindications for ethambutol[2–4] are (1) inability to report symptoms; (2) lacking reasonable vision for carrying out activities of daily living independently[2]; and (3) renal insufficiency. These contraindications are encountered most commonly in the elderly population in which TB is becoming increasingly prevalent. It is advisable to obtain informed consent (preferably with documentation in the medical record) before prescribing ethambutol, especially when relative contraindications exist.

Measures against Ocular Toxicity

Prevention is important because there is no specific treatment for ocular toxicity caused by anti-TB treatment. Measures against ocular toxicity may be classified into seven categories: judicious prescription, appropriate dosage, prompt self-reporting of symptoms, reasonable baseline vision, periodic testing, therapeutic drug monitoring, and zinc supplement. The first four are the most important.

Judicious Prescription

The best strategy for preventing ocular toxicity during anti-TB treatment is to prescribe ethambutol only when it is indicated. The need for supplementing isoniazid, rifampicin and pyrazinamide with

streptomycin or ethambutol in the initial phase of chemotherapy has been questioned for patients with fully sensitive organisms. Trials in Singapore[19] and Poland[20] have shown no loss of efficacy if streptomycin is omitted. The same is probably true of ethambutol which is a less potent anti-TB drug.[2] Thus ethambutol may be omitted in patients with a low risk of resistance to isoniazid.[2]

Nonetheless, it may not be advisable to omit ethambutol in the initial phase in Hong Kong because the prevalence of isoniazid resistance rate in Hong Kong exceeds 4%, unless a favourable initial drug susceptibility pattern is known upon commencement of treatment. Furthermore, treatment with isoniazid, rifampicin and pyrazinamide in the absence of streptomycin or ethambutol is preferably prescribed daily and daily treatment in comparison with intermittent treatment is more toxic and less compatible with the implementation of directly observed treatment (DOT).[21] Ethambutol is also preferred to streptomycin for several reasons: the prevalence of resistance to streptomycin is higher than that of ethambutol[22]; the respective risks of ototoxicity and nephrotoxicity caused by streptomycin are no less than 1%[4]; streptomycin injection is painful; injection carries risk of needle-prick injury and infection.

Appropriate Dosage

Appropriate dosage is very important because retrobulbar neuritis is dose-related. The American Thoracic Society used to recommend 25 mg/kg daily during the initial phase (8 weeks) followed by 15 mg/kg daily during the continuation phase of treatment.[16] Its latest recommended dosage for patients with normal renal function is 15 to 20 mg/kg daily.[4] Local experts recommend 15 mg/kg daily and 30 mg/kg thrice weekly in accordance with the international recommendations.[2-4,15,23] A daily dose of 20 to 25 mg/kg may be used for young patients with extensive TB disease in the first two months of treatment in the presence of normal visual and renal functions.

Renal failure increases the risk of retrobulbar neuritis[24] because approximately two-thirds of ethambutol is excreted unchanged in urine.[15] Renal function should always be checked upon commencement of anti-TB treatment.[2] It has been suggested that ethambutol should be avoided in renal failure whenever possible,[2] but this is not always possible. For the prescription of ethambutol in the context of renal failure, different professional bodies have made different recommendations. The British Thoracic Society recommends reducing dosages substantially unless dialysis is given.[2] The American Thoracic Society favours increasing the dosing interval[25,26] rather than reducing the dose because of concern about suboptimal serum concentration.[27,28] Thus the American Thoracic Society recommends 15 to 25 mg/kg thrice weekly for patients with creatinine clearance less than 30 mL/min or patients receiving haemodialysis (post-procedure), and standard doses with measurement of serum concentration for patients with creatinine clearance above 30 mL/min.[4] Other international authorities recommended the following dosages of ethambutol[3,15]: 25 mg/kg thrice weekly when creatinine clearance equals 50 to 100 mL/min, 25 mg/kg twice weekly when creatinine clearance equals 30 to 50 mL/min, 10 to 15 mg/kg daily when creatinine clearance equals 10 to 30 mL/min, and 5 mg/kg daily when creatinine clearance is less than 10 mL/min. A dosage of 15 mg/kg every 48 hours has been recommended for patients on continuous ambulatory peritoneal dialysis.[15] Different dosages and schedules have been recommended for patients on haemodialysis: 15 to 25 mg/kg thrice weekly, or 45 mg/kg twice weekly, or 90 mg/kg once weekly (all given after haemodialysis) according to the frequency of haemodialysis,[15] or 25 mg/kg four to six hours before dialysis.[3]

As intermittent standard regimens are effective, less toxic and more compatible with DOT,[21] the benefit of incorporating ethambutol into a standard six-month thrice-weekly regimen may outweigh the risk of ocular toxicity after appropriate adjustment of dosages in a patient who is relatively contraindicated for ethambutol only because of renal impairment. As the current recommendations for the dosing of ethambutol are not entirely tailored for prescription in a thrice-weekly regimen, we recommend the following doses for ethambutol given thrice weekly with isoniazid, rifampicin and pyrazinamide: 30 mg/kg when renal function is normal; 25 to 30 mg/kg when creatinine clearance equals 50 to 100 mL/min; 15 to 25 mg/kg when creatinine clearance equals 10 to 50 mL/min; and 15 mg/kg when creatinine clearance is less than 10 mL/min. We also recommend using the lean body weight for calculation,[4] especially in the context of obesity.[15] The creatinine clearance (when renal impairment is stable in the absence of severe liver disease or malnutrition) and lean body weight may be estimated by the following formulae[15]:

Estimated creatinine clearance (mL/min) for men
= (140 – age) x lean body weight (kg)/ [815 x serum creatinine (mmol/L)]
Estimated creatinine clearance (mL/min) for women
= 0.85 x (140 – age) x lean body weight (kg)/ [815 x serum creatinine (mmol/L)]
Estimated lean body weight for women
= 45 kg + 0.9 kg per cm of height above 150 cm
Estimated lean body weight for men
= 50 kg + 0.9 kg per cm of height above 150 cm

Prompt Self-reporting of Symptoms

Early diagnosis of optic neuropathy depends heavily on self-reporting of symptoms. It is generally recommended that ethambutol be prescribed only in patients who are capable of reporting symptoms.[2] For this reason, ethambutol is generally not recommended for routine use in children whose visual acuity cannot be monitored,[4] and in unconscious patients with stage III TB meningitis[2]. However, a review of the literature concluded that, for children aged five years or more, ethambutol can be recommended at a dosage of 15 mg/kg daily for routine treatment without taking more precautions than for adults, and that ethambutol could also be used without undue fear of side effects for younger children.[29] The American Thoracic Society also recommends that ethambutol should be used if a child has adult-type TB suspected or proven to be resistant to isoniazid.[4] Adult-type TB refers to TB associated with sputum production and characterised by upper lobe infiltration and cavitation.[4]

Patients or their family members should be instructed to be alert of a change in vision during treatment with ethambutol, and upon recognition of such symptoms, to seek medical attention immediately.[2,4] A semi-urgent ophthalmological opinion is indicated.[15] Ethambutol should be stopped immediately and not given again when there are signs of ocular toxicity complicating its use.[4]

Optic neuritis of isoniazid as a cause of ocular toxicity during anti-TB treatment should also be considered when ethambutol has not been used. It has been suggested that both isoniazid and ethambutol be stopped in the event of severe optic neuritis and that isoniazid be stopped in less severe cases in which vision fails to improve within six weeks after stopping ethambutol.[30]

Reasonable Baseline Vision

International experts recommend baseline assessment of visual acuity[3,4,15] and red–green colour perception[4,15] for every patient before starting ethambutol. Any history of eye disease should also be documented.[6] Visual acuity and colour vision can be checked by Snellen chart[4,6] and Ishihara tests[4] respectively. Documenting the baseline visual acuity, colour vision, and underlying eye diseases is important for interpretation of any abnormality that may be detected subsequently.

The British Thoracic Society recommends that ethambutol should only be used in patients who have reasonable baseline visual acuity,[2] which may be interpreted as the minimum vision that is compatible with independent activities of daily living. A patient without reasonable baseline vision is probably not sensitive to visual disturbance and thus unable to report symptoms promptly. However, it is sometimes difficult to avoid ethambutol. If ethambutol is indicated, the Ministry of Health of New Zealand recommends formal baseline ophthalmological assessment for those with abnormal visual acuity.[15] Given the low risk of ocular toxicity when ethambutol is prescribed in a proper dosage, it may not be necessary to defer prescription of ethambutol if ophthalmological assessment can be arranged shortly.

It is contentious whether congenital colour weakness or blindness *per se* contraindicates ethambutol. There is no reason to believe that abnormal colour vision should predispose an individual to developing ocular toxicity in the first place. Furthermore, colour vision change occurring in isolation is a very uncommon manifestation of retrobulbar neuritis. A study of the ocular toxicity of ethambutol that involved biweekly monitoring of visual acuity, red-green colour vision, and visual field showed that colour vision loss only occurred concurrently with impairment of visual acuity

after the first two months of treatment.[5] In a study of spinal TB in Korean children receiving ethambutol in doses of 15 to 25 mg/kg for 9 to 18 months, there was no evidence of ocular toxicity despite routine measurement of colour vision, macular threshold, and visual fields.[6] Thus, although abnormal baseline colour vision *per se* may make it less easy to detect loss of colour vision, a putative early sign of retrobulbar neuritis, it is probably safe to prescribe ethambutol in this scenario. It is advisable to obtain informed consent beforehand.

Periodic Testing

Whether periodic testing of visual acuity and colour discrimination may facilitate early diagnosis of ocular toxicity is uncertain. The American Thoracic Society recommends these should be done monthly for the following patients: those taking doses greater than 15 to 20 mg/kg daily, those receiving the drug for longer than two months, and those with renal insufficiency. British experts have doubted the value of routine visual acuity tests during treatment because these tests are neither sensitive nor specific for the diagnosis of retrobulbar neuritis.[6,31] Routine tests of colour vision and visual fields might be more useful but difficult to carry out routinely.[6] The Ministry of Health of New Zealand recommends regular ophthalmological assessment for patients with renal impairment and receiving ethambutol.[15]

Therapeutic Drug Monitoring

Therapeutic drug monitoring may help to prevent ocular toxicity and verify whether it is dose-related, especially in patients with renal impairment. Both the British Thoracic Society and the Ministry of Health of New Zealand recommend monitoring of serum ethambutol levels in patients with renal impairment.[2,15] The American Thoracic Society suggests that therapeutic drug monitoring should be restricted to a few clinical scenarios which include renal insufficiency.[4] The practical feasibility of this recommendation is problematic in the local setting before therapeutic drug monitoring becomes easily accessible as a reliable and regular laboratory service.

Zinc Supplement

The role of zinc supplement for preventing ethambutol-induced ocular toxicity is not established. By reference to the postulated mechanism of retrobulbar neuritis, the use of zinc supplement for the malnourished patients with low zinc level prior to treatment with ethambutol appears sensible, but there is insufficient data to support the benefit of such strategy. Animal studies showed that zinc supplement may augment the pathological changes in retinal cultures with established ethambutol-induced vacuolar degeneration and neuronal loss.[32] Furthermore, correction of zinc deficiency with zinc supplementation must be done cautiously because excessive zinc can interfere with the metabolism of copper and zinc.[33]

Conclusions

Ethambutol is a useful first-line anti-TB agent. The risk of ocular toxicity is very low at the currently recommended dosage of ethambutol (15 mg/kg daily or 30 mg/kg thrice weekly) when renal function is normal. Judicious prescription with appropriate modification in the presence of renal impairment and due precautions during treatment help to prevent ocular toxicity during anti-TB treatment.

References

1. Russo PA, Chaglasian MA. Toxic optic neuropathy associated with ethambutol: implications for current therapy. J Am Optom Assoc 1994;65:332–8.
2. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax 1998;53:536–48.
3. ERS, WHO, IUATLD (Europe Region) Task Force. Tuberculosis management in Europe: Recommendations of a task force of the European Respiratory Society, the World Health Organization and the International Union Against Tuberculosis and Lung Disease (Europe Region). Eur Respir J 1999;14:978–92.
4. American Thoracic Society/ Centers for Disease Control and Prevention/ Infectious Diseases Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603–62.
5. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. Ann NY Acad Sci 1966;135:904–9.

6. Citron KM, Thomas GO. Ocular toxicity from ethambutol. Thorax 1986;41:737–9.
7. Griffith DE, Elliott-Brown BA, Shephard S, McLarty J, Griffith L, Wallace RJ Jr. Ethambutol ocular toxicity in treatment regimens for *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 2005;172:250–3.
8. Jimenez-Lucho VE, Busto RD, Odel J. Isoniazid and ethambutol as a cause of optic neuropathy. Eur J Respir Dis 1987;71:42–5.
9. Carr RE, Henkind P. Ocular manifestations of ethambutol. Arch Ophthalmol 1962;67:566–71.
10. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther 1997;13:473–7.
11. Kahana LM. Toxic ocular effects of ethambutol. Can Med Assoc J 1987;137:213–6.
12. De Palma P, Franco F, Bragliani G. The incidence of optic neuropathy in 84 patients treated with ethambutol. Metab Pediatr Syst Ophthalmol 1989;12:80–2.
13. Chatterjee VKK, Buchanan DR, Friedmann AI, Green M. Ocular toxicity following ethambutol in standard dosage. Br J Dis Chest 1986;80:288–90.
14. Tuberculosis Research Centre Madras. Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis – a controlled trial of four regimens. Tubercle 1981;61:13–29.
15. Ministry of Health. 2002. Guidelines for Tuberculosis Control in New Zealand 2003. Wellington: Ministry of Health.
16. Bass JB Jr, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. Am J Respir Crit Care Med 1994;149:1359–74.
17. World Health Organization. Treatment of tuberculosis - guidelines for national programmes 1997. WHO, Geneva, 1997.
18. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Am Rev Respir Dis 1999;143:700–6.
19. Singapore Tuberculosis Service and British Medical Research Council. Clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1985;132:374–8.
20. Snider DE, Graczyk DE, Bek E, et al. Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin and pyrazinamide with or without streptomycin. Am Rev Respir Dis 1984;130:1091–4.
21. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946 – 1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3:S231–S279.
22. Hong Kong Tuberculosis and Chest Service. Annual Report of the Tuberculosis and Chest Service for 2003. Hong Kong: Department of Health 2003.
23. Tam CM, Yew WW, Leung CC, Chan HS Chemotherapy of Tuberculosis in Hong Kong. Update in 2001. A consensus statement of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Annual Report (Supplement) 2001, Tuberculosis & Chest Service, Department of Health, Hong Kong.
24. O'Brien RJ. The treatment of tuberculosis. In: Tuberculosis - a comprehensive international approach. Reichman LB, Hershfield ES (eds). M. Dekker Inc., New York, Basel, Hong Kong, 1993, pp.207–40.
25. Strauss I, Erhardt F. Ethambutol absorption, excretion and dosage in patients with renal tuberculosis. Chemotherapy 1970;15:148–57.
26. Malone RS, Fish DN, Spiegel DM, Childs JM, Peloquin CA. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide and ethambutol. Am J Respir Crit Care Med 1999;159:1580–4.
27. Peloquin CA. Antituberculosis drugs: pharmacokinetics. In: Drug susceptibility in the chemotherapy of mycobacterial infections. Heifets L (editor). Boca Raton, FL: CRC Press; 1991. pp59–88.
28. Peloquin CA. Using therapeutic drug monitoring to dose the antimycobacterial drugs. Clin Chest Med 1997;18:79–87.
29. Trebucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. Int J Tuberc Lung Dis 1997;1:12–5.
30. Sivakumaran P, Harrison AC, Marschner J, Martin P, Ocular toxicity from ethambutol: a review of four cases and recommended precautions. NZ Med J 1998;111:428–30.
31. Doster B, Murray FJ, Newman R, Woolpert SF. Ethambutol in the initial treatment of pulmonary tuberculosis. Am Rev Respir Dis 1973;107:177–90.
32. Yoon YH, Jung KH, Sadun AA, Shin HC, Koh JY. Ethambutol-induced vacuolar changes and neuronal loss in rate retinal cell culture: mediation by endogenous zinc. Toxicol Appl Pharmacol 2000;162:107–14.
33. Yolton DP. Nutritional effects of zinc on ocular and systemic physiology. J Am Optom Assoc 1981;52:409–14.

Chapter 11

The DOTS Strategy

MY Wong, KC Chang, CM Tam

Summary points:

1. Treatment adherence is a key factor in treatment success for tuberculosis, while unsupervised treatment is associated with low cure rates and emergence of drug resistance.
2. The DOTS strategy is one of the cornerstones advocated in TB control. It consists of five principal elements: government commitment, sputum microscopy, short-course treatment under DOT, regular drug supply, and a reporting system.
3. For DOTS to be successful, a package of holistic care extending beyond the five principal elements is required. Implemented under an optimal setting, DOTS is cost-effective for attaining high cure or treatment completion rates, reducing default, avoiding emergence of drug resistance, and preventing relapse.
4. DOT, a pivotal element of DOTS, is probably the most reliable and well established way of ensuring adherence. Under DOT, the patient swallows the medications under the direct observation of qualified or trained personnel, in a way that is sensitive and supportive to the patient's needs.
5. The local DOTS infrastructure is in place. In the chest clinic, DOTS is promoted through affordability, availability, accessibility, and acceptability.
6. Challenges and obstacles do exist locally while there is a mobile population with freedom of choice. Patient acceptance is not an uncommon problem, and the attending physician has an important role to play.
7. Default, defined as interruption of treatment for two consecutive months or more, represents an extreme case of poor treatment adherence.
8. Treatment non-adherence is more difficult and costly to manage when it becomes default. The best means is to prevent its occurrence in the first place through early promotion of DOTS.
9. Case detection and treatment success rates are monitoring parameters of the DOTS programme. Much effort is still required to achieve internationally set targets.

Introduction

There had been no effective treatment for tuberculosis (TB) until late 1940s and early 1950s. With the availability of streptomycin, isoniazid and para-aminosalicylic acid, combination chemotherapy marked a big step forward in TB curative treatment. Ambulatory outpatient care was soon found to be effective and became the standard in replacing the long-used sanatoria regime. This paradigm shift was triggered by a milestone study in Madras,[1] which demonstrated that treatment at home was as effective as treatment in sanatoria, and did not lead to any increase in TB infection rate among close household contacts.

However, the problem of treatment non-adherence became evident. Treatment failure, drug resistance, and spread of infection emerged as serious consequences. Recognising the importance of this phenomenon, Fox gave a succinct description:[2] "… self-administration was a major problem in spite of repeated counselling advice and emphasis on the need of treatment adherence to both the patient and the whole family…".

The treatment completion rate in Hong Kong in the 1950s was only about 25%.[3] In early 1960s, on the suggestion of Fox and in parallel with the move towards supervised therapy in Madras, Allan Moodie,[4] the architect of Hong Kong's ambulatory care system, started supervision of oral medication in addition to streptomycin injection under health care staff on a trial basis. Recognised as an effective way of ensuring treatment adherence, supervised drug treatment was delivered regularly on a service basis since 1970s and became one of the cornerstones of the TB programme. The advent

of intermittent regimes and short-course chemotherapy in 1979 facilitated its implementation. In early 1990s, supervised treatment was widely renamed as "directly observed treatment (DOT)".[5]

The Global Resurgence and DOTS Recommendation

In late 1980s and early 1990s, despite the availability of effective short course treatment, TB made a significant resurgence alongside drug resistance and HIV co-infection in various parts of the world. TB was declared a global emergency by the World Health Organisation (WHO) in April 1993. Today, TB continues to be an important global problem.[6,7] Among various measures advocated for curbing this global epidemic, DOTS was one of the most important strategies.[8]

In the early 1990s, the term "DOTS" was at first an acronym referring to "directly observed treatment, short course". Later, this term was used in a broader sense to describe the basic methods for diagnosis and treatment of TB. Thus, the DOTS strategy was described as consisting of five principal elements.[9] (Table 11.1) Among these, DOT (directly observed treatment) is a pivotal element. Under DOT, the patient swallows the medications under the direct observation of a trained and authorised person, in a way that is sensitive and supportive to the patient's needs.[8] This is in contrast to "self-administered therapy" (SAT). As TB is a communicable disease with public health significance, and the main control strategy lies in effective treatment, the attending physician has the responsibility to ensure successful treatment as far as possible, in collaboration with the public health programme wherever appropriate.[10]

Table 11.1. The five principal elements of DOTS strategy[9]

(i)	Government commitment to ensuring sustained, comprehensive tuberculosis control activities.
(ii)	Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
(iii)	Standardised short-course chemotherapy using regimens of six to eight months, for at least all confirmed smear-positive cases. Good case management includes DOT during the intensive phase for all new sputum smear-positive cases, the continuation phase of rifampicin-containing regimens and the whole re-treatment regimen.
(iv)	A regular, uninterrupted drug supply of all essential anti-tuberculosis drugs.
(v)	A standardised recording and reporting system that allows assessment of case-finding and treatment results for each patient and of the tuberculosis control programme performance overall.

Note: The current concept regarding DOTS strategy is that it consists of a package of holistic care, extending beyond the five principal elements. It encompasses elements in case detection (smear microscopy) as well as treatment success (short course regime under DOT). Thus, the basic monitoring parameters for the strategy are the case detection rate and treatment success rate.

WHO promoted the strategy through its DOTS expansion plan.[11] The mode of delivery of DOTS vary in different places. However, with expansion of DOTS, the quality of DOTS has to be upheld through the work of qualified staff like health care workers or other trained personnel.[11] Delegating the job of DOT to less qualified or untrained persons (e.g., lay family members) is generally not preferred owing to concern about quality.[12] WHO recommends that DOT should be provided for all new smear-positive cases at least during the initial phase and in the rifampicin-containing continuation phase, and for all retreatment cases.[9] (Table 11.1) Preferably, DOT is to be conducted throughout the course of treatment.

Successful implementation of DOTS calls for holistic care in an optimal infrastructure with supporting elements or services such as incentives, enablers, patient-centered approaches, health education, staff motivation, and defaulter tracing.[13,14] Thus, DOTS programmes frequently extend beyond the five principal elements to meet the requirements of different circumstances.

To assure control of drug-resistant TB, the framework of DOTS has been further expanded to become the "DOTS-plus" strategy by incorporating additional elements: drug susceptibility tests,

continuous surveillance of drug resistance pattern, and modification of drug regimen according to susceptibility tests.[15, 16]

Controversies

The two main reasons for deploying DOT are the association of unsupervised treatment with low cure rates and emergence of drug resistance,[17] and poor predictability of treatment adherence.[2,18-20] Universal DOT is recommended as it avoids the necessity, and potential conflict, of having to determine before the start of treatment who will comply and who will not. Currently, DOTS is considered as one of the most cost-effective interventions in medicine,[8] and it has been said that "we can't afford not to try it".[21] In an optimal setting, DOT is cost-effective for attaining high cure or treatment completion rates,[22-28] avoiding emergence of drug resistance,[29-31] and preventing relapse.[32]

Theoretically randomised controlled trials are the best design for evaluating the role of DOT. Contrary to international recommendations, three out of the four published randomised controlled trials have cast doubt on the role of DOT.[33-36] The caveat is the failure of all treatment arms in these negative trials in achieving satisfactory cure or treatment completion rates. It was commented that lack of an optimal infrastructure and other supporting elements were probably the contributing factors. Thus, DOT may not work on its own. Holistic care is essential.[13,14,37]

Management of Defaulters

"Default" may be regarded as an extreme case of non-adherence. WHO defines "default" as treatment interruption for two consecutive months or more.[9] An association between default and spread of TB in the community has been demonstrated.[38] Accessibility to treatment in terms of distance, cost of transport, time and wages lost, quality and speed of drug delivery, levels of knowledge about TB and the need to complete treatment, and flexibility for transfer to another facility, were the major reasons of non-adherence.[12]

Non-adherence is more difficult and costly to manage when it becomes default. Defaulter tracing is a time-consuming and labour-intensive activity that demands good communication skills, friendly attitude and patience. The reasons for defaulting and the need for social or financial support should be explored. Explanation and counselling are often needed with emphasis on the risk of acquiring drug resistance and spreading TB in the community. Hospitalisation may be required in some cases.

Coercive measures have been used for managing defaulters. For example in Baltimore, DOTS also includes "involuntary hospital admission and jail for patients who default from treatment".[23] However, the use of coercive measures in TB control is a very controversial subject that requires careful consideration of local epidemiology, culture, and public acceptance. Possible aggravation of social stigma and discrimination may adversely affect efforts in case finding.

The DOTS Strategy in Hong Kong

TB is endemic in Hong Kong. Although there has been an overall decline in the past 40 to 50 years, the notification rate of TB is still high, being slightly below 100 per 100,000 population. Hong Kong has been classified by WHO as a place of intermediate TB burden with good health infrastructure, similar to some neighbouring countries like Japan, Malaysia, Republic of Korea and Singapore.[9]

In the Tuberculosis & Chest Service (TB&CS) of the Department of Health, "DOTS" is promoted through affordability, availability, accessibility, and acceptability. TB-related medical services are delivered free of charge (*affordable*). A walk-in system is adopted for consultation without the need to make prior appointment, while DOT is provided at extended times beyond office hours (*available*). Currently, a total of 18 chest clinics serve different parts of the territory (*accessible*). Patients can attend any chest clinic for DOT. Regarding delivery of care, a "mutualistic" approach (see Table 11.2) is advocated (*acceptable*).[39] Thus, a good rapport has to be established from the very beginning to enhance case holding. Table 11.3 summarises some practical points which may help to enhance implementation of DOT at the clinic level. For patients who have ambulatory difficulties, DOT may

be delegated to community nurses or nursing staff in old age homes after individual assessment. Essentially, all doses of TB medication are to be given under DOT throughout the treatment course.

Table 11.2. Types of relationship between patient and the health-care provider[39]

Input from patient	Input from health-care provider	
	Low	High
Low	Default	Paternalistic
High	Consumerism	Mutualistic

Table 11.3. Promoting DOT at the clinic level

1. Adopt a mutualistic and holistic approach to establish a mutually agreed care plan. Explore patient's difficulties and offer assistance where appropriate.
2. Use DOT from the very beginning.
3. Explain the rationale of DOT with written information where appropriate:
   - DOT is an internationally recommended mode of treatment delivery
   - TB is not only an individual problem but a public health problem. Every TB patient's cooperation is very important. Human "rights" and "responsibilities" are equally important.
   - The serious consequences of treatment non-adherence are notorious from historical facts.
   - DOT can also facilitate monitoring and early detection of drug adverse events, which are sometimes severe and occasionally life-threatening.
4. Give standard intermittent regimens as far as possible.

In the chest clinic, every patient will be traced immediately after defaulting even one dose of medication, by every possible means: phone call, mail, and home visit. Special effort will be made to trace and deal with potentially infectious patients and 'frequent' treatment defaulters. Under a friendly atmosphere, defaulters are counselled and health education reinforced. Relevant support and referral for social assistance may be offered. If indicated, the patient may be admitted to hospitals, in particular the chest hospitals, for further management.

A standardised recording and reporting system for cohort evaluation is another essential element of DOTS. A set of standardised "Programme Forms" (Appendices 12 and 14) has been used and updated since 1996. These forms are completed upon commencement of treatment, and thereafter at 6 months, 12 months, and 24 months to capture data on patient demographics, clinical features, treatment details and outcomes.

Thus, DOTS implemented by the Hong Kong TB&CS employs a combination of measures, including education for patients and their families, intermittent client-focused regimens, incentives such as nutrition allowances, referrals for social services, and defaulter tracing. Treatment outcomes are regularly reported to WHO and the results, alongside those of other countries, are disseminated through the WHO's annual global TB reports. Hong Kong has been classified as a place implementing DOTS with high coverage (>90%, category 4).[40]

Evaluation of the Local DOTS Programme

The first local evaluation of treatment outcomes based on WHO definitions[41] was conducted for the cohort of patients registered in the year 1996 through the use of programme forms. A total of 5,757 TB patients were recruited in the analysis.[42] The overall treatment completion rates at 12 and 24 months were 80.4% and 84.8% respectively. Males and patients aged 60 years or older had lower treatment completion rates. Non-adherence, transfer to other services, and mortality among the elderly were key factors affecting treatment outcomes. Co-morbidity was associated with better case holding, and this more than compensated for its effect on prolongation of treatment and mortality.

As discussed, DOTS encompasses the elements of case detection and treatment success (Table 11.1). WHO has defined a target case detection rate of 70% and treatment success rate of 85%.[9] Table 11.4 shows the case detection rates and treatment success rates for Hong Kong and some neighbouring

countries. While these estimates are based on a number of assumptions and may not be exact, it is clear that much effort is still required to achieve WHO's targets.

Table 11.4. Case detection and treatment success rates for Hong Kong and some neighbouring countries[9]

Country/ place	2003 cohort			2002 cohort
	Case detection rate (all cases) (%)	Case detection rate (new smear +ve) (%)	DOTS case detection rate (%)	DOTS treatment success rate (as at 12 month) (%)
Mainland China	46	45	43	93
Hong Kong (China)	**103**	**73**	**58**	**79 ***
Japan	79	60	40	76
Malaysia	61	69	69	76
Republic of Korea	81	59	23	83
Singapore	92	75	44	87

(* over 85% at 24 month)

Despite a DOTS infrastructure being in place, challenges and obstacles do exist. On the part of the patient, acceptance is not an uncommon problem because of various reasons, like job factors, geographical inconvenience, physical problems, and human rights claims. Currently, the treatment defaulter rate is about 5%.[43] Approximately 41% of the defaulters defaulted within the first 2 months.[20] Undesirable treatment adherence, and history of default,[20] were two of the several key risk factors identified associated with default. Among patients with pulmonary TB, multidrug-resistance was found to be associated with default from treatment also.[44] According to a local study (unpublished data), out of 102 treatment defaulters, a total of 87, 76 and 72 still defaulted at 1 year, 2 years, and 3 years respectively. Thus, promoting compliance through optimal implementation of DOT will be much more effective than devoting resources to defaulter tracing.[12]

In a retrospective cohort study of 988 patients, a total of 142, 140, and 21 patients switched from DOT to non-DOT within 2 months, 2 to 6 months, and after 6 months respectively.[24] Analysis showed that patients staying on DOT in the first 2 months had a significantly higher cure rate than those not on DOT (92.7% vs. 83.9%, p=0.002). A nested case-control study of risk factor for early relapse of TB showed that an increase of 10% of DOT during the intensive phase significantly reduced the risk of relapse by 15.8%.[32] This suggested that failure to take supplied medication may be more common than expected.

In the local setting where there is a relatively mobile and ageing population with freedom of choice in seeking medical treatment, a number of factors affect case finding as well as case holding. The attending doctor should emphasise the concept of treatment adherence and DOT from the very beginning. Early promotion of this knowledge would enhance patient acceptance and treatment success (see Table 11.3).

Notwithstanding the challenges and obstacles, surveillance of *Mycobacterium tuberculosis* drug resistance in Hong Kong during the period from 1986 to 1999 showed a significant decline in the rates of drug resistance.[29] The overall resistance to one or more drugs was reduced from approximately 17% to 12% for new patients and from 36% to 25% for retreatment patients, while the corresponding figures for multidrug-resistance (resistant to at least isoniazid and rifampicin) were reduced from 2.7% to 1.0% and from 15.9% to 8.3% respectively. These findings have been quoted as an example of the success of the DOTS strategy.[30]

Conclusions

DOTS is one of the cornerstones in TB control. By investing now, a higher cost can be prevented in the future. The local DOTS infrastructure is in place and is promoted through affordability, availability, accessibility, and acceptability in the chest clinic. In spite of this, there are obstacles and challenges. In Hong Kong where there is a mobile population and freedom of choice, more effort will

be required in the promotion of DOTS. As TB is endemic locally, medical practitioners in all sectors will encounter TB cases from time to time. The attending physician has the responsibility to ensure successful treatment of TB as far as possible, and in collaboration with the public health programme wherever appropriate.[10]

References

1. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. Bull World Health Organ 1959;21:51-144.
2. Fox W. The problem of self-administration of drugs; with particular reference to pulmonary tuberculosis. Tubercle 1958;39:269-74.
3. Hong Kong Tuberculosis and Chest Services of the Department of Health. Annual Report. Hong Kong: Department of Health, 1975.
4. Moodie AS. Mass ambulatory chemotherapy in the treatment of tuberculosis in a predominantly urban community. Am Rev Respir Dis 1967;95:384-97.
5. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. Lancet 1995;345:1545-8.
6. World Health Organisation. Fact sheet N°104 - tuberculosis. Available at http://www.who.int. Accessed on 1 September 2005.
7. World Health Organisation. Global tuberculosis control – WHO Report 2005.
8. Maher D, Mikulencak M. What is DOTS? – A guide to understanding the WHO-recommended TB control strategy known as DOTS. WHO/CDS/CPC/TB/99.270.
9. World Health Organisation Western Pacific Region. Tuberculosis control in South-east Asia and Western Pacific Regions 2005 – a bi-regional report.
10. American Thoracic Society/ Centres for Disease control and Prevention/ Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
11. World Health Organisation. Global tuberculosis control – surveillance, planning, financing. WHO Report 2005. WHO/HTM/TB/2005.349.
12. World Health Organisation. Treatment of tuberculosis: guidelines for national programmes, 3rd ed. WHO/CDS/TB/2003.313. Geneva, Switzerland: WHO 2003.
13. Grange JM. DOTS and beyond: towards a holistic approach to the conquest of tuberculosis. Int J Tuberc Lung Dis 1997;1:293-6.
14. Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. Lancet 2000;355:1345-50.
15. Farmer P, Kim JY. Community based approaches to the control of multidrug-resistant tuberculosis: introducing "DOTS-plus". BMJ 1998;317:671-4.
16. Iseman MD. MDR-TB and the developing world - a problem no longer to be ignored: the WHO announces 'DOTS Plus' strategy. Int J Tuberc Lung Dis 1998;2:867.
17. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City – turning the tide. N Engl J Med 1995;333:229-33.
18. Fox W. Self-administration of medicaments: a review of published work and a study of the problems. Bull Int Union Tuberc 1962;32:307-31.
19. Sbarbaro JA. The patient-physician relationship: compliance revisited. Ann Allergy 1990;64:326-32.
20. Chang KC, Leung CC, Tam CM. Risk factors for defaulting from anti-tuberculosis treatment under directly observed treatment in Hong Kong. Int J Tuberc Lung Dis 2004;8:1492-8.
21. Iseman MD, Cohn DL, Sbarbaro JA, Directly observed treatment of tuberculosis. N Engl J Med 1993;328:576-8.
22. Mathema B, McGowan JE, Houston RA, Pande SB, Jochem K, Bam DS. Tuberculosis treatment in Nepal: comparison of outcomes at government centres under different supervision strategies. Int J Tuberc Lung Dis 1997;1:S72-3.
23. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for tuberculosis. JAMA 1995;274:945-51.
24. Wong MY, Leung CC, Tam CM, Lee SN. Directly observed treatment of tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2005;9:443-9.
25. Chowdhury AMR, Chowdhury S, Islam MN, Islam A, Vaughan JP. Control of tuberculosis by community health workers in Bangladesh. Lancet 1997;350:169-72.
26. Balasubramanian VN, Commen K, Samuel R. DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala state, India. Int J Tuberc Lung Dis 2000;4:409-13.
27. Chaulk CP, Pope DS. The Baltimore City Health Department program of directly observed therapy for tuberculosis. Clin Chest Med 1997;18:149-54.
28. Alwood K, Keruly J, Moore-Rice K, Stanton DL, Chaulk CP, Chaisson RE. Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. AIDS 1994;8:1103-8.
29. Kam KM, Yip CW. Surveillance of mycobacterium tuberculosis drug resistance in Hong Kong, 1986-1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001;5:815-23.
30. Espinal MA, Gupta R, Raviglione MC. The future may not be so dark. Int J Tuberc Lung Dis 2001;5:787-8.
31. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 1994;330:1179-84.
32. Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. Am J Respir Crit Care Med 2004;170:1124-30.
33. Zwarenstein M, Schoeman JH, Vundule CJ, Tatley M. Randomized controlled trial of self-supervised and directly observed treatment of tuberculosis. Lancet 1998;352:1340-3.

34. Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomized controlled trial in Pakistan. Lancet 2001;357:664-9.
35. Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomized controlled trial of lay health worker as direct observers for treatment of tuberculosis. Int J Tuberc Lung Dis 2000;4:550-4.
36. Kamolratanakul P, Sawert H, Lertmaharit S, et al. Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. Trans R Soc Trop Med Hyg 1999;93:552-7.
37. Garner P. What makes DOT work? Lancet 1998;352:1326-7.
38. O'Brien JK, Sandman LA, Kreiswirth BN, Rom WN, Schluger NW. DNA fingerprints from Mycobacterium tuberculosis isolates of patients confined for therapy noncompliance show frequent clustering. Chest 1997;112:387-92.
39. Stewart M, Roter D. Communicating with medical patients. New York: Sage Publications 1989:21.
40. World Health Organisation. Global tuberculosis control – WHO Report 2003.
41. World Health Organisation, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis 2001;5:213-5.
42. Tam CM, Leung CC, Noertjojo K, Chan SL, Chan-Yeung M. Tuberculosis in Hong Kong – patient characteristics and treatment outcome. Hong Kong Med J 2003;9:83-90.
43. Hong Kong Tuberculosis and Chest Services of the Department of Health. Annual Report. Hong Kong: Department of Health, 2003.
44. Chan-Yeung M, Noertjojo K, Leung CC, Chan SL, Tam CM. Prevalence and predictors of default from tuberculosis treatment in Hong Kong. Hong Kong Med J 2003;9:263-8.

CHAPTER 12

CONTACT INVESTIGATION

SN Lee, KM Kam, RWH Yung

Summary points:

1. Contact investigation is an important supplementary measure in TB control. It serves to identify active tuberculosis and latent tuberculous infection in targeted close contact. It also provides a good opportunity for health education, particularly on early awareness of symptoms suspicious of tuberculosis.
2. In general, assessment of the risk of tuberculosis in contacts is based on the infectiousness of the index case, degree of closeness of contact, and susceptibility of the contact person.
3. Definition of the priority and extent of investigation follows the stone-in-the-pond or concentric circle principle. Contacts with the highest risk are examined first, and if the initial result shows evidence of transmission, investigation will be extended sequentially to involve those with a lesser degree of risk.
4. Symptom recognition, chest radiographic examination, and sputum microbiological studies are the useful screening tools for active tuberculosis. Tuberculin skin test is the most widely adopted tool for screening of latent tuberculous infection. Newer molecular tools that produce DNA fingerprints, such as restriction fragment length polymorphism, are useful supplementary tests in outbreak investigation.
5. For all contacts, health education on preventive measures and symptom awareness should be useful. Adjustment of social and environmental condition may be indicated. For those screened positive for active tuberculosis or latent infection, relevant treatment would be indicated.
6. Overall, contact screening accounts for less than 2% of all notified tuberculosis cases in Hong Kong. As the yield of active disease is only modest even among close household contacts, a careful cost-benefit assessment is required in formulating the local screening strategies. A targeted approach is similarly required in the screening and treatment of latent tuberculosis infection.

Introduction

Contact tracing and examination is one of the key strategies for successful control of different kinds of infectious diseases. Ideally, further transmission of the infection and progression to disease should come to a halt if all contacts of index cases can be identified promptly, with isolation and/ or preventive treatment given appropriately. Theoretically, a reproductive number close to zero would mean that the epidemic can be rapidly curbed and put under control.

The situation is, however, quite different for tuberculosis (TB). Firstly, TB is one of the most common infectious diseases in the world. One third of all global incident cases occur in the South-East Asia Region, and around 20% in the Western Pacific Region.[1] Secondly, it is estimated that about 19% to 43% of the world's population have already been infected with *Mycobacterium tuberculosis* (MTB),[2] and the latent period from TB infection to disease is often long and variable.[3] Thirdly, the existing diagnostic and treatment tools for latent TB infection (LTBI)[4] are far from perfect. Nevertheless, TB contact investigation is still a useful tool for active case finding and it also provides an invaluable opportunity to educate contacts and the public about TB.

The World Health Organisation (WHO) and Centres for Disease Control and Prevention of the United States have recently conducted a survey on the policy, scope, coverage, and characteristics of TB contact investigations in various countries, with a view to developing a new comprehensive set of guidelines for TB contact tracing.[5] However, it was found that the actual procedures followed and the extent of contact investigation vary considerably between countries, and thus the outcomes of TB

contact investigation differ a lot.[6-8] Moreover, standard definitions for the type, duration, closeness, duration of exposure, criteria for expanding investigations and procedures for identifying contacts are lacking. Such diversity likely arises as a result of great differences in the background epidemiology and the consequential variations in cost-effectiveness of various contact investigation procedures.

Aims of Contact Investigation for Tuberculosis

The aims of contact investigation for TB in the local setting are as follows:
- To identify infected contacts who have developed active TB disease
- To identify contacts who have LTBI and offer them preventive treatment
- To identify the source of infection, if possible
- To identify uninfected contacts who may be eligible for BCG vaccination (children under 15 years old who have never been vaccinated with BCG)
- To educate contacts about TB, so that they can take appropriate preventive measures and seek medical advice early in case of signs and symptoms suspicious of TB in the future

Risk Assessment

After exposure to index cases with infectious TB, up to one third of close contacts may be infected.[9,10] About 10% of those infected will develop active TB as a lifetime risk, with half of them occurring in the first 2 years after contracting the infection.[4] Three basic aspects have to be considered in assessing the risk of transmission of infection and progression to disease, namely "person" factors (infectiousness of the index case and susceptibility of the contact), "time" factors (the duration and intensity of exposure), and "place" factors (the characteristics of the environment like home or institutional settings).[10]

Infectiousness of the Index Case

Pulmonary TB or laryngeal TB is much more infectious than diseases of other sites. Higher bacilli load as reflected by a positive sputum smear is associated with a greater risk.[11,12] Patients with smear results positive only after sputum induction or other passive methods (e.g. bronchoscopy, endobronchial aspirate, etc.) are generally considered less infectious.[3,13] Cavitary pulmonary TB also signifies heavy bacilli load and greater infectiousness.[6,12] Smear-negative and culture-positive pulmonary cases are far less infectious, but they still carry significant risk to close contacts.[6,14] The presence of symptoms of intractable cough is indicative of a higher chance of spreading the bacilli into the environment.[15] In general, infectiousness decreases markedly after two weeks of effective chemotherapy.[10]

The infectiousness of extrapulmonary TB is generally considered as negligible and contact investigation is not routinely recommended in many low incidence countries.[6,13,16,17] However, contact investigation may still be useful for selected high risk populations.[14,18,19]

Degree of Exposure

The risk of contracting TB infection is also determined by the degree of exposure to the infective source. Thus, contacts who have shared the same indoor air with the index case for prolonged periods have the greatest risk and are usually referred to as "**close contacts**". In general, such close contacts are predominantly found among household members, although situations simulating the household settings may also occur in some institutions (e.g. nursing homes, sheltered workshop, correctional facilities, institutions for the mentally disabled, etc).

Casual contacts are contacts with lesser degrees of exposure. Contacts at work are usually considered as casual contacts. Sometimes, proper classification of contacts may require detailed assessment of the social and cultural background of the cases.[10,16] Screening casual contacts is usually not productive. In a survey in England and Wales of 56 incidents, each involving more than 100 casual contacts, only 0.375% of those screened were found to have active TB.[20] The yield was low despite the fact that among these cases, either the index patients were particularly infectious or the contacts were extraordinarily susceptible. Similar observations were found in Hong Kong, where about 6,000 to 7,000 contacts were screened annually during mass contact examinations conducted in institutions like

schools, elderly homes and handicapped centres. The yield of active TB was found to be well below 1% during the years 1999 to 2002 (unpublished data).

From 2002 to 2004, an increasing number of close contacts were screened with tuberculin skin test (TST) in the TB & Chest Service (TB&CS) of Department of Health (DH). About 30% to 40% household contacts of smear-positive index cases agreed for TST and around one third of them were found to be eligible for treatment of LTBI after evaluation. Finally, only 3% to 5% were started on treatment for LTBI (unpublished data). The acceptance of a relatively long course of treatment is often a problematic issue for asymptomatic clients,.

For the purpose of contact investigation, the duration of exposure should be determined by counting from the date of symptom onset of the index person, in particular symptom of cough. When the time of symptom onset cannot be recalled reliably, a reasonable practice is to take it as 3 months before the commencement of anti-TB treatment.[10,16,17]

Susceptibility of the Contact Person

The risk of progression from infection to disease depends mainly on the susceptibility of the contact person, and the associated medical conditions, if any. The most striking one is HIV infection. The estimated rate of progression from latent infection to active TB among HIV-positive contacts is high, up to 5% to 10% per year.[4] Other conditions include silicosis, diabetes mellitus, alcoholism, drug addiction, gastrectomy, immunosuppressive therapy (e.g. prolonged corticosteroid treatment), haematological and reticuloendothelial diseases (e.g. lymphoma and leukaemia), end-stage renal disease, malignancy (e.g. head and neck cancer), and extremes of age including young children and elderly.[4,10]

Basic Strategy

The conventional strategy for TB contact investigation has been described as the “stone-in-the-pond” or “concentric circle” approach.[21] Individuals with the utmost closeness to the index case, in terms of duration and proximity, are examined first. This is followed by contacts with lesser degree of exposure in sequential order if there is evidence of further spread of the infection.

Tools for Contact Investigation

Clinical symptoms, chest radiographic examination (CXR), sputum microscopy, and TST are the four basic tools for TB contact investigation. The former three are screening tools for active disease, while the last one is primarily for LTBI.

Since TB may develop at a highly variable latency period after infection, health education about early symptom awareness is of salient importance. About 80%[22] to 90%[23] TB patients have pulmonary involvement which commonly manifest as abnormalities on the chest radiograph.[4,22]. However, culture-positive pulmonary TB with unremarkable findings on chest radiograph in apparently immunocompetent hosts have also been increasingly recognised.[24] Direct microscopic examination of concentrated sputum continues to play a key role in the diagnosis of pulmonary TB because it is inexpensive, rapid, and easy to perform.[22] Using culture as the gold standard, the sensitivity of smear examination was found to range from 22% to 78%, depending on the site of disease, number of specimens collected and the presence of cavities.[25] (See also Chapter 4.)

Since the early 1930s, TST has become a commonly used tool for screening apparently healthy persons for LTBI. It is still widely employed by many Western countries as the initial screening step in contact investigation.[13,17,26] However, its sensitivity and specificity are affected by a number of factors. (See Chapters 13 and 14.)

Cost-benefit Consideration

In the TB&CS of DH, even among close contacts, the yield of active TB disease from screening examination is only around 1% to 2%.[14,23] Less than 2% of notified TB cases were detected through

contact investigation.[23] In low incidence countries such as the United Kingdom, contact investigation may be more fruitful in terms of active disease detection. Even so, only up to 10% of all active TB cases were detected by contact tracing.[16] Thus, cost-benefit assessment should be considered carefully in the practice of contact investigation. Some of the relevant factors in such assessment are listed in Table 12.1, and the related costs or benefits may also vary with the epidemiological situation and individual circumstances.

Table 12.1. Factors to be considered during cost-benefit assessment of contact investigation

Cost	Benefit
Cost of the tests	Yield of the test
- Direct cost - Side effects (minimal) - False +ve (over-treatment) - False –ve (false sense of security)	- Yield of suitable candidates ~ for active TB: 1-2% ~ for LTBI: less than 1 in 3 - Coincidental findings
Cost of treatment (Active TB/LTBI)	Benefit from treatment
- Direct cost - Side effects - Over-treatment (9 out of 10 infected would not develop TB even without treatment of LTBI) - Minimum 6 months of LTBI treatment (issue of acceptance and compliance)	- Benefit in treating active TB - Benefit in treating LTBI ~ depends on risk of disease and compliance ~ risk of possible re-infection

Molecular Epidemiology of Tuberculosis

In the mid-1980s, the use of *IS6110* restriction fragment length polymorphism (RFLP) (or DNA fingerprinting) in differentiating strains of MTB was well studied.[27,28] Clustering of cases sharing similar *IS6110* fingerprint patterns is highly suggestive of recent transmission.[29,30] Hence, the test provides useful information in the investigation of transmission of infection during outbreak situations.[31,32]

In various population-based molecular epidemiology studies in low TB prevalence countries, the proportion of cases due to recent transmission had been found to be much higher than that estimated by conventional studies.[33,34] Moreover, underestimation of transmission beyond household contacts[35,36] or overestimation of transmission in outbreaks[37] by the conventional method have been demonstrated with the help of molecular tools.

However, the RFLP test is technically demanding and labour intensive. As it is commonly done after primary culture isolation, only culture-positive cases could be analysed and a relatively long period is required before the RFLP results are ready. As a result, its role in routine contact investigation is still limited.

More recently, a polymerase chain reaction (PCR)-based typing method using variable number tandem repeats (VNTRs) on the mycobacterial interspersed repetitive units (MIRUs) in 12 minisatellite-like regions of the MTB genome has been developed and produced some initial promising results[38,39] in molecular epidemiological studies. Rapid, automatic protocols of using this method were also proposed and practised in some laboratories.[40] Despite the supposedly high differentiation power for MTB strains, a large scale study on its discriminatory power for the locally predominant Beijing genotype[41] revealed that MIRU-based typing may not provide sufficient resolution for epidemiological studies within this specific MTB family.[42] Further refinement is required before this test can be put into routine use in the local setting.

Practice of Contact Screening in the Local Setting

Though the practice of contact investigation is rather variable, the TB&CS of DH and Hospital Authority (HA) formulated some general guidelines for the local setting, based on general principles, expert opinion, as well as international recommendations where appropriate.

General Procedures

Contacts should be assessed according to their risk profile as discussed in the earlier parts of this Chapter. BCG vaccination is recommended for all children aged below 15 who have never received BCG before. TST and/ or chest radiographic examination will be performed as shown in Table 12.2. All contacts with symptoms suspicious of TB should be medically evaluated. Asymptomatic contacts with negative initial findings will be discharged after provision of health education. Advice is emphasised on preventive measures and the need to seek early medical assessment if suspicious symptoms are encountered in the future. Further follow up is generally not indicated except in situations when the contact is immunocompromised or the index case has multidrug-resistant TB (MDR-TB).

Table 12.2. Tuberculosis contact investigation in the Tuberculosis & Chest Service, Department of Health

Target groups	Circumstances	Strategy
Close contacts (household) < 5 years old	Index case smear –ve Index case smear +ve	TST ± CXR (see Fig 12.1) CXR and TST/ treatment of LTBI (see Appendix 9)
Close contacts (household) 5-34 years old	Index case smear –ve Index case smear +ve	CXR CXR and TST/ treatment of LTBI (see Appendix 9)
Close contacts (household) ≥ 35 years old	Index case smear –ve/ +ve	CXR (or follow Appendix 9 in special circumstances)
HIV +ve	Index case smear –ve/ +ve	CXR and TST/ treatment of LTBI (see Appendix 10)
Social contacts	Special high risk situations	Assessment on a case-by-case basis
TB contact examination in institutions (elderly homes, schools, etc)	Index case smear +ve and/ or signs of spread of infection (e.g. clustering of cases)	Mass contact examination (after assessment on a case-by-case basis)

Note: CXR = chest X-ray examination

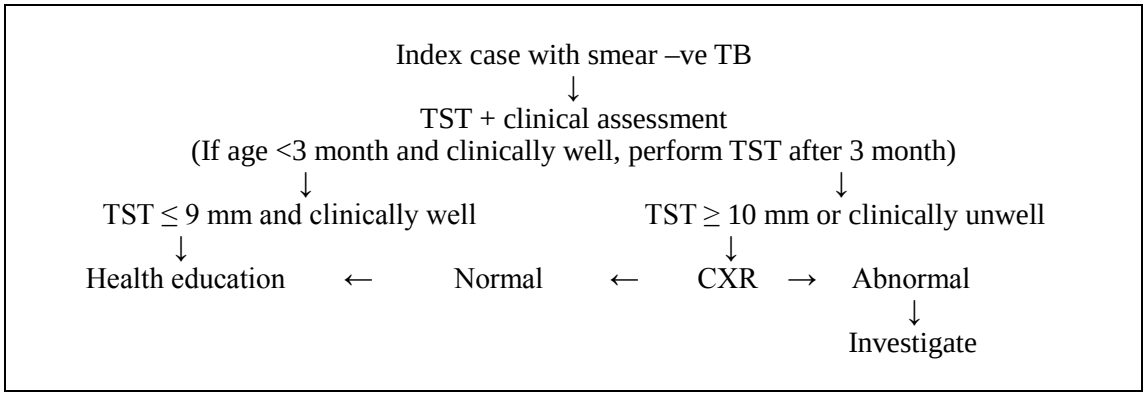


Figure 12.1. Contact investigation of close contacts aged below 5 with smear-negative index cases
* If the index case has smear-negative TB and the close contact case is aged below five, the contact case is first evaluated by tuberculin skin test alongside clinical assessment. If the contact case is aged below 3 months and clinically well, the tuberculin test can be postponed until the contact case is 3 months old. If the contact case is clinically well and the tuberculin skin test result is 9 mm or less, health education is all that is required. If the contact case is clinically unwell or the tuberculin skin test result is 10 mm or more, chest X-ray is taken. If chest X-ray is normal, only health education is required. Otherwise, further investigation may be considered.

Multidrug-resistant Tuberculosis Patients

Patients with multidrug-resistant TB (MDR-TB) are generally more difficult to treat and their duration of infectiousness may be prolonged. Hence, based on the assessment of their infectiousness as suggested by sputum smear status and clinical-radiological condition, regular surveillance (e.g. 6 to 12 monthly) would be desirable for their household contacts. Health education is re-emphasised. Early medical assessment is strongly advised should symptoms suspicious of TB develop. There is no well documented regime for treatment of latent MDR-TB infection. If this is deemed necessary, individualised regimen according to index case's drug susceptibility pattern may be considered (see Chapter 14). Social and environmental background of the index and contact cases should be assessed in depth and adjustment might be necessary to prevent transmission of MDR-TB. If a contact is diagnosed as having active TB, it is important to correlate with the drug susceptibility pattern of the index case, apart from susceptibility tests done directly on culture isolates of the contact. RFLP testing may also be considered.

Health Care Settings

Hong Kong is a place with intermediate TB burden. Significant ongoing risk of exposure to infectious TB patients is likely for health care workers. In spite of this, the reported rate of active TB in health care workers has not been found to be higher than the population incidence even after adjustment for age.[43] This would suggest that contact screening of health care workers is, in general, unlikely to give an overly high yield.[43] In most cases, contact examination only plays a supplementary role in the control of TB within health care settings.[44] However, when the index case is highly infectious or the contacts are exceptionally susceptible, contact investigation with follow up reassessment may be indicated. In case of suspected outbreaks or clustering of cases in a hospital, the Infection Control Team of the hospital should be consulted and closely liaised with in the investigation process. Relevant administrative and environmental controls should be evaluated and strengthened wherever appropriate.[43] (See also Chapter 16.) No single rule is likely to apply to the diversified clinical settings.[44] The necessity and extent of contact investigation should be assessed on a case-by-case basis. The recommendations by HA for the management of contacts in the health care settings can be summarised as follows: [44]

- Examination may be considered for
    - those in close and prolonged contact with highly infectious TB patients
    - symptomatic contacts
    - highly vulnerable patients with lesser degree of contact
- Some points to note during the procedures
    - liaison with Infection Control Team
    - compiling a contact list if mass contact examination is indicated, e.g. outbreaks or clustering of TB cases in time/ space
    - tools to be employed in contact examination
        - chest radiographic examination is commonly used
        - certain groups like the immunocompromised or the very young, may benefit from TST and treatment of LTBI (see also Chapter 14)
        - health education for promotion of knowledge and early awareness of symptoms
        - molecular tests like RFLP may be useful

Tuberculosis and Air Travel

A review of the risk of TB transmission during air travel was conducted by the World Health Organisation a few years ago.[45] The overall results of seven related studies suggested that air travel does not carry a particularly higher risk of TB transmission than other public transport. Since the ventilation system of most modern aircraft nowadays allows cabin air to be filtered and re-circulated at a high rate, rapid removal of infectious airborne particles is facilitated. Although no case of active TB has been reported so far after exposure to TB during air travel, there is some evidence that the infection has been transmitted during long flights (more than 8 hours). This is more likely to occur when contacts are staying close enough, say within two rows, to an infectious index case. An overall probability of infection has been estimated to be in the order of one in 1,000 when a symptomatic infectious source is present.[46]

For public health reasons, persons known to have infectious TB should not travel by public air transportation until they are rendered non-infectious. In case of retrospective recognition of exposure to MTB infection during air travel, tracing and informing the flight crew and passengers may be necessary under certain circumstances as summarised in Table 12.3.

Table 12.3. Criteria for evaluation of the risk of tuberculosis transmission and informing flight crew and passengers of the potential exposure[45]

Factors for consideration	Criteria
Infectiousness of the index patient with active TB	All conditions should be met: 1. sputum smear positive for AFB 2. sputum culture positive for MTB (if this is available) 3. symptomatic with cough at the time of the flight (not required for index patients with laryngeal TB) 4. not yet on effective treatment, or no evidence of response despite treatment already started
Duration of the flight	The flight should be at least eight hours duration (including ground delays, etc.).
Time interval between the flight and notification of the case to the health department	The flight should have taken place within 3 months before notification of the case to the health department. (If the period is over 3 months, information retrieval and medical evaluation are often very difficult to be carried out.)
Proximity of the exposed persons to the index case	It is often advisable to inform only those passengers seated close to the index case, and crew members working in the same cabin area.

Conclusions

Contact screening is an important supplementary measure in the control of TB. Overall, it accounts only for less than 2% of all notified TB cases in Hong Kong. As the yield of active disease is only modest even among close household contacts, a careful cost-benefit assessment is required in formulating the local screening strategies. A targeted approach is similarly required in the screening and treatment of LTBI.

References

1. World Health Organisation. Fact sheet N°104 – tuberculosis. Available at <http://www.who.int>. Accessed 1 September 2005.
2. Surdre P, Dam GT, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Org 1992;70:149-159.
3. Piessens WF, Nardell E. Pathogenesis of tuberculosis. In: Tuberculosis - a comprehensive international approach. Reichman LB, Hershfield ES (eds). Marcel Dekker, New York 2000, pp241-60.
4. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376-95.
5. Reichler MR, Etkind S, Taylor Z, Castro KG. Tuberculosis contact investigations. Int J Tuberc Lung Dis 2003;7:S325-7.
6. Reichler MR, Reves R, Bur S, et al. Evaluation of investigations conducted to detect and prevent transmission of tuberculosis. JAMA 2002;287:991-5.
7. Kamat SR,Dawson JJY, Devadatta S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period of close family contacts in South India. Bull World Health Organ 1966;34:517-32.
8. Topley J, Maher D, Nyong'onya M L. Transmission of tuberculosis to contacts of sputum positive adults in Malawi. Arch Dis Child 1996;74:140-3.
9. World Health Organisation Communicable Diseases. Global tuberculosis control. WHO Report 2000. Geneva, Switzerland: WHO 2000.
10. Etkind SC, Veen J. Contact follow-up in high- and low-prevalence countries. In: Tuberculosis - a comprehensive international approach. Reichman LB, Hershfield ES (eds). Marcel Dekker, New York 2000, pp377-99.

11. Lippo KK, Kulmala K, Tala EOJ. Focusing tuberculosis contact tracing by smear grading of index case. Am Rev Respir Dis 1993;148:235-6.
12. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH. Outcomes of contact investigations of infectious tuberculosis patients. Am J Respir Crit Care Med 2000; 162:2033-8.
13. Reid M, NSW Health Department, Australia. Tuberculosis contact tracing. Circular 2001/76.
14. Noertjojo K, Tam CM, Chan SL, Tan J, Chan-Yeung M. Contact Examination for tuberculosis in Hong Kong is useful. Int J Tuberc Lung Dis 2002;6:19-24.
15. Loudon RG, Romans WE. Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 1969;99:109-11.
16. Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: Code of Practice 2000. Thorax 2000;55:887-901.
17. Calder L. Contact investigation. Guidelines for Tuberculosis Control in New Zealand 2003.
18. Irish C, Jolly E, Baker T, et al. Contact tracing of smear negative and non-pulmonary tuberculosis in a high incidence area. Thorax 1997;52(Suppl 6):A34.
19. Underwood BR, White VL, Baker T, Law M, Moore-Gillon JC. Contact tracing and population screening for tuberculosis – who should be assessed? J Public Health Med 2003;25:59-61.
20. Stoddart H, Noah N. Usefulness of screening large numbers of contacts for tuberculosis: questionnaire based review. BMJ 1997;315:651.
21. Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. Tuberc Lung Dis 1992;73:73-6.
22. Lobue PA, Perry S, Catanzaro A. Diagnosis of tuberculosis. In: Tuberculosis - a comprehensive international approach. Reichman LB, Hershfield ES (eds). Marcel Dekker, New York 2000, pp341-75.
23. Annual Report 1999-2003. Tuberculosis & Chest Service of the Department of Health, Hong Kong SAR.
24. Marciniuk DD, McNab BD, Martin WT, Hoeppner VH,. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Chest 1999;115:445-52.
25. Christie JD, Callihan DR. The laboratory diagnosis of mycobacterial diseases. Challenges and common sense. Clin Lab Med 1995;15:279-306.
26. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994;149:1359-74.
27. Eisenach KD, Crawford JT, Bates JH. Genetic relatedness among strains of *Mycobacterium tuberculosis* complex: analysis of restriction fragment heterogenicity using cloned DNA probes. Am Rev Respir Dis 1986;133:1065-8.
28. Shoemaker SA, Fisher JH, Jones WE Jr, Scoggin CH. Restriction analysis of chromosomal DNA defines different strains of *Mycobacterium tuberculosis*. Am Rev Respir Dis 1986;134:210-3.
29. Pena MJ, Caminero JA, Campos-Herrero MI, et al. Epidemiology of tuberclosis in Gran Canaria: a 4 year population study using traditional and molecular approaches. Thorax 2003;58:618-22.
30. Glynn JR, Bauer J, de Boer AS, et al. Interpreting DNA fingerprint clusters of *Mycobacterium tuberculosis*. European Concerted Action on Molecular Epidemiology and Control of Tuberculosis. Int J Tuberc Lung Dis 1999;3:1055-60.
31. Diel R, Meywald-Walter K, Gottschalk R, Rusch-Gerdes S, Niemann S. Ongoing outbreak of tuberculosis in a low-incidence community: a molecular epidemiological evaluation. Int J Tuberc Lung Dis 2004;8:855-61.
32. Ruddy MC, Davies AP, Yates S, et al. Outbreak of isoniazid resistant tuberculosis in north London. Thorax 2004;59:279-85.
33. Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular method. N Engl J Med 1994;330:1703-9.
34. Moro ML, Salamina G, Gori A, et al. Two-year population-based molecular epidemiological study of tuberculosis transmission in the metropolitan area of Milan, Italy. Eur J Clin Microbiol Infect Dis 2002;21:114-22.
35. Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. Lancet 2004;363:212-4.
36. Chan-Yeung M, Tam CM, Wong H, et al. Molecular and conventional epidemiology of tuberculosis in Hong Kong: a population-based prospective study. J Clin Microbiol 2003;41:2706-8.
37. Dahle UR, Nordtvedt S, Winje BA, et al. Tuberculosis in contacts need not indicate disease transmission. Thorax 2005;60:136-7.
38. Supply P, Mazars E, Lesjean S, Vincent V, Gicquel B, Locht C. Variable human minisatellite-like regions in the Mycobacterium tuberculosis genome. Mol Microbiol 2000;36:762-71.
39. Supply P, Lesjean S, Savine E, Kremer K, van Soolingen D, Locht C. Automated high-throughput genotyping for study of global epidemiology of *Mycobacterium tuberculosis* based on mycobacterial interspersed repetitive units. J Clin Microbiol 2001;39:3563-71.
40. Evans JT, Hawkey PM, Smith EG, Boese KA, Warren RE, Hong G. Automated high-throughput mycobacterial interspersed repetitive unit typing of Mycobacterium tuberculosis strains by a combination of PCR and nondenaturing high-performance liquid chromatography. J Clin Microbiol 2004;42:4175-80.
41. Chan MY, Borgdorff M, Yip CW, et al. Seventy percent of the *Mycobacterium tuberculosis* isolates in Hong Kong represent the Beijing genotype. Epidemiol Infect 2001;127:169-71.
42. Kam K.M, Yip CW, Tse LW, et al. Utility of Mycobacterial interspersed repetitive unit typing to differentiate multidrug-resistant *Mycobacterium tuberculosis* of the Beijing Family. J Clin Microbiol 2005;43:306-13.
43. Seto WH. Preventing nosocomial *Mycobacterium tuberculosis* transmission in international settings. Emerg Infect Dis 2001;7:245-8.
44. Hospital Authority Task Force in Infection Control. Control of transmission of TB in healthcare settings in the Hospital Authority. Updated Jan 2003.
45. World Health Organisation. Tuberculosis and air travel: guidelines for prevention and control. WHO/TB98.256.Genewa, Switzerland: World Health Organization, 1998.
46. Ko G, Thompson KM, Nardell EA. Estimation of tuberculosis risk on a commercial airliner. Risk Anal 2004;24:379-88.

CHAPTER 13

TUBERCULIN SKIN TEST

SN Lee, CY Tam, KWT Tsang

Summary points:

1. The tuberculin skin test is a classical test for the diagnosis of tuberculosis infection. Recent infection is demonstrated by conversion of tuberculin test from negative to positive.
2. The role of tuberculin test in the diagnosis of active tuberculosis disease is limited, as only a small proportion of infected individuals will develop tuberculosis in their life-time.
3. In places where BCG vaccination is not widely practised and prevalence of non-tuberculous myocbacterial infection is low, tuberculin test is a useful epidemiological tool. Annual risk of infection could be estimated from carefully conducted tuberculin test surveys.
4. Specificity of tuberculin test is limited by cross-reactivity with BCG vaccination, infections by mycobacteria other than tuberculosis, and the booster effect. However, a tuberculin reading of 15 mm or more in the local setting is suggestive of infection by *Mycobacterium tuberculosis*.
5. There is no single cut-off value for positivity ideally suited for all clinical situations. A higher cut-off value, with higher specificity, should be considered for BCG vaccinated subjects or candidates living in areas endemic for mycobacteria other than tuberculosis. A lower cut-off value should be considered for individuals judged clinically to have a high risk for tuberculosis.
6. Boosting, conversion and reversion should be recognised in the interpretation of tuberculin test results. Boosting is best distinguished from conversion on clinical grounds, supplemented by the absolute size and size increment of the tuberculin test reading. An increase of 10 mm is a useful cut-off value for diagnosing conversion.
7. A number of interferon-γ-based blood assays have been introduced for the diagnosis of latent tuberculosis infection in recent years. Some promises have been demonstrated, especially in improving the specificity and/ or sensitivity. However, further evaluation is required before their application in routine clinical practice.

Introduction

In 1890, Robert Koch first prepared an extract from a heat-sterilised culture of *Mycobacterium tuberculosis* (MTB) through filtering and evaporation. The product was known as old tuberculin. Koch initially tried but failed to use this as a therapeutic agent. Its diagnostic value was subsequently recognized by Clemens von Priquet in 1907. Mantoux was the first person to introduce the intradermal technique, which still bears his name.[1]

Seibert extracted a purified protein derivative (PPD) from autoclaved mycobacteria grown on artificial media in 1934. Tuberculin skin test (TST) using this PPD proved to be more reproducible and specific. After repeated standardisation, a large quantity of PPD Standard (PPD-S) was prepared by Seibert and Glenn in 1939. PPD-S has since become the international standard for all tuberculins.[1] Tween, a detergent that minimizes the adsorption of tuberculin protein by glass or plastic surfaces, was later added, which permits prolonged storage and enhances the reproducibility of TST.[2,3]

The vast majority of our knowledge of TST in diagnostic and epidemiological work comes from studies using PPD-S. Various strengths of tuberculin test materials, from 1 to 250 TU of the old graduated system of administration, had been evaluated. In general, a smaller test dose results in a lower sensitivity, and a larger dose a lower specificity.[4,5] A positive reaction to 5 TU (tuberculin unit) of PPD-S was found to have best correlation with the degree of contact with tuberculosis (TB) and the risk of developing TB.[6]

Five TU dose of PPD-S, contained in a PPD-S dose of 0.1mg/0.1ml, is recommended by the

American Thoracic Society (ATS) as a standard regimen for TST.[7] PPD-RT23, developed by the Serum and Statens Institute of Copenhagen, is another widely used tuberculin test material outside North America since 1957. It has been standardised against PPD-S and is recommended for use in diagnostic and epidemiological work by World Health Organisation (WHO).[8,9] Although there is no uniform translation factor between the tuberculin unit of PPD-RT23 and PPD-S, approximately 2 TU of PPD-RT23 are accepted as bio-equivalent to 5 TU of PPD-S by WHO and International Union Against Tuberculosis And Lung Diseases (IUATLD).[10] In Hong Kong, PPD-RT23 has been the only available PPD, with 2 TU of PPD-RT23 (in 0.1ml) as the recommended dose, for TST, since 2000.[11]

Immunological Basis for the Tuberculin Reaction

The reaction to intradermally injected tuberculin is a classical example of delayed hypersensitivity reaction to tuberculoproteins. T-cells sensitised by prior TB infection are recruited to the skin site where they release lymphokines. Local vasodilatation, oedema, fibrin deposition, and recruitment of other inflammatory cells to the site of injection lead to the formation of an induration. The reaction usually begins 5 to 6 hours after administration of TST. Maximal induration takes place at 48 to 72 hours, and subsides over a period of days.[7] However, TST is not specific for MTB. As a result of cross-reactivity to similar antigens, infection with mycobacteria other than TB (MOTT) and BCG vaccination could also give a positive result.

Although TST reactions have often been equated with protective immunity status, these are separate phenomena. The delayed hypersensitivity reaction of TST is not a good measure of protective cell-mediated immunity.[12] A higher risk of TB was found among previously vaccinated and tuberculin-positive schoolchildren in a local study.[13] In another study from Malawi, persistent vaccine-associated hypersensitivity to mycobacterial antigens did not correlate with vaccine-derived protection against mycobacterial diseases.[14] These findings, therefore, do not support the use of TST in detecting the immunity conferred by neonatal BCG vaccination.

Administration and Reading of Tuberculin Skin Test

The Mantoux method of intradermal injection and the multiple puncture technique are the two most commonly used methods for TST administration. The quantity of tuberculin introduced into the skin by the multiple puncture technique cannot be precisely controlled and a lower sensitivity has also been found.[15] The Mantoux intradermal method is, therefore, recommended.[7,16]

In the Mantoux method, 0.1 ml tuberculin test material that contains 5 TU PPD-S, or other bioequivalent PPD, is injected intradermally into the volar (or dorsal) aspect of the forearm. The chosen skin area should be free of lesions and away from veins. The injection is made using a disposable tuberculin syringe. The latter is a special 1 ml syringe graduated in hundredths of millilitres. It has a short (one quarter to one-half inch) 26- or 27-gauge needle with blunted bevel.[16,17] The tuberculin should be injected just beneath the epidermis, with the needle bevel upward at an angle to the forearm. A discrete, pale wheal with a diameter of 6 to 10 mm should be produced after proper injection. If the first test was improperly administered, another test dose could be given immediately afterwards at a site several centimetres away from the original injection[7] or on the opposite forearm.[16] The final site for the second test should be clearly recorded.

The test should be read between 48 to 72 hours after injection. The reading is focused only on the size of induration, measured with the traditional palpation technique or the Sokal's ballpoint pen method.[17-19] The pen method is done by drawing a perpendicular line to the long axis of the forearm with a ballpoint pen until it stops on the raised area on either side of the induration. The distance between the ink lines is then measured. The pen method has been shown to have superior inter-observer variability, imprecision, and sensitivity.[18,20-22] The largest transverse diameter of induration, measured in millimetres, relative to the long axis of the forearm should be taken.[7] Results of "0 mm", instead of "negative", should be recorded in the absence of an induration.

Interpretation of Tuberculin Test Reaction

Only about one-tenth of all infected individuals will eventually develop active TB in their lifetime.

As there is no gold standard for diagnosing latent TB infection, the sensitivity of TST is often only indirectly inferred from the test responses among patients with bacteriologically-confirmed TB, and specificity from those with a low risk for TB infection.

False-negative and false-positive results are common for TST. False negative TST may result from technical and biological causes as shown in Table 13.1.[1,7] About one-fifth and up to one-third of patients with active TB may fail to yield a positive reaction (≥10 mm induration) to TST. [2,23,24] Active TB cannot, therefore, be excluded simply by a negative TST result.

Table 13.1. Factors associated with a false-negative tuberculin test[1,7]

Technical and avoidable issues:	
- Tuberculin material	Factors relating to storage, dilution, contamination, and dose
- Administration of tuberculin material	Faulty techniques of injection
- Reading of induration reaction	Recorder's error and bias, and inappropriate timing for test reading
Patient characteristics:	
- Infections	Viral infections (e.g. HIV, measles, mumps), bacterial infections (e.g. typhoid fever, pertussis), miliary tuberculosis, and fungal infections
- Live virus vaccination	Measles, mumps, polio, varicella
- Extremes of age	Elderly and newborns
- Immunocompromisation	Chronic renal failure, malignancies, lymphoma, drugs (e.g. corticosteroids and immunosuppressive agents)
- Miscellaneous	Stress (e.g., burns, severe illnesses), graft-versus-host reactions, hypoproteinaemia

Apart from technical errors, past BCG vaccination and cross-reactivity to MOTT are the two main reasons responsible for false positive TST results. Although BCG vaccination of tuberculin negative individuals will almost invariably result in tuberculin conversion within 4-8 weeks, these reactions generally wane over time. Reversion of TST to negative within 5 years is commonly found in subjects who receive BCG vaccination in infancy.[25] Of those vaccinated at an older age, tuberculin reactions are larger and wane more slowly. After more than 10 years, no further waning is apparent and tuberculin reactions persist in a subgroup of 15-25%.[1] BCG vaccination appears to be an important cause of tuberculin reaction in subjects from low-incidence countries, but is less important in subjects from high-prevalence countries.[26] A recent meta-analysis shows that strongly positive TST reaction (>15 mm) is more likely to be caused by TB infection than false positive effect of past BCG vaccination, especially if the BCG vaccination was given more than 15 years previously.[27]

Environmental MOTT exist in soil and water, particularly in warm and moist climate.[28] Similarity of MOTT antigens to MTB antigens causes cross-reactivity in TST.[29] However, tuberculin reactions in persons infected with MOTT are generally of smaller sizes than in persons infected with MTB[7] and are more likely to revert later.[5] Several MOTT skin tests (e.g. using mycobacterium avium sensitin instead of PPD) have been prepared for the diagnosis of MOTT infections. However, these suffer from low sensitivity and specificity.[7,30,31] Although the potential value of dual skin testing (using both mycobacterium avium sensitin and PPD skin testings at the same time) had been shown by some studies,[32,33, 34] further evaluation is required to define their clinical and epidemiological values.

Sensitivity and specificity of TST depends on the cut-off values chosen for positive reactions. A higher cut-off value improves specificity by lowering the possibility of false positive results due to BCG or MOTT, but at the expense of sensitivity. The most appropriate compromise between sensitivity and specificity should be determined by the local epidemiological situation.

The likelihood that a positive TST test represents a true acute TB infection (i.e. the positive predictive value, is affected by the prevalence of TB, as clearly shown in Table 13.2.[7]

Table 13.2. Positive and negative predictive values of tuberculin skin test (TST)

Prevalence of TB infection of the tested population (%)	TST with low cut-off point (assuming 90% sensitivity and 70% specificity)		TST with high cut-off point (assuming 70% sensitivity and 90% specificity)	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)
0.1	0.30	99.99	0.70	99.97
1	2.94	99.86	6.60	99.66
10	25.00	98.44	43.75	96.43
20	42.86	96.55	63.64	92.31
30	56.25	94.23	75.00	87.50
40	66.67	91.30	82.35	81.82
50	75.00	87.50	87.50	75.00
60	81.82	82.35	91.30	66.67
70	87.50	75.00	94.23	56.25
80	92.31	63.64	96.55	42.86
90	96.43	43.75	98.44	25.00

Note: PPV = positive predictive value; NPV = negative predictive value

In the interpretation of TST, it is important to consider the overall clinical situation. Different cut-off values (5, 10 or 15 mm) have been recommended for defining a positive tuberculin reaction with different clinical scenarios.[7,35] The incidence of development of TB during a follow up period of 2 to 20 years is related to TST reactivity, as shown in eleven prospective studies.[36] Generally, individuals who are at high risk of developing TB, e.g. young children, HIV-positive or those on immunosuppressive therapy, should have a lower cut-off value (≥5 mm). A cut-off value ≥10 mm would otherwise remain a useful criterion.[1] Higher cut-off values are adopted for situations when a higher specificity is desirable at the expense of sensitivity.

Although TST correlates well with risk of TB development, it does not delineate the current TB activity status. In other words, a larger TST induration does not simply imply a higher chance of concurrent TB activity.[37]

Repeated Tuberculin Testing: Boosting, Conversion and Reversion

Repeated tuberculin testing is sometimes administered to detect new infection in individuals with initially negative TST results, especially after recent exposure or for surveillance purpose in low-incidence areas.

The differences in administration, reading and minor variation in TST response result in a 2 to 3 mm standard deviation.[38,39] Random variation should, therefore, result in increased or decreased reactions of less than 6 mm (two standard deviations) in 95% of cases. Any repeated TST change of more than 6 mm should represent conversion or boosting in addition to the remote possibility of variation by chance.

Boosting is defined as a recall of immunity in the absence of new infection. It is generally believed that there could be too few sensitised circulating lymphocytes to produce a significant skin response in the first TST among subjects with old infection. The second testing therefore results in rapid increase in sensitised lymphocytes in the circulation, leading to a much greater TST induration. In the absence of prior infection or BCG vaccination, a repeated TST will not induce a positive skin test reaction by itself.[7] Boosting is maximal if the interval between the first and second test is within 1 to 5 weeks,[40] and minimal if the interval is only 48 hours[41] or more than 60 days.[40] In elderly patients, boosting may occur after a third[42] or even a fourth[43] sequential test.

Conversion is defined as a development of new hypersensitivity to mycobacteria following new infection either with MTB or MOTT, or following BCG vaccination. The interval between initial

infection and development of positive tuberculin reaction together with clinical illness is between 3 to 8 weeks.[1] Clinical grounds need to be considered to distinguish between "boosting" or "conversion" in the event of an increased reaction of a second TST. Recent history of close contact with an infectious index case or BCG vaccination would suggest conversion, particularly if several prior skin tests were negative. The absolute size of the second TST reaction and/ or the increase in size from first TST could also be adjunctive measure to help differentiate boosting from conversion. Although there is no ideal single cut-point available for defining conversion for diverse clinical situations,[1] an increase of at least 10 mm is the current consensus.[7,35,44] The absolute size for defining conversion could still be problematic. Generally, a higher cut-point has higher specificity for BCG-vaccinated populations and/ or those living in areas endemic for MOTT, whereas a lower cut-point provides better sensitivity for those individuals with increased risk of TB development, such as young children and immunocompromised patients.[1,7,35]

A two-step method is recommended by some authorities, including the ATS, when repeating TST. Subjects with negative initial TST should undergo a second test 1 to 3 weeks afterwards. The result of the second test should be considered as the "correct" result.[7] Two-step TST has a higher sensitivity for remote (i.e. "happened in the distant past") TB infection, but lower specificity for those with past BCG vaccination.[40] In Hong Kong, the high background prevalence of active TB disease and the practice of universal neonatal BCG vaccination strongly limit its clinical value.

Tuberculin reversion occurs when a negative TST response appears after a prior positive result. This has been demonstrated in some patients who have completed treatment for latent TB infection (LTBI).[45,46] Reversion is more common in older age,[47,48] Rate of reversion from 4.8% to 22.2% had been shown among different age groups of positive reactors retesting after one year,[49] Initial TST reaction of ≤15 mm[45-47] or reaction due to boosting effect[43,47] are associated with higher chance of reversion. Once an individual is tested as "tuberculin positive", further TST does not add more information in routine clinical management.[1]

Indications for Tuberculin Skin Test

Although TST has its limitations, it is nonetheless useful in the diagnosis of latent TB infection and subsequent consideration for preventive treatment clinically. A well-designed TST survey is helpful in estimating the prevalence of MTB infection in a defined birth cohort which also provides data on average annual risk of infection and the trend of infection.[16,50]

Adverse Reactions

Adverse reactions to TST are rare.[1] As with any injection, vasovagal reactions could occur. Severe blistering and even ulceration is seen in 1 to 2% of patients with strongly positive reactions, but no benefit is demonstrated by treatment with hydrocortisone cream.[51] Immediate local hypersensitivity responses with wheal and flare to 10 TU of PPD occurs in 2.3% of patients.[52] Immediate systemic hypersensitivity reactions to tuberculin material, manifesting as angioedema, urticaria or dyspnoea could also occur. Froeschle et al[53] reviewed all spontaneous adverse events reports over an eleven-year period for Tubersol, which was one of the two commercially available PPD in the United States manufactured by Pasteur Merieux-Connaught Laboratories. There were 24 reports and no deaths. The apparent incidence was 0.08 per million doses of Tubersol. There have also been isolated reports of irreversible optic neuropathy in a child with multiple sclerosis,[54] suppurative and foreign body giant cell reaction involving the injection site,[55] and severe anaphylaxis.[56]

There is no evidence that TST is contraindicated in pregnancy[1] or that tuberculin reactions are influenced by pregnancy.[57]

Recent Advances in the Diagnosis of TB infection

A number of interferon-γ-based blood assays have been introduced for the diagnosis of latent TB infection in recent years. The earlier version measures the production of interferon-γ (IFN-γ) in T-lymphocytes upon stimulation with PPD.[58] In the newer assays, PPD is replaced by the early secretory antigenic target 6 kDa protein (ESAT-6) and culture filtrate protein 10 (CFP10), which are

specific for MTB and not present in BCG and most MOTT. In one assay, the stimulation of lymphocytes in fresh whole blood is followed by quantification of IFN-γ by enzyme-linked immunosorbent assay.[59] Another assay involves the isolation of lymphocytes from fresh blood, incubation with appropriate antigens, and then detection of INF-γ-producing T-lymphocytes by enzyme-linked immunospot assay.[60] These assays have various potential advantages over TST as diagnostic tools of TB infection. Firstly, they are theoretically more specific for MTB infection than TST. Secondly, repeated testing will not lead to any booster effect. Thirdly, only one proper blood testing is required for these assays instead of two visits for TST. However, these tests require prompt transport of fresh blood specimens and are technically much more demanding. Clinical experience is limited at this stage, and further research is needed to define their roles in routine clinical practices.

Conclusions

TST is a useful diagnostic and epidemiological tool for identifying TB infection, provided it is administered and interpreted properly in the relevant clinical and epidemiological context. Newer diagnostic tools may offer some promise in improving the specificity, although they require further clinical evaluation.

References

1. Menzies RI. Tuberculin Skin Testing. In: Tuberculosis. Reichman LB, Herschfield E (eds). Marcel Dekker, New York 2000, pp279-322.
2. Holden M, Dubin MR, Diamond PH. Frequency of negative intermediate- strength tuberculin sensitivity in patients with active tuberculosis. N Engl J Med 1971;285:1506-9.
3. Landi S, Held HR, Tseng MC. Disparity of potency between stabilized and nonstabilized dilute tuberculin solutions. Am Rev Respir Dis 1971;101:385-93.
4. Murtagh K. Unreliability of the Mantoux test using 1 TU PPD in excluding childhood tuberculosis in Papua New Guinea. Arch Dis Child 1980; 55:795-9.
5. Gryzbowski S, Brown MT, Stothard D. Infections with atypical mycobacteria in British Columbia. CMAJ 1969;100:896-900.
6. Palmer CE. Tuberculin sensitivity and contact with tuberculosis. Am Rev Tuberc 1953;68:678-94.
7. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161:1376-95.
8. Guld J, Bentzon MW, Bleiker MA, Griep WA, Magnuson M, Waaler H. Standardization of a new batch of purified tuberculin (PPD) intended for international use. Bull WHO 1958;19:845-951.
9. The WHO Standard Tuberculin Test. Geneva: World Health Organization, 1963.
10. Comstock GW, Edwards LB, Philip RN, Winn WA. A comparison in the United States of America of two tuberculins, PPD-S and PPD-RT 23. Bull WHO 1964;31:161-70.
11. Tuberculosis and Chest Service, Department of Health of HKSAR. Annual report 2000.
12. Youmans GP. Relation between delayed hypersensitivity and immunity in tuberculosis. Am Rev Respir Dis 1975;111:109-18.
13. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. Int J Tuberc Lung Dis 2001;5:717-23.
14. Fine PE, Sterne JA, Ponnighaus JM, Rees RJ. Delayed-type hypersensitivity, mycobacterial vaccines and protective immunity. Lancet 1994;344:1245-9.
15. Chaparas SD. Multiple puncture tuberculin tests. Pediatr Infect Dis J 1987;6:496-7.
16. Arnadottir T, Rieder HL, Trebucq A, Waaler HT. Guidelines for conducting tuberculin skin test surveys in high prevalence countries. Tuberc Lung Dis 1996;77:S1-20.
17. Bouros D, Zeros G, Panaretos C, Vassilatos C, Siafakas N. Palpation vs pen method for the measurement of skin tuberculin reaction (Mantoux test). Chest 1991;99:416-9.
18. Jordan T, Sunderam G, Thomas L, Reichman LB. Tuberculin reaction size measurement by the pen method compared to traditional palpation. Chest 1987;92:234-6.
19. Sokal JE. Measurement of delayed skin-test responses. N Engl J Med 1975;293:501-2.
20. Longfield JN, Marsileth AM, Golden SM, Lazoritz S, Bohan S, Cruess DF. Inter-observer and method variability in tuberculin skin testing. Pediatr Infect Dis 1984;3:323-6.
21. Pouchot J, Grasland A, Collet C, Coste J, Esdaile JM, Vinceneux P. Reliability of tuberculin skin test measurement. Ann Intern Med 1997;126:210-4.
22. Carter ER, Lee CM. Interpretation of the tuberculin skin test reaction by paediatric providers. Pediatr Infect Dis J 2002;21:200-3
23. Korzeniewska-Kosela M, Krysl J, Muller N, Black W, Allen E, FitzGerald JM. Tuberculosis in young adults and the elderly. A prospective comparison study. Chest 1994;106:28-32.
24. Huebner RE, Schein MF, Cauthen GM, et al. Evaluation of the clinical usefulness of mycobacterial skin test antigens in adults with pulmonary mycobacterioses. Am Rev Respir Dis 1992;145:1160-6.
25. Pabst HF, Kreth HW. Ontegeny of the immune response as a basis of childhood disease. J Pediatr 1980;97:519-34.

26. Menzies RI, Vissandjee B, Amyot D. Factors associated with tuberculin reactivity among the foreign-born in Montreal. Am Rev Respir 1992;146:752-6.
27. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guerin vaccination on tuberculin skin test measurements. Thorax 2002;57:804-9.
28. Kirschner RA, Parker BC, Falkinham JO. Epidemiology of infection by nontuberculosis mycobacteria. Am Rev Respir Dis 1992;145:271-5.
29. Haimi-Cohen Y, Zeharia A, Mimouni M, Soukhman M, Amir J. Skin induration in response to tuberculin testing in patients with nontuberculosis mycobacterial lymphadenitis. Clin Infect Dis 2001;33:1786-8.
30. Dascalopoulos GA, Loukas S, Constantopoulos SH. Wide geographic variations of sensitivity to MOTT sensitins in Greece. Eur Respir J 1995;8:715-7.
31. Von Reyn CF, Barber TW, Arbeit RD, et al. Evidence of previous infection with Mycobacterium avium-Mycobacterium intracellulare complex among healthy subjects: an international study of dominant mycobacterial skin test reactions. J Infect Dis 1993;168:1553-8.
32. Von Reyn CF, Green PA, McCormick D, et al. Dual skin testing with Mycobacterium avium sensitin and purified protein derivative: an open study of patients with M. avium complex infection or tuberculosis. Clin Infect Dis 1994;19:15-20.
33. Von Reyn CF, Williams DE, Horsburgh CR Jr, et al. Dual skin testing with Mycobacterium avium sensitin and purified protein derivative to discriminate pulmonary disease due to M. avium complex from pulmonary disease due to Mycobacterium tuberculosis. J Infect Dis 1998;177:730-6.
34. Hersh AL, Tosteson AN, Von Reyn CF. Dual skin testing for latent tuberculosis infection: a decision analysis. Am J Prev Med 2003;24:254-9.
35. Martin P. Mantoux Testing. Guidelines for Tuberculosis Control in New Zealand 2003.
36. Watkins R.E., Brennan R, Plant AJ. Tuberculin reactivity and the risk of tuberculosis: review. Int J Tuberc Lung Dis 2000;4:895-903.
37. Zahrani KAL, Jahdali HAL, Menzies D. Does size matter? Utility of size of tuberculin reactions for the diagnosis of mycobacterial disease. Am J Respir Care Med 2000;162:1419-22.
38. Erdtmann FJ, Dixon KE, Liewellyn CH. Skin testing for tuberculosis. Antigen and observer variability. JAMA 1974; 228:479-81.
39. Chaparas SD, Mac Vandiviere H, Melvin I, Koch G, Becker C. Tuberculin test: variability with the Mantoux procedure. Am Rev Respir Dis 1985;132:175-7.
40. Cauthen GM, Snider DE, Onorato IM. Boosting of tuberculin sensitivity among Southeast Asia refugees. Am J Respir Crit Care Med 1994;149:1597-600.
41. Thompson NJ, Glassroth JL, Snider DE, Farer LS. The booster phenomenon in serial tuberculin testing. Am Rev Respir Dis 1979;119:587-97.
42. Gordin F, Perez-Stable E, Flaherty D, et al. Evaluation of a third sequential tuberculin skin test in a chronic care population. Am Rev Respir dis 1988;137:153-7.
43. Perez-Stable EJ, Flaherty D, Schecter G, Slutkin G, Hopewell PC. Conversion and reversion of tuberculin reactions in nursing home residents. Am Rev Respir Dis 1988;137:801-4.
44. Canadian Thoracic Society. FitzGerald JM, ed. Canadian Tuberculosis Standards. Ottawa: Canandian Lung Assoiciation, 1996.
45. Houk VN, Kent DC, Sorenson K, Baker JH. The eradication of tuberculosis infection by isoniazid chemoprophylaxis. Arch Environ Health 1968;16:46-50.
46. Hsu KHK. Tuberculin reaction in children treated with isoniazid. Am J Dis Child 1983;137:1090-2.
47. Gordin FM, Perez-Stable EJ, Reid M, et al. Stability of positive tuberculin tests: are boosted reactions valid? Am Rev Resp Dis 1991;144:560-3.
48. Menzies D. Interpretation of Repeated Tuberculin Tests. Am J Respir Crit Care Med 1999;159:15-21.
49. Grzybowski S, Allen EA. The challenge of tuberculosis in decline. Am Rev Respir Dis 1964;90:707-20
50. Leung CC, Yew WW, Tam CM, et al. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. Thorax 2005;60:124-9.
51. Hanson ML, Comstock GW. Efficacy of hytrocortisone ointment in the treatment of local reactions to tuberculin skin tests. Am Rev Respir Dis 1968;97:472-3.
52. Tarlo SM, Day JH, Mann P, Day MP. Immediate hypersensitivity to tuberculin in vivo and in vitro studies. Chest 1977;71:33-7.
53. Froeschle JE, Ruben FL, Bloh AM. Immediate hypersensitivity reactions after use of tuberculin skin testing. Clin Infect Dis 2002;34:E12-3.
54. Linssen WH, Kruisdijk JJ, Barkhof F, et al. Severe irreversible optic neuritis following Mantoux tuberculin skin test in a child with multiple sclerosis – a case report. Neuropediatrics 1997;28:338-40.
55. Kim Y, Dawes-Higgs E, Zagarella S. Foreign body reaction involving a Mantoux test site. Australas J Dermatol 2005;46:169-71.
56. Wright DN, Ledford DK, Lockey RF. Systemic and local allergic reactions to the tine test purified protein derivative. JAMA 1989;262:2999-3000.
57. Present PA, Comstock GW. Tuberculin sensitivity in pregnancy. Am Rev Respir Dis 1975;112:413-6.
58. Mazurek GH, LoBue PA, Daley CL, et al. Comparison of a whole-blood interferon gamma assay with tuberculin skin testing for detecting latent Mycobacterium tuberculosis infection. JAMA 2001;286:1740-7.
59. Mazurek GH, Villarino ME; CDC. Guidelines for using Quanti-FERON-TB test for diagnosing latent mycobacterium tuberculosis infection. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003,31;52(RR-2):15-8.
60. Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assays with tuberculin skin test for diagnosis of mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet 2003;361:1168-73.

CHAPTER 14

TREATMENT OF LATENT TUBERCULOSIS INFECTION

WS Law, M Chan-Yeung, CC Leung

Summary points:

1. Treatment of latent tuberculosis infection is one of the important strategies for TB control.
2. Tuberculin skin test is the most widely adopted tool to identify clients with latent tuberculosis infection.
3. Targeted tuberculin test minimises unnecessary preventive treatment.
4. The cut-off value of tuberculin skin test for identification of latent tuberculosis infection depends on factors like history of BCG vaccination, client's immune status and local data on the rates of tuberculosis at different cut-off points of tuberculin skin test.
5. Treatment of latent tuberculosis infection with isoniazid monotherapy remains the most widely adopted regimen because of its proven efficacy and safety.

Introduction

For effective control of tuberculosis (TB), the primary strategy is prompt diagnosis and treatment of infectious TB patients. In areas where national TB programmes have already achieved good case finding and satisfactory treatment completion rates, the next step would be treatment of latent tuberculosis infection (LTBI) among targeted groups. In places where the TB incidence is low, like the United States, treatment of LTBI forms an essential component of the TB elimination strategy. With a higher burden of TB in Hong Kong, this strategy remains an important supplementary measure and a more targeted approach is required.

Targeted Tuberculin Testing

Traditionally, LTBI is identified by tuberculin skin test (TST). In order to minimise the chance of false positive reactions and unnecessary preventive treatment, TST is performed in persons with the highest risk of developing TB, including those presumed to have recent infection or those who are susceptible because of coexisting medical conditions.

(1) Persons with presumed recent TB infection

It refers to those who have recently come into close contact with an infectious source, often within the household settings, and are found to have evidence of LTBI either in the form of TST conversion or a strongly positive TST reaction. The risk of developing active disease is greatest shortly after infection. Previous large scale trials have shown that the risk of developing active TB was 12.9 cases per 1,000 person-years within the first year of TST conversion, as compared to 1.6 cases per 1,000 person-years in following 7 years.[1] In Hong Kong, TST is regularly offered to household contacts aged under 35 of smear-positive index source (Appendix 9).[2] For contacts aged 35 or above, TST and treatment of LTBI may still be considered if there is documented tuberculin conversion after significant exposure or in special circumstances.

(2) Conditions associated with progression to active TB

A number of medical conditions increase the risk of progression from LTBI to active TB.[1] Human immunodeficiency virus (HIV) infection and silicosis are well known examples.[3-5] Rates of progression to TB among HIV-infected TST-positive persons ranged from 12 to 162 per 1,000 person-years of observation,[3] while the incidence of TB among silicotic patients was as high as 9 times that of the local population matched for age and sex.[4] In Hong Kong, targeted screening and treatment of LTBI is also regularly offered to these two groups of patients.[6-8]

In patients with other immunocompromised conditions, the degree of impairment of immunity versus the risk of TB varies with the underlying condition. Treatment of LTBI has to be assessed on a case-by-case basis. The use of immunosuppressive drugs such as systemic steroid or anti-tumor necrosis factor (anti-TNF) greatly escalates the risk of TB.[9-12] Although specific thresholds on dose and duration of corticosteroids that could increase the risk of TB are unknown, in general, the longer the duration and the higher the mean daily dose, the greater the risk.[9] With regard to the anti-TNF therapy in rheumatoid arthritis (RA), the relative risk of TB in infliximab-treated versus non-infliximab-treated RA patients was reported to be as high as 11.7 to 19.9 in a Spanish multicentre study.[12] In view of this potential complication of anti-TNF therapy, a local consensus statement has been published in 2005 on recommendations of screening and treatment of LTBI for patients receiving anti-TNF therapies.[13]

Diagnosis of Latent Tuberculosis Infection

TST with 2 units of purified protein derivative PPD-RT23 (more or less bioequivalent to 5 units of PPD-S adopted in the United States) is used traditionally for the diagnosis. The reaction is read in 48 to 72 hours. An induration of 15 mm or more is used as the cut-off value for recommending treatment of LTBI among recent contacts. For subjects whose initial reaction is below 15 mm, TST will be repeated at 3 months to look for conversion (Appendix 9). For contacts aged below 1 and for HIV-infected patients, a lower cut-off point of 5 mm is used (Appendices 9 and 10). In silicotic patients and patients receiving anti-TNF therapies, the respective value is set at 10 mm (Table 14.1).

Table 14.1. Cut-off values of tuberculin test for diagnosis and treatment of latent tuberculosis infection

Target group	Cut-off value for a positive TST
• Immunocompetent household contacts aged below 1 • HIV infected persons	≥ 5 mm
• Patients with silicosis • Patients receiving anti-TNF therapy	≥ 10 mm
• Immunocompetent household contacts aged 1 to 34	≥ 15 mm

Owing to the following considerations, the cut-off point for household contacts aged 1 to 34 has been set at a relatively high value of 15 mm:

1. Although the recommended cut-off value for recent contacts by the American Thoracic Society (ATS) is 5 mm,[1] the United States Advisory Council for the Elimination of Tuberculosis (ACET) recommended a higher cut-off value of ≥10 mm for TB contacts with history of BCG vaccination.[14]
2. In Hong Kong, neonatal BCG and primary school revaccination programmes have been practised, though the revaccination programme is stopped after the year of 2000.
3. Even in the absence of significant contact history, 20% of children in Hong Kong have a tuberculin response ≥10 mm. However, the absolute risk of disease among them is low. A local study also suggested that the use of 10 mm as a cut-off point for children aged 6 to 9 might have overestimated the annual risk of tuberculosis infection by three-fold.[15]

Acceptance and adherence is often a problem among asymptomatic subjects, unless an excess disease risk can be clearly communicated to them. In general, the larger the size of TST reaction, the more likely it is to indicate true LTBI. In Hong Kong, a cut-off value of ≥15 mm for recommendation of treatment of LTBI appears most cost-effective.

In immunocompromised persons or persons otherwise at risk, a lower cut-off value may be adopted.[1] Caution should be taken in interpretation of TST results in immunosuppressed persons. A higher dose of steroid was found to suppress TST response,[16] and reversion of TST has been shown to occur

in most of the patients taking prednisolone of 40 mg/day after a mean interval of 13.6 days.[17] Therefore, if time allows, it may be better to screen the patients for treatment of LTBI before institution of immunomodulating drugs.[11]

Treatment of LTBI

Rationale of the Treatment of LTBI

In general, the rates of drug resistance mutation range from 10^{-6} to 10^{-10} per cell division. The average mutation rates for isoniazid, rifampicin, streptomycin and ethambutol are 10^{-8}, 10^{-10}, 10^{-8} and 10^{-7} respectively.[18] In a cavitary lesion of active pulmonary TB, the number of tubercle bacilli is around 10^8 to 10^9. In LTBI, the total number of bacilli should be very much smaller. It is also known that the combined resistance rate of new and re-treatment cases to isoniazid is around 5% in Hong Kong.[19] Hence, the use of isoniazid monotherapy should suffice in most of the situations in our locality.

Regimen and Duration

Isoniazid monotherapy is widely adopted throughout the world, largely because of its proven efficacy and safety as demonstrated by previous studies.[6,20-25] In the International Union Against Tuberculosis (IUAT) trial, a daily 52-week regimen of isoniazid was shown to be more effective than a 24-week regimen of isoniazid for preventing TB in persons with fibrotic lung disease.[20] Whereas the former reduced the risk of TB by 75%, the latter only resulted in 65% reduction. However, the 24-week regimen prevented more cases of TB per case of drug-induced hepatitis.[20] Treatment of longer duration, such as up to 2 years, did not confer further benefit.[26,27] In another cost-effective analysis, the cost per case of TB prevented by 6-month isoniazid was shown to be half of that by the 12-month regimen.[28] This may be the reason for the wider adoption of the 6-month regimen. Nevertheless, the protection conferred by 9-month isoniazid is greater than that conferred by 6-month.[29] Hence, 6 to 9 month treatment with isoniazid in immunocompetent persons are reasonable choices.

For patients suffering from silicosis, a local randomized control trial (RCT) showed that chemoprophylaxis with either daily isoniazid for 24 weeks (6H), isoniazid and rifampicin for 12 weeks (3HR) or rifampicin alone for 12 weeks (3R) could half the rate of TB in 5 years.[6] Another recent RCT studying the use of 6H versus 2-month rifampicin and pyrazinamide (2RZ) was stopped prematurely due to a high rate of hepatotoxicity in the 2RZ arm.[7] Currently, after exclusion of active TB, 6H regimen is routinely offered to newly diagnosed silicotic patients who have positive TST but no history of anti-tuberculosis treatment.

In HIV-infected patients, large scale clinical trials have shown that treatment of LTBI in PPD-positive patients were useful in reducing the risk of TB whereas in PPD-negative persons, no such effects were observed.[30,31] Daily isoniazid given for 9 months or up to 12 months is currently recommended by Centres for Disease Control and Prevention (CDC) and the local authority on AIDS respectively.[1,8]

Safety of Isoniazid

The risk of hepatotoxicity with isoniazid was reported to be in the range of 0.5% to 1% in the IUAT trial involving 20,840 subjects[20] and the United States Public Health Service (PHS) multicentre study which included 13,838 persons.[25] The risk was highest in the first 3 months of treatment and increased with age.[20,23-25] In the PHS study, isoniazid-associated hepatitis occurred in 0.3% of those aged from 20 to 34, 1.2% from 35 to 49 and 2.3% from 50 to 64, but 0% of those aged under 20. In addition, daily alcohol consumption is also an important risk factor.[25]

With regard to the possible deaths resulting from isoniazid-associated hepatitis, a rate as high as 5.8 per 10,000 persons was reported in the PHS study.[25] However, subsequent analysis showed that cirrhosis might have been a confounding factor and further surveys conducted in 1970s to 1980s suggested the mortality rate to be in the range of 1.4 to 2.3 per 10,000.[32] With close clinical monitoring of patients since 1990s, isoniazid-associated deaths were further minimised.[23]

Short-course Regimen

Adherence is always a potential problem in the treatment of LTBI when the benefit cannot be easily perceived. Despite earlier favourable reports on the use of a shorter regimen of 2RZ in the treatment of LTBI among the HIV-infected PPD-positive persons,[31,33,34] such regimen was associated with a high incidence of hepatotoxicity in immunocompetent subjects and the local silicotic patients.[7,35-37] Among 7,737 subjects taking RZ-chemoprophylaxis from January 2000 to June 2002 in the United States, 7 fatal cases were reported (9 per 10,000) and hepatotoxicity occurred in 4.5% of subjects.[37] These rates of major side-effects are unacceptable for a prophylactic therapy. Hence, the updated statement from ATS and CDC recommended that this regimen should generally not be offered to persons with LTBI.[37]

Contacts of Index Cases with Drug-resistant Tuberculosis

For contacts of index cases with known isoniazid-resistant TB, rifampicin alone for 4 months may be an acceptable alternative.[1,6] For contacts of patients with multi-drug resistant TB (resistant to both isoniazid and rifampicin), solid data and consensus are still lacking. If treatment of LTBI is deemed necessary, a drug regimen based on susceptibility results of the index patient may be considered after balancing the potential risks and benefits.

Conclusions

Treatment of LTBI has been described in some targeted groups. There are likely to be many other different scenarios with diverse risk factors, where data are lacking. The general principles on work practice for treatment of LTBI is summarised in Table 14.2. With the limitations in currently available diagnostic and treatment tools, the decision to screen and treat LTBI has to be based on a careful balance of multiple factors like potential benefits, patient acceptance, and side effects. Continuous evaluation will provide more information on the cost-effectiveness and necessity of updating the practice. Hopefully, new diagnostic tests like antigen-specific T cell-based assays, new drugs or drug regimens which are shorter and safer may help to overcome these problems in future.

Table 14.2. Work practice for treatment of latent tuberculosis infection

- Initial clinical evaluation and diagnosis of LTBI
  - Use of TST and definition of positivity (cut-off value depends on risk level and purpose)
  - In Hong Kong: 2TU of PPD-RT23
    - 15 mm in the general population
    - 10 mm in the silicotic patients and patients receiving anti-TNF therapy
    - 5 mm in the HIV+ve patients or infants aged below 1
- Before treatment of LTBI
  - Clients who have history of past treatment for TB or LTBI are generally not candidates to be evaluated for further treatment of LTBI
  - Rule out active TB
  - Discuss with client the pros and cons
  - Choose regimen: drug tolerance, index case INH-resistance, duration
- During treatment
  - monitor for side effects of drugs, adherence, and possible development of active TB
- Stop treatment when
  - treatment completed
  - poor adherence
  - development of adverse reactions
  - development of active TB

References

1. American Thoracic Society and Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161(4 Pt 2):S221-47.
2. Tuberculosis and Chest Service, Department of Health of HKSAR 2005: Guidelines on tuberculin testing and treatment of latent TB infection among immunocompetent household contacts of smear-positive pulmonary tuberculosis patients in Hong Kong. Available at http://www.info.gov.hk/tb_chest.
3. Cohn DL, El-Sadr WM. Treatment of latent tuberculosis infection. In: Tuberculosis - A comprehensive international approach, 2nd ed. Reichman LB, Hershfield E (ed). Marcel Dekker, New York 2000, pp471-502.
4. Chang KC, Leung CC, Tam CM. Tuberculosis risk factors in a silicotic cohort in Hong Kong. Int J Tuberc Lung Dis. 2001;5:177-84.
5. Westerholm P, Ahlmark A, Maasing R, Segelberg I. Silicosis and risk of lung cancer or lung tuberculosis: a cohort study. Environ Res 1986;41:339-50.
6. Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. A double-blind placebo-controlled clinical trial of three anti-tuberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992;145:36-41.
7. Leung CC, Law WS, Chang KC et al. Initial experience of a randomized controlled trial on the treatment of latent tuberculosis infection among silicotic subjects in Hong Kong: two months of rifampin and pyrazinamide versus six months of isoniazid. Chest 2003;124:2112-8.
8. Scientific Committee on AIDS of Hong Kong Advisory Council on AIDS. 2002: Recommendations on the treatment of latent TB infection in HIV-positive persons in Hong Kong. Available at http://www.info.gov.hk/aids.
9. Kim HA, Yoo CD, Baek HJ et al. Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population. Clin Exp Rheumatol. 1998;16:9-13.
10. Agrawal PN, Gupta D, Aggarwal AN, Behera D. Incidence of tuberculosis among patients receiving treatment with oral corticosteroids. J Assoc Physicians India 2000;48:881-4.
11. Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha--California, 2002-2003. MMWR 2004;53:683-6.
12. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD; BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003;48:2122-7.
13. Mok CC. Consensus statements on the indications and monitoring of anti-tumor necrosis factor (TNF) therapy for rheumatic diseases in Hong Kong. HK Bull Rheumat Dis 2005;5:1-7.
14. Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement. MMWR 1996;45(RR-4):1-18.
15. Leung CC, Yew WW, Tam CM et al. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. Thorax 2005;60:124-9.
16. Schatz M, Patterson R, Kloner R, Falk J. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med 1976;84:261-5.
17. Bovornkitti S, Kangsadai P, Sathirapat P, Oonsombatti P. Reversion and reconversion rate of tuberculin skin test reactions in correlation with use of prednisone. Dis Chest 1960;38:51-5.
18. David HL. Probability distribution of drug resistant mutants in unselected populations of Mycobacterium tuberculosis. Applied Microbiology 1970;20:810-4.
19. Hong Kong Tuberculosis and Chest Service, Department of Health. Annual report of Tuberculosis and Chest Service 2003; Part I: Appendix 19.
20. International Union Against Tuberculosis, Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis. Bull World Health Organ 1982;60:555–64.
21. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993;342:268-72.
22. Whalen CC, Johnson JL, Okwera A et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med 1997;337:801-8.
23. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy. JAMA 1999;281:1014-8.
24. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med 2003;168:443-7.
25. Kopanoff DE, Snider DE, Caras GJ. Isoniazid-related hepatitis: A US Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978 ;117:991-1001.
26. Falk A, Fuchs GF. Prophylaxis with isoniazid in inactive tuberculosis. A Veterans Administration Cooperation Study XII. Chest 1978;73:44-8.
27. Comstock GW, Baum C, Snider DE. Isoniazid prophylaxis against Alaskan Eskimos: a final report of the Bethel Isoniazid Studies. Am Rev Respir Dis 1979;119:827-30.
28. Snider DE, Carasn GJ, Koplan JP. Preventive therapy with isoniazid: cost-effectiveness of different durations of therapy. JAMA 1986;255:1579-83.
29. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis 1999;3:847-50.
30. Whalen CC, Johnson JL, Okwera A et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med 1997;337:801-8.

31. Mwinga AG, Hosp M, Godfrey-Faussett P et al. Twice-weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS 1998:12:2447-57.
32. Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494-7.
33. Halsey NA, Coberly JS, Desormeaux J et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet 1998;351:786–792.
34. Gordin F, Chaisson RE, Matts JP et al. Rifampicin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. JAMA 2000;283:1445–50.
35. Jasmer RM, SaukkonenJJ, Blumberg HM et al. Short-course rifampicin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 2002;137:640-47.
36. Stout JE, Engemann JJ, Cheng AC, Fortenberry ER, Hamilton CD. Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. Am J Respir Crit Care Med 2003;167:824-7.
37. Centers for Disease Control. Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection. MMWR 2003;52:735-9.

CHAPTER 15

BCG (BACILLE CALMETTE-GUÉRIN) VACCINATION

ECC Leung, CC Leung, SL Chan

Summary points:

1. BCG (bacille Calmette-Guérin) is a live attenuated vaccine derived from Mycobacterium Bovis and is given as an intradermal injection.
2. Different sub-strains of BCG are available worldwide. Their efficacies differ due to genetic drift with time.
3. BCG is effective in preventing miliary tuberculosis and tuberculous meningitis in children with efficacy of 75% to 86%.
4. BCG protection against adult pulmonary tuberculosis is controversial among different studies, ranging from 0% to 80%.
5. Booster dose of BCG vaccines has no proven additional protective effect and is not recommended by WHO.
6. The Advisory Committee on Immunisation of the Department of Health in Hong Kong has recommended that:
   - BCG vaccination to be given to all newborn babies in Hong Kong;
   - For children under age 15 and residing in Hong Kong, and who have never had BCG vaccination before, direct BCG vaccination is recommended and prior tuberculin test is not required;
   - Local BCG revaccination programme for primary school children in Hong Kong was stopped in 2000.
7. Local reactions to BCG vaccines include superficial scar in most recipients, rarely ulceration and regional lymph node enlargement. Disseminated infection is rare and only occurs in patients with impaired immunity.
8. According to WHO, the only contraindications to BCG vaccination are symptomatic HIV infection (i.e. AIDS) and pregnancy.

History of BCG

BCG (bacille Calmette-Guérin) is one of the oldest and most controversial vaccines in the world. In 1908, the French investigators Calmette and Guérin worked on a virulent strain of mycobacterium isolated from a cow with tuberculous mastitis. They added beef bile to diminish the virulence of bovine bacillus (thus the original name of "Bilieux de Calmette et Guérin"[1]). After 13 years and 230 subcultures, the organism used in this vaccine was finally obtained. It was given to human volunteers as an oral vaccine in 1921.

The original BCG strain was lost during the German occupation of Northern French during World War I.[2] From the original strain, hundreds of 'daughter' strains were produced in different laboratories. Because of differences in subculture methods of each individual laboratory, and the natural occurrence of spontaneous mutations, the daughter BCG strains differed markedly from one another. Among currently available strains, there is heterogeneity in colony morphology (spreading vs non-spreading), biochemical composition,[3] drug resistance, immunogenicity (in animals and humans),[4] and virulence (in animals).

Nowadays, four main strains account for more than 90% of the vaccines currently in use worldwide: the French Pasteur strain 1173P2, the Danish (Copenhagen) strain 1131, Glaxo strain 1077 and Tokyo strain 172. The Pasteur strain currently serves as the international reference strain of vaccine.[5]

Despite World Health Organisation's (WHO's) attempt to standardise vaccine production, there are still considerable variations in their characteristics as well as numbers and proportions of viable and

dead organisms per dose of vaccine. According to animal studies on immunogenicity, some vaccines are labelled as consisting of "strong" strains (Pasteur 1173P2 and Danish 1331), whereas others are "weak" strains (Glaxo strain 1077 and Tokyo 172).[6] However, no study has clearly demonstrated superiority of one strain over another in the protection against tuberculosis (TB).

BCG Vaccination Policies

BCG vaccination schedules vary greatly between countries. This can be broadly classified into four groups[7]:

1. BCG vaccination only at birth: This is the currently recommended schedule of the WHO Expanded Programme of Immunisation (EPI), and is the policy practised in most of the world today, including Hong Kong. BCG was incorporated into the WHO/EPI in 1974.
2. BCG vaccination once in childhood or adolescent: For example, BCG is given to tuberculin negative adolescents in the United Kingdom. (However, this universal BCG vaccination programme delivered through schools has been replaced with an improved programme of targeted vaccination for those individuals who are at greatest risk, starting from July 2005.[8])
3. Repeated/ booster BCG vaccination: This is carried out in some European countries (e.g. Switzerland, Portugal), with BCG vaccination in infancy and then at school entry or leaving.
4. No routine BCG vaccination: The United States and the Netherlands do not recommend routine universal use of BCG. The vaccine is considered only for selective use among high risk individuals (e.g. household contacts and immigrants).

Some countries have shifted from routine BCG use to selective BCG vaccination in view of their declining TB rate and consequential reduction of the cost-effectiveness of the BCG vaccination programme. The International Union Against Tuberculosis and Lung Disease[9] (IUATLD) has suggested criteria upon which it is reasonable for a country to shift away from routine BCG use:

1. an efficient notification system is in place and
2. either
    a. the average annual notification rate of smear-positive pulmonary TB is less than 5 per 100,000, or
    b. the average annual notification rate of tuberculous meningitis in children under five years of age is less than 1 per 10 million population over the previous five years, or
    c. The average annual risk of tuberculous infection is less than 0.1%.

Hong Kong Situation

The first record of BCG vaccination in Hong Kong was in September 1950.[10] In 2000, the Advisory Committee on Immunisation in the Department of Health in Hong Kong recommended the following practice[11]:

1. BCG vaccination for all newborn babies in Hong Kong.
2. For children under age 15 and residing in Hong Kong, and who have never had BCG vaccination before, direct BCG vaccination is recommended and prior tuberculin testing is not required.
3. Local BCG revaccination programme for primary school children was stopped in the year 2000.

In Hong Kong, newborns are vaccinated with BCG free of charge, the vaccine being provided by Department of Health. In turn, statistics are provided to DH on coverage of BCG vaccination in newborns. Usually, BCG is given intradermally at the insertion of deltoid on the left arm (to facilitate searching of BCG scar later in life).Currently, the neonatal BCG vaccination coverage rate in Hong Kong is above 99%.[12] (Fig 15.1)

Vaccine Efficacy

There has not been a vaccine that produced so much argument about its efficacy than BCG. The effectiveness of BCG vaccine ranges from 0% up to 80%[13] of protection down to negative 56%.[14] (See Fig 15.2). Several mechanisms have been proposed for such extra-ordinary variability, though there is no universally accepted explanation:

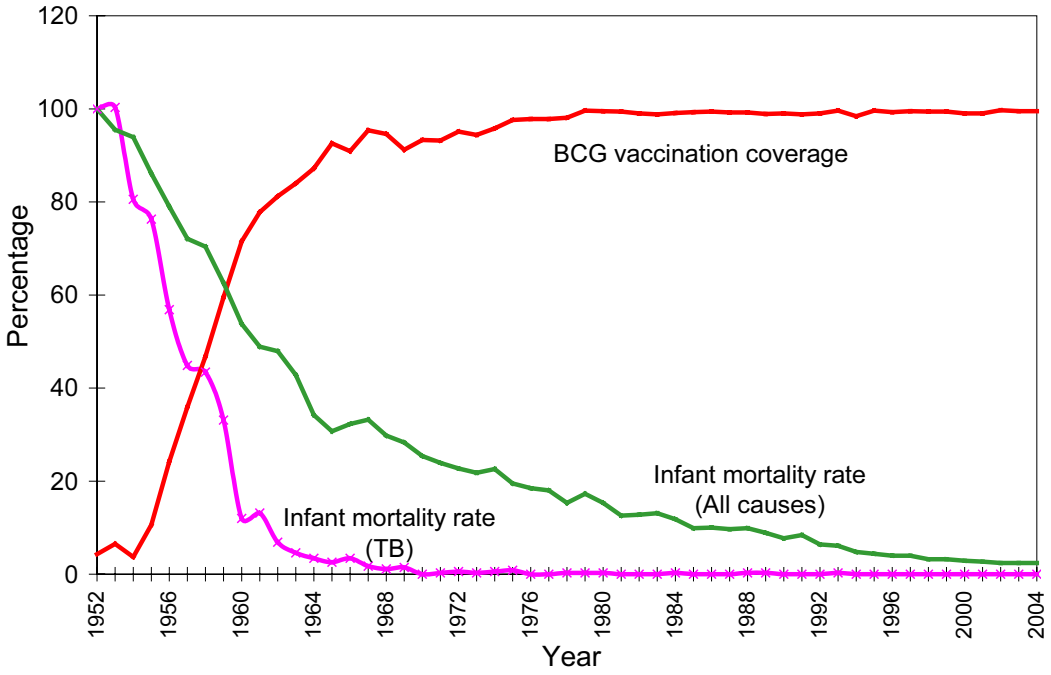


Figure 15.1. Neonatal BCG vaccination coverage

1. Environmental mycobacteria

Prior infection with environmental non-tuberculous mycobacteria could confer some protection against active TB.[15] The efficacy of BCG vaccine tends to be lower in population settings in warmer and wetter regions (close to equator) and presumably with a wide prevalence of environmental non-tuberculous mycobacteria.[16] Natural infection with these mycobacteria may provide protection against TB and will mask the effect of BCG vaccination by decreasing the susceptibility of the unvaccinated group, thereby, decreasing the protective effects in the vaccinated group. A review by Colditz and Wilson[17] estimated that latitude could account for 41% of the variance among the different studies.

2. Difference between BCG vaccines

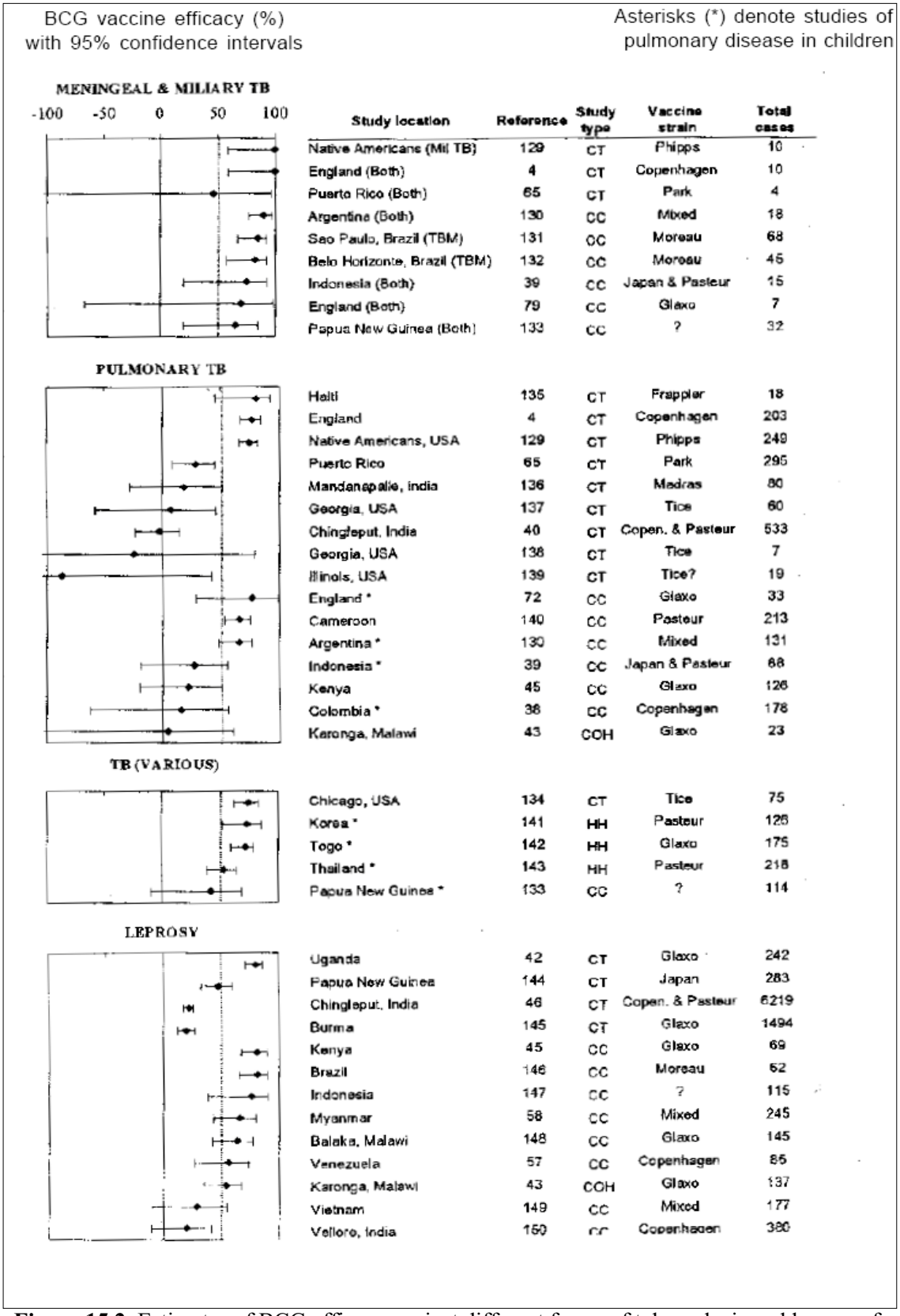
As stated above, difference in the potency and immunogenicity of individual vaccine strains may contribute to the variability of vaccine efficacy. However, a review of BCG efficacy data for different BCG strains showed little evidence to suggest that the strain used for vaccination was a significant factor in the overall effectiveness against TB.[18]

3. Host factor

The immune response to BCG is partly regulated by genes on chromosome 2.[19] It has been proposed that population genetic differences might explain the varying vaccine efficacy. Slightly higher protection against TB was observed among Blacks as compared with white in the USPHS trials.[20] However, appreciable protection against TB was observed among Asians with BCG in England[21] despite the absence of protection found in South India.[22] Therefore, the evidences for such an explanation are conflicting.

Despite all these controversies, currently available evidences support that BCG is efficacious in protecting against TB in children, in particular against tuberculous meningitis and miliary disease. The results of relevant meta-analyses are summarised in Table 15.1.[23-26]

WHO has estimated that a case of childhood TB is prevented by every 1,300 to 2,600 infant vaccinations, at a cost of US$0.1 to 0.2 per dose.[27] The 100 million doses given around the world each year prevent an estimated 50,000 cases of severe disease, including 25,000 to 40,000 cases of tuberculous meningitis, in children.[27,28]



Study location	Reference	Study type	Vaccine strain	Total cases
MENINGEAL & MILIARY TB				
Native Americans (Mil TB)	129	CT	Phipps	10
England (Both)	4	CT	Copenhagen	10
Puerto Rico (Both)	65	CT	Park	4
Argentina (Both)	130	CC	Mixed	18
Sao Paulo, Brazil (TBM)	131	CC	Moreau	68
Belo Horizonte, Brazil (TBM)	132	CC	Moreau	46
Indonesia (Both)	39	CC	Japan & Pasteur	15
England (Both)	79	CC	Glaxo	7
Papua New Guinea (Both)	133	CC	?	32
PULMONARY TB				
Haiti	135	CT	Frappier	18
England	4	CT	Copenhagen	203
Native Americans, USA	129	CT	Phipps	249
Puerto Rico	65	CT	Park	295
Mandanapalle, India	136	CT	Madras	80
Georgia, USA	137	CT	Tice	60
Chingleput, India	40	CT	Copen. & Pasteur	533
Georgia, USA	138	CT	Tice	7
Illinois, USA	139	CT	Tice?	19
England *	72	CC	Glaxo	33
Cameroon	140	CC	Pasteur	213
Argentina *	130	CC	Mixed	131
Indonesia *	39	CC	Japan & Pasteur	68
Kenya	45	CC	Glaxo	126
Colombia *	38	CC	Copenhagen	178
Karonga, Malawi	43	COH	Glaxo	23
TB (VARIOUS)				
Chicago, USA	134	CT	Tice	75
Korea *	141	HH	Pasteur	126
Togo *	142	HH	Glaxo	175
Thailand *	143	HH	Pasteur	218
Papua New Guinea *	133	CC	?	114
LEPROSY				
Uganda	42	CT	Glaxo	242
Papua New Guinea	144	CT	Japan	283
Chingleput, India	46	CT	Copen. & Pasteur	6219
Burma	145	CT	Glaxo	1494
Kenya	45	CC	Glaxo	69
Brazil	146	CC	Moreau	52
Indonesia	147	CC	?	115
Myanmar	58	CC	Mixed	245
Balaka, Malawi	148	CC	Glaxo	145
Venezuela	57	CC	Copenhagen	85
Karonga, Malawi	43	COH	Glaxo	137
Vietnam	149	CC	Mixed	177
Vellore, India	150	CC	Copenhagen	380

Figure 15.2. Estimates of BCG efficacy against different forms of tuberculosis and leprosy, from clinical trials (CT), case control (CC), cohort (COH) and household contact studies (HH). *Reproduced with permission from WHO*[7]

Table 15.1. Results of meta-analyses on BCG efficacy

Target disease	Efficacy (95% CI)	Remarks	Reference
TB at all sites	74% (62-83%)	4 RCTs in newborns and infants	23
TB at all sites	52% (38-64%)	9 Case control studies in newborns and infants	23
Death	65% (12-86%)	5 RCTs in newborns and infants	23
Meningeal TB	64% (30-82%)	5 Case control studies in newborns and infants	23
Disseminated TB	78% (58-88%)	3 Case control studies in newborns and infants	23
Laboratory confirmed TB	83% (58-93%)	3 Case control studies in newborns and infants	23
Meningeal TB and disseminated TB	86% (65-95%)	All ages, 7 RCTs	24
Disseminated TB	75% (61-84%)	All ages, 6 case control studies	24
Overall TB risk	51% (30-66%)	All ages	25,26
Overall TB death	71% (47-84%)	All ages	25,26

Note: RCT = randomised controlled trial

Duration of Protection

Besides the continuing debate over efficacy, there is also uncertainty over the duration of protection. A meta-analysis in 1998 showed that the efficacy of BCG does wane with time, and probably lasts no longer than 15 years.[29] However in a recent 50-years follow up study among American Indians,[30] the vaccine efficacy was shown to be 52%. There was slight, but statistically insignificant, waning of the efficacy of BCG vaccination over time, greater among men than women.

Booster Dose/ Revaccination

A large study in Malawi showed that booster dose of BCG did not protect against pulmonary TB (RR: 1.43; 95% CI = 0.88-2.35).[31] Another study in Hong Kong showed that revaccination of school children did not confer further protection against TB (RR: 1.28; 95% CI = 0.92-1.77).[32] A study in Finland also showed similar results.[33] WHO does not recommend the practice of BCG revaccination.[34]

BCG Vaccination among Health Care Workers

Some studies suggested that BCG vaccination is effective in reducing the incidence of TB among health care workers (HCW). In a decision analysis to determine the optimal strategy to prevent TB in HCW with a negative tuberculin test,[35] BCG vaccination was compared with annual tuberculin skin testing (TST) (positive reactors with treatment given for LTBI) in TST negative HCW. The outcome measures were the number of cases and deaths from TB and BCG and/or isoniazid adverse reactions over ten years. They found that annual TST (plus LTBI treatment) decreased the number of TB cases by 9% and BCG vaccination decreased the number by 49% relative to no preventive intervention. This was based on a number of assumptions, including a workplace incidence of TB infection greater than 0.06% per year. The study concluded that BCG was an imperfect vaccine, but it was "less imperfect" when compared to annual TST and isoniazid chemoprophylaxis in protecting HCW from TB. Another decision analysis on the use of BCG in HCW exposed to multidrug-resistant TB (MDR-TB) reached a similar conclusion.[36]

However, in a review by Brewer et al,[37] it was stated that the studies of BCG in HCWs had too many methodological flaws for a quantitative meta-analysis to be done and an overall BCG efficacy to be calculated.

The CDC paper in 1997[38] recommended that BCG for HCW should be considered on an individual basis in health care settings where:

1. there is a high percentage of patients with MDR-TB;

2. transmission of such strain of resistant TB to HCW is likely;
3. comprehensive TB infection control precautions have been implemented and not successful.

In Hong Kong, documentation of TB outbreaks in the health care settings is not common. The annual reported number of TB infection in HCW ranged from 29 to 57 between 1998 and 2004 and the estimated rate is not high as compared to that of the general population.[12] A high background TB prevalence and selective social factors may be some of the reasons for this observed phenomenon. Under-reporting may contribute, but the Occupational Safety and Health Ordinance of 1997 mandates reporting and provides channel for compensation.

In Hong Kong, the bulk of the population has received BCG vaccination at some point in time. In health care settings, a comprehensive infection control programme should be the priority and routine vaccination of HCW is not recommended. Nevertheless, for HCW who have never received BCG before, they should be counselled on the risks and benefits associated with BCG vaccination, as well as the possible roles of tuberculin surveillance and treatment of LTBI. Under special high risk circumstances, e.g., situations with a high risk of exposure to MDR-TB, BCG may be considered for previously unvaccinated individuals who are tuberculin tested to be negative and are thus likely to be free of past TB infection.[39,40]

Administration

BCG vaccine was first given through oral route in 1921.[41] It was later replaced by intradermal or percutaneous route for the following reasons:

1. Oral vaccine requires a much higher dose (10-300 versus 0.1 mg) of BCG than intradermal injection, and is thus more expensive.
2. The effective oral dose is difficult to control as some mycobacteria are inactivated by the acidic gastric environment.
3. Intradermal method proves more effective in inducing tuberculin reaction.
4. There have been reports of cervical lymphadenopathy and middle ear infection attributed to oral administration of BCG vaccine.

Subcutaneous injection is generally avoided as it may produce large abscesses.

The percutaneous method is described as follows:

The baby's left arm was held and one drop of the vaccine was placed on the left upper arm at the deltoid region, using a glass rod. The vaccine was spread over an area of about 6 cm^2, using a heat-sterilised number 3 straight suture needle. The point of the needle was then pressed and lifted away taking with it a small portion of the epidermis. This was repeated 20 times, in 4 rows of 5 punctures. The vaccine was allowed to dry on the arm without dressing.

The percutaneous method was used in the older days when it could be given by health care workers in some maternity centres with lesser degree of technical difficulty than the intradermal method, as the newborn's skin is generally rather thin. This method is seldom used nowadays as the dose delivered is usually less predictable than the intradermal method. Another percutaneous method delivering the vaccine through a modified Heaf gun was not used in Hong Kong.[42]

In Hong Kong, the current practice of BCG administration is intradermal injection. This is due to the particular strain used (Danish 1331) which is recommended for intradermal injection only.[43] The intradermal method is described as follows[44]:

1. Stretch the skin taut, hold the syringe parallel to (almost resting on) the skin surface, insert the needle, bevel up, under the first one or two layers of skin. (Tip of the needle would be visible just below the surface of the skin.).
2. Slowly inject the content of the syringe. A slight resistance would be felt.
3. A firm, white round wheal, about 6 mm diameter, should appear at the injection site immediately.

For intradermal injection, the recommended dose is 0.05 ml for infant below one year of age and 0.1 ml for those above age of one.

Side Effects

BCG is considered to be one of the safest vaccines available. Side effects are uncommon, apart from minor reactions or complications at the vaccination sites.

Vaccination Site

Following intradermal administration, an indurated papule appears within 2 to 3 weeks. A pustule develops in 6 to 8 weeks and heals by 3 months, leaving a scar at the vaccination site. This indicates tissue infection or an allergic reaction to the vaccinating material has probably occurred. There is no evidence that presence of BCG scar correlates with development of body immunity.[45]

In a local study in relation to complications resulting from BCG vaccination,[46] among 2,475 vaccinations given to primary schoolchildren during a two-week period in December 1990, the injection site was inspected at 3 to 4 weeks after the vaccination. The results were: 1.4 % had induration, 82.7% had scab formation, 3.0% had ulcer formation, and 1.8% had pustule formation. Among the 119 with ulcer or pustule formation, 63 had mismanaged the vaccination site. Further follow-up of these 119 students at week 8 showed that the vast majority of lesions had healed either with induration or scab formation (111 healed, 2 still had a healing ulcer, 2 with pustules, 4 could not be contacted).

BCG given to areas near the acromion process has been reported to have a higher chance of ugly keloid formation.[47] Hence, it is recommended that BCG should be given at the insertion of deltoid muscle.

The current recommendation in Hong Kong for the care of the BCG injection site is[44]:

1. The vaccination site should be kept clean and dry. If necessary, it can be cleansed with distilled water and dried up with gauge afterwards. Bath should be taken as usual.
2. No medication or ointment should be applied to the vaccination site. The site should not be covered with adhesive plaster or dressing. Tight clothing should be avoided.

Lymphadenitis

A prospective study of two million vaccinations between 1979 and 1981 estimated the risk of lymphadenitis to be 0.387 per 1,000 for infant (below 1 year of age) vaccinees and 0.025 per 1,000 for 1 to 20-year-old vaccinees.[48] Among 6,000 reported cases of regional lymphadenitis, the majority occurred within the first 5 months after vaccination.[49] *M. Bovis* was cultured from 7% of cases. Factors that are found to contribute to regional lymphadenitis include:

1. vaccine strain (outbreak of lymphadenitis in 1988 was due to a switch from the less reactogenic Glaxo to the more reactogenic Pasteur strain in some countries[50,51]);
2. total number of viable and non-viable bacilli in the vaccine preparation;
3. doses of BCG vaccine given;
4. age of person receiving the vaccine.

In a comparative study between the Glaxo and Pasteur strain of the BCG vaccine in Hong Kong in 1982-86, the Pasteur strain caused more lymphadenopathy than the Glaxo strain.[52,53] The BCG currently used in Hong Kong is produced in Denmark by Statens Serum Institute (Danish strain 1331).

There is little consensus on the most appropriate form of treatment. Options range from giving antimicrobial (such as erythromycin or isoniazid) to no treatment. Meta-analysis showed that treatment of BCG adenitis with oral erythromycin or anti-tuberculous drugs does not reduce the frequency of suppuration.[54] Uncomplicated cases generally resolve spontaneously on observation.

Osteitis

Reports of osteitis vary from country to country. Between 1948 and 1974, 291 cases of BCG-related osteitis were reported. It was typically associated with change in BCG vaccine strain. Anti-TB therapy, coupled with surgical debridement, usually results in healing of the skeletal lesion.

Disseminated BCG Disease

Systemic BCGosis is a rare but usually fatal complication of BCG vaccination. A multi-centre study showed that children with severe combined immunodeficiency (SCID), chronic granulomatous disease, Di George syndrome and homozygous complete or partial interferon-γ deficiency[55,56] are at risk of developing this complication. Between 1954 and 1980, 34 cases were reported in the global literature.[57] Treatment of disseminated BCG disease is similar to those of active TB with the exception that pyrazinamide is not used because all bovine strains are resistant to this drug.

BCG and HIV Infection

More than 28 cases of disseminated BCG disease have been reported in HIV-infected children and adults.[58,59] Disseminated disease usually occurs several months to years after vaccination. BCG vaccination is generally contraindicated in children or adults with symptomatic HIV infection (or AIDS).

To date, there are no controlled studies of the safety and efficacy of BCG vaccination in asymptomatic adults or children with HIV. Balancing the risk and benefit, WHO recommends BCG vaccination for asymptomatic HIV-infected children who are at risk of TB infection.[60,61]

Contraindication

BCG is a live organism. It is generally contraindicated in pregnancy. In the WHO/EPI guidelines, the only other major contraindication is symptomatic HIV infection.[62] In the United Kingdom, BCG is also contraindicated for individuals with impaired immunity, malignant condition, positive tuberculin reaction, febrile condition, and generalised septic skin condition.[63]

Protection against Other Diseases

BCG is recognised as an immune modulator and has been used in the treatment of some neoplasms (e.g. bladder cancer). It has also been found to be efficacious in the protection against at least two other mycobacterial infections.

Leprosy

A number of controlled trials and 10 observational studies on BCG have all shown some protection against leprosy, efficacy ranging from 20% to 80%. Comparison within the same population suggests that BCG offers greater protection against leprosy than TB.[64]

Buruli Ulcer

BCG provides some protection against Buruli ulcer (*M. ulcerans* infection) and against glandular disease attributable to other 'environmental' mycobacteria, in particular *M. avium intracellulare*.[65]

New Vaccine Development

Because of the limited and controversial efficacy of BCG, a novel, more effective vaccine is required. The deciphering of the whole genome of *M. tuberculosis*[66] and the significant progress on sequencing that of BCG have helped in development of potentially more effective vaccines.

1. Live attenuated vaccine: By deleting the gene responsible for virulence factors from *M. tuberculosis*, mutant or auxotropic vaccine is under development.[67] The purpose of the auxotropic vaccine is to set up a time-limited infection in the host but still inducing an immune response. Conversely, more effective BCG vaccine can be created by adding a gene to the pre-existing BCG strain to improve its immunogenicity. One of the potential candidates is the rBCG30 vaccine, which is under phase one trial in South Africa in 2004.[68] By knocking out the urease gene and adding lysin gene, another new recombinant BCG was found to have improved immuogenicity against virulent MTB.[69,70]

2. Subunit vaccine: This utilises the immunogenic compound, such as protein, lipid, or carbohydrate, derived from mycobacteria to elicit a host immune response. It was found that vaccinia recombinants expressing *M. tuberculosis* proteins were able to induce antibody response when injected into mice.[71] Data evaluating these vaccines in animal model are forthcoming.

3. DNA vaccine: The gene for a mycobacterial antigen can be inserted into a plasmid, which, when injected into the host, causes RNA transcription and production of foreign protein. Long lasting protection can be achieved with relatively few side effects.[72] Mycobacterial genes for secreted proteins have shown promising results in stimulating T cell production and reducing bacterial load in the lungs of animals challenged with virulent *M. tuberculosis*.[73,74]

Conclusions

BCG is one of the oldest live-attenuated vaccines in the world. It has proven to be effective against disseminated disease in children. However, the protection against adult disease is uncertain. The cost of production of BCG is low and BCG is a vaccine recommended by the WHO/EPI programme. New vaccines are under development. However, because of the long safety track record of BCG, it will likely remain the routine TB vaccine for some time in the foreseeable future.

References

1. C John Clements. Vaccination - the current status of BCG in Mycobacteria and TB; issue in infectious disease, Eds Kaufmann and Hahn, 2003 volume 2:46-66.
2. Lanrange PH. Le bacille bilie de Calmette et Guerin: Bull Inst Pasteur 1984;82:53-65.
3. International Union Against Tuberculosis. Phenotypes of BCG vaccines seed lot strains: results of an International Co-operative study. Tubercle, 59,139,1978.
4. Gheorghiu M, LaGrange PH. Viability, heat stability and immunogenicity of four BCG vaccines prepared from four different BC strains. Ann Immunol 1983;134C:125.
5. Milstein JB, Gibson JJ. Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety. Bull WHO 1990;68:93-108.
6. Smith D, Harding G, Chan J. Potency of 10 BCG vaccines as evaluated by their influence on the bacillaemic phase of experimental airborne tuberculosis in guinea pigs. J Biolo Stand 1979;7:179-197.
7. Fine PEM et al. Issues relating to the use of BCG in immunisation programmes – a discussion document. WHO/V&B/99.23;1999:1-42.
8. Smith J. Changes to the BCG vaccination programme (letter dated 6 July 2005). Available at http://www.dh.gov.uk. Accessed on 1.October 2005.
9. International Union Against Tuberculosis and Lung Disease. Criteria for discontinuation of vaccination programmes using Bacille Calmette Guerin (BCG) in countries with a low prevalence of tuberculosis. Tubercle and Lung Disease 1994;75:179-181.
10. Lee HL. BCG vaccination against tuberculosis. The Bulletin of the Hong Kong Chinese Medical Association, Dec 1950:43-48.
11. Tam CM, Leung CC. Public Health and Epidemiology Bulletin 2000;9:25-27.
12. Annual Report 2003, Tuberculosis & Chest Service, Department of Health, HKSAR.
13. Romanus V: Chilhood tuberculosis in Sweden. Tubercle 1983;64:101-10.
14. Comstock GW, Webster RG. Tuberculosis studies in Muscogee County, Georgia VII: a twenty year evaluation of BCG vaccination in a school population. Am Rev Respir Dis 1969;100:839-45.
15. Palmer CE, Long MW. Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. Am Rev Respir Dis 1966;94:553-68.
16. Fine PEM. Variation in protection by BCG: implication of and for heterogeneous immunity. Lancet 1995;346:1339-45.
17. Colditz GA Wilson ME. Geographic latitude and the efficacy of BCG vaccine. Clin Infect Dis 1995;20:982-991.
18. Brewer TF and Colditz GA. Relationship between BCG strains and the efficacy of BCG vaccine in the prevention of tuberculosis. Clin Infect Dis 1995;20:126.

19. Blackwell JM. Bacterial infections, in Genetics of Resistance to Bacterial and Parasitic Infections Wakelins D and Blackwell JM eds., Taylor and Francis, 1988.
20. Comstock GW, Palmer CE. Long-term results of BCG vaccination in the southern United States. Am Rev Respir Dis 1966;93:171-83.
21. Rodrigues LC, Gill N, Smith PG. BCG vaccination in the first year of life protects children of Indian subcontinent ethnic origin against tuberculosis in England. J Epidemiol Community Health 1991;45:78-80.
22. Tuberculosis Prevention Trial Madras. Trial of BCG vaccines in South India for tuberculosis prevention. Indian J Med Res 1980;72 (Suppl):174.
23. Colditz GA, Berkey CS, Mosteller F, et al. The efficacy of Bacille Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analysis of the published literature. Pediatrics 1995;96:29-35.
24. Rodrigues LC, Diwan VD, Wheeler JG. Protective effect of BCG against tuberculous meningitis and military tuberculosis: a meta analysis . Int J epidemiol 1993;22:1154-8.
25. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. JAMA 1994;271:698-702.
26. Brewer TF. Preventing tuberculosis with bacillus Calmette-Guerin vaccine: a meta-analysis of the literature. Clin Infect Dis. 2000 Sep;31 Suppl 3:S64-7.
27. Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues relating to the use of BCG in immunization programmes. WHO V&B 99.23 1999:1–42.
28. Bourdin Trunz B. Global Impact of BCG Vaccination on Childhood TB Meningitis and Miliary TB. London, England/Geneva, Switzerland: London School of Hygiene & Tropical Medicine/World Health Organization; 2004.
29. Sterne JAC, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination ? Int J Tub Lung Dis 1998;2:200-207.
30. Naomi E A, Mathuram S etal. Long-term Efficacy of BCG Vaccine in American Indians and Alaska Natives A 60-Year Follow-up Study. JAMA 2004;291:2086-91.
31. Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet 1996;348:17-24.
32. Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. Int J Tuber Lung Dis 2001;5:717-723.
33. Tala Heikkila M, Tuominen JE, Tala E. Bacillus Calmette Guerin revaccination questionable with low tuberculosis incidence. Am J Respir Crit Care Med 1998;157:1324-7.
34. WHO. Global Tuberculosis Programme and Global Programme on Vaccines: Statement on BCG revaccination for the prevention of tuberculosis. WHO Wkly Epidem Rec 1995;70:229-36.
35. Marcus AM, Rose DN, Sacks HS, et al. BCG vaccination to prevent tuberculosis in health care workers: A decision analysis. *Prevent Med* 1997;26:201–7.
36. Stevens JP, Daniel TM. Bacille Calmette Guérin immunization of health care workers exposed to multidrug-resistant tuberculosis: a decision analysis. Tuberc Lung Disease 1996;77:315-21.
37. Brewer TF, Colditz GA.Bacille Calmette-Guerin vaccination for the prevention of tuberculosis in health care workers. Clin Infect Dis. 1995;20:136-42.
38. Centers for Disease Control and Prevention. Immunisation of health care workers. MMWR 1997;46:1-42.
39. Tuberculosis & Chest Service of Department of Health, Hong Kong. Guidelines on tuberculin testing and treatment of latent TB infection among immunocompetent household contacts of smear-positive pulmonary tuberculosis patients in Hong Kong 2004. Available at http://www.info.gov.hk/tb_chest. Accessed on 12.5.2004.
40. Hospital Authority. Control of transmission of tuberculosis in the health care settings in the Hospital Authority. Jan 2002.
41. Weil-Halle B: Oral vaccination: in Rosenthat SR (ed): BCG vaccine: Tuberculosis-Cancer. Littleton/Mass, PSG publishing, 1980;165-70.
42. Cundall DB, Ashelford DJ, Pearson SB. BCG immunisation of infants by percutaneous multiple puncture. BMJ 1988;297:1173-4.
43. Drug insert BCG Vaccine SSI from Statens Serum institute.
44. TB & Chest Service, Department of Health, HKSAR. Nursing Manual 2004.
45. Hart PD, Sutherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in tuberculin sensitivity and to technical variations in the vaccines. Tubercle 1967;48:201–10.
46. Tam CM Leung CC, Chan SL. Complications of BCG vaccination in primary school children Proceeding of the 2nd Guangdong, Hong Kong and Macau Conference on Preventive Medicine in 1996.
47. Lawerence CM, Summerly ME. Keloid formation after BCG vaccination. BMJ 1982;226:326-7.
48. Lotto A, Wasz-hockert O. Second IUATLD study on complications induced by intradermal BCG vaccination. Bull Int Union Tuberc Lung Dis 1988;93:47-59.
49. Lotto A. BCG complications. Adv Tubercke Res 1984;21:107.
50. Hengster P, Schnapka J etal. Occurrence of suppurative lymphadenitis after a change in BCG vaccine. Archives of Disease in Childhood 1992;67:952-5.
51. Kabra SK Jain Y, Seth MV BCG associated adenitis. Lancet 1993;341:970.
52. ten Dam HG. BCG vaccine and vaccination policy. EPI/GAG/90/WP.8. 1990.
53. Chan SL, Allen G, Pio A et al. Comparison of the efficacy of two strains of BCG vaccine for the prevention of tuberculosis among newborn children in Hong Kong(abstract). Bull Int Union Tubercle 61:36-37.
54. Goraya, JS, Virdi VS. Treatment for BCG adenitis: a meta-analysis. Pediat Infect Dis J 2001;632-4.
55. Jouanguy E, Altare F, Lamhamedi S, et al. Interferon-receptor deficiency in an infant with fatal Bacille Galmette Guerin infection. N Engl J Med 1996;335:1956-61.
56. Casanova JL, Jouanguy E etal; immunological conditions in children with BCG disseminated infection. Lancet 1995;346:581.

57. Lotte A, wasz-Hocket O, et al. A bibliography of the complications of BCG vaccination: A comprehensive list of world literature since the introduction of BCG up to July 1982. Adv Tuberc Res 1984;21:194-215.
58. O'Brien KL, Ruff AJ, Louis MA, et al. Bacillus Calmette Guerin complications in children born to HIV infected women with a review of the literature. Pediatrics 1995;95:414-8.
59. Talbot E, Perkins MD. Disseminated BCG disease after vaccination; case report and review. Clin Infect Dis 1997;24:1139-46.
60. WER. Special programme on AIDS and Expanded Programme on Immunisation. Joint Statement. Consultation on human immuno deficiency virus and routine childhood immunisation. Wkly Epidemiol rec 1987;62:297-9.
61. Clements CJ, von Reyn CF. HIV infection and routine childhood immunisation: a review. Bull WHO 1987;65:905-1.
62. Global Programme for Vaccines and Immunization. Immunization Policy. Geneva: WHO, 1996;1-51.
63. Immunisation against Infectious Disease. London: HMSO, 1996;1-290.
64. Ponnighaus JM, Fine PEM, Sterne JAC, et al. Efficacy of BCG against leprosy and tuberculosis in Northern Malawi. Lancet 1992;339:636-9.
65. Smith PG, Revill WDL, Lukwago E, Rykushin YP. The protective effect of BCG against Mycobacterium ulcerans disease: a controlled trial in an endemic area of Uganda. Trans R Soc Trop Med Hyg 1976;70:449-57.
66. Cole ST, Brosch R, Parkhill J, et al. Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence. Nature 1998; 93: 537–44.
67. Guleria I, Teitelbaum R, etal. Auxotrophic vaccines for tuberculosis. Nature Med 1996;2:334-7.
68. Xavier B. Tuberculosis vaccine trial gets underway. Lancet Infectious Disease 4:10:598.
69. Kaplan G. Rational Vaccine Development – A new trend in tuberculosis control. N Engl J Med 2005;353:1624-5.
70. Grode L, Seiler P, Baumann S, et al. Increased vaccine efficacy against tuberculosis of recombinant Mycobacterium bovis bacille Calmette-Guerin mutants that secrete listeriolysin. J Clin Invest 2005;115:2472-9.
71. Lyon J, Sinos C. expression of Mycobacterium tuberculosis and Mycobacterium leprae proteins by vaccinia virus. Infect. Imm 1990;58:4098.
72. Huygen K et al. DNA vaccines: application to tuberculosis. Int J tuberc and Lung Dis 1998;2:971.
73. Orme I et al. Progress in development of vaccines against tuberculosis. Int J Tuberc Lung Dis 1997;1:95.
74. Lowrie DB Silva CL et al. Protection against tuberculosis by a plasmid DNA vaccine. Vaccine 1997;15:834-838.

Chapter 16

TUBERCULOSIS CONTROL MEASURES IN THE HEALTH CARE SETTINGS

ECC Leung, WW Yew, WH Seto

Summary points:

1. Tuberculosis is an endemic airborne infection. Infection control is of paramount importance in containing its transmission in the health care settings.
2. Tuberculosis in health care worker is a notifiable occupational disease under the Occupational Safety and Health Ordinance (Cap 509), as well as a compensable occupational disease under the Employees' Compensation Ordinance (Cap 282).
3. Infection control can be broadly divided into administrative controls, engineering controls and personal controls.
4. Administrative controls include efforts for early diagnosis and policies to ensure rapid respiratory isolation and prompt treatment.
5. Engineering controls include room ventilation, use of high efficiency particulate air (HEPA) filtration unit and ultraviolet (UV) germicidal irradiation. The priority lies in ventilation design, while the other two are recommended as supplementary measures.
6. Personal controls include the use of respiratory protective devices, BCG (bacille Calmette–Guérin) vaccination, tuberculin skin testing and preventive therapy with isoniazid.

Introduction

Tuberculosis (TB) is a common infectious disease in Hong Kong. Currently, there are around 6,000 active cases notified each year and over 80% affect the lungs.[1] The airborne route of transmission, as well illustrated by the classical Wells-Riley experiment[2,3] has important implications in its control, especially in health care settings with selective concentration of infectious patients.

In several TB outbreaks, environmental parameters alongside contact evaluation could be documented, thus permitting estimation of the infectivity of TB through airborne transmission. Since the number of infectious nuclei required to infect a person is generally unknown, Wells defined a "quantum" of infection as a unit infectious dose, which comprised one or more infectious particles.[4] (See also Chapter 3.) The estimated dissemination rates and concentrations of infectious particles vary greatly in different clinical scenarios (Table 16.1).[2-7] The bronchoscopy suite and autopsy room are at relatively higher risk when compared with TB wards. Thus, different levels of protection are warranted. On the other hand, the dissemination rate in quanta per hour for measles is much higher. Such observations are in line with local experiences, that TB is generally not as infectious as other airborne infectious diseases like chickenpox or measles. In general, exposure for some duration is usually needed before infection takes place, and clinical disease develops only among a minority of those infected. However, a prudent approach should be adopted as recent epidemiological studies using molecular techniques do show that transmission can also occur during casual contact, particularly when a susceptible individual is in close proximity with a highly infectious source.[8,9]

TB in health care workers (HCW) has been included as one of the notifiable occupational diseases under the Occupational Health and Safety Ordinance (Cap 509) (Appendix 2) in Hong Kong since 1997. All cases of occupational TB should be dually notified to the Director of Health and the Commissioner for Labour. (For further information, please refer to Chapter 2 on tuberculosis surveillance.) Patients with occupational TB are entitled for compensation under the Employees' Compensation Ordinance (Cap 282). (Appendix 3) The number of reported TB cases among HCW ranged from 29 to 57 per year from 1998 through 2004 (Table 16.2).[10] Despite some uncertainty about the denominator, it may be reassuring to note that their estimated age-adjusted TB rate is not higher than that of the general population.

Table 16.1. Estimated dissemination rates and concentrations of infectious particles (tuberculosis and measles) in different clinical scenarios

Setting	Study	Dissemination rate (quanta/ hr)	1/Concentration (cubic ft/quanta)
TB wards (long stay)	Riley 1961[2]	N/A	24,000
TB ward (newly treated patient)	Riley 1962[3]	1.25	11,000-12,500
Cavitary TB in poorly ventilated building	Nardell 1991[5]	13	N/A
Laryngeal TB	Riley 1962[3]	60	200
Bronchoscopy	Catanzaro 1982[6]	250	69
Autopsy	Templeton 1995[7]	N/A	3.5
Measles outbreak at school	Riley 1978[4]	Index case: 5,500 Secondary case: 500	N/A

N/A = not available

Table 16.2. Number of reported cases of tuberculosis in health care workers (1997 – 2004)[10]

Year	Number
1997	10
1998	39
1999	57
2000	39
2001	41
2002	29
2003	30
2004	42

Hierarchy of Controls

Nonetheless, it is essential to control the nosocomial transmission of TB for the protection of both HCW and co-hospitalised patients. This is best achieved by a variety of measures - the so-called hierarchy of administrative, engineering and personal controls as outlined in CDC (Centres for Disease Control and Prevention, United States) 1994 and 2003 guidelines.[11,12]

1. **Administrative controls** include efforts to minimise delay in diagnosis, as well as implementation of policies for prompt and appropriate use of respiratory isolation for suspected TB patients, the tracing of close contacts (especially for smear-positive index cases), and surveillance of TB among HCW.

2. **Engineering controls** include ventilation design, use of HEPA (high efficiency particulate air) filter and UV (ultraviolet) light.

3. **Personal controls** include masks and personal respirators, BCG (bacille Calmette-Guérin) vaccination, tuberculin skin testing and preventive therapy with anti-tuberculosis agents.

As for other occupational safety measures, effective implementation is a critical element for success. For engineering and personal controls, the extent of application is often limited in the actual field situations by factors such as capital/ recurrent costs, building designs/ constraints and/ or staff comfort/ compliance throughout a working day. In this regard, administrative controls usually take precedence over engineering controls and the latter over personal controls. Many of the

recommendations by overseas authorities are based on expert opinions specific for their local circumstances rather than solid evidences which can be generalised to other settings. It has been estimated that to fully comply with the CDC guidelines targeted primarily for United States, the cost implication can be tremendous in other areas with differing epidemiology,[13] and there are practical and logistic issues, which may be difficult to overcome. A sensible balance is therefore needed in tailoring such measures to the local situation, and at the same time avoiding over-restrictive applications of these precautions.

Administrative Controls

It is desirable that health care facilities should have an infection control programme covering TB. Mechanisms should be in place for developing, implementing, reviewing and evaluating the programme. The key issue is prompt recognition of TB patients with early diagnosis, isolation as well as prompt initiation of chemotherapy. Constant awareness and a high index of suspicion on the part of the clinicians is essential.

Infectivity of TB Patient

The infectivity of a pulmonary TB patient rests on the smear status. Various studies[14-16] have shown that this risk correlates with index case smear-positivity. The infectivity of pulmonary TB patients is greatly reduced by effective treatment through two mechanisms:

1. Reduction in bacillary load by hundred- to thousand-fold[17]
2. Reduction in amount of sputum produced and cough frequency[18]

However, particular attention should be paid to special circumstances where the period of infectivity may be prolonged despite treatment, viz

1. high bacillary burden as in the case of extensive or cavitary disease
2. high aerosol generation as in the case of laryngeal TB
3. drug-resistant TB
4. non-adherence to therapy
5. immunocompromised patients because of inherent medical conditions (such as HIV infection, diabetes, renal failure or malnutrition), or treatment with corticosteroid, cytotoxics, or other immuno-suppressive drugs.

There are indeed controversies on the duration of contagiousness of TB patients after they have been started on treatment. In general, smear-negative patients are considered not infectious while smear-positive patients are regarded not significantly infectious after two weeks of effective chemotherapy.[19] However, this view is challenged by some recent research findings. Certain studies have even found that smear-negative patients may be infectious,[20,21] and smear-positive patients may remain infectious for more than two weeks after starting treatment as long as their smear or culture are still positive.[22-24] Thus, it appears that the decision to discontinue isolation has to be considered on a case-by-case basis, and various other factors which will be discussed have to be taken into consideration.

Extra-pulmonary TB patients are generally regarded as non-infectious. However, there are reports in the literature that when aerosol-generating procedures were performed on some patients (like irrigation of infected abscess[21]), a certain degree of infectivity arose. Thus, precautions should also be taken under special circumstances.

Isolation

The following precautions should be observed when a patient is isolated in a hospital:

1. The patient should remain in the isolation room, and only leave the room when necessary with a face mask put on properly.
2. Limit the number of people entering the room, in particular young children or other susceptible persons.

3. Persons entering the room should wear appropriate types of masks properly. N95 is recommended when cough inducing or other high-risk procedures are being conducted. Otherwise, surgical mask would be acceptable if the patient is already on effective treatment and improving. More caution should be exercised for drug-resistant cases.
4. Instruct patient to cover mouth and nose when coughing or sneezing.
5. Instruct patients, visitors, and health care staff about the importance of adhering to the isolation precautions.

Discontinuation of isolation precautions

Isolation may be discontinued when patient is assessed to be non-infectious. As discussed previously, there are controversies. A good response after two weeks of effective treatment would be a somewhat useful guide for non-infectiousness as alluded, although each case should be assessed individually. Evidences and considerations to support this approach are based on the followings:

1. In the famous Baltimore V.A. Hospital experiment done by Riley[3] the effluent air from the TB ward of patients undergoing chemotherapy became non-infectious to guinea pigs after two weeks of effective treatment.
2. Evidence that there are 1 to 2 log reductions in sputum bacillary load in TB patients after 2 weeks of effective chemotherapy.[17]
3. The frequency of coughing - the likely source of airborne infectious particle - is greatly reduced in TB patients after receiving chemotherapy for 2 weeks.[18]

In 1994, because of reports of institutional outbreaks of multidrug-resistant TB (MDR-TB), largely among HIV-infected persons, CDC issued new guidelines for discontinuation of isolation of TB patients. The revised guidelines required three consecutive smear-negative sputum specimens before discontinuation of isolation. However, study findings showed that this would take a mean of 33 days after treatment,[26] which was considered to be too stringent by some health authorities,[27] and therefore was not universally adopted.

Some recommendations by the Hong Kong Hospital Authority are summarised as follows[28]:

1. In general, the recommended period for isolation of infectious cases is two weeks after effective treatment.
2. Avoid mixing TB patients with HIV or other immuno-compromised patients until the former are documented non-infectious.
3. Patients with MDR-TB are to be isolated until smear conversion to negativity.
4. Cohort isolation in different compartments of naturally well-ventilated wards is a more practicable and acceptable alternative in specialised hospital settings where a large number of TB patients are being managed.

Uncomplicated cases of tuberculosis are usually managed as outpatients. Inpatients showing satisfactory improvement may also be discharged earlier for ambulatory care. Study in Madras showed that chance of contracting TB is no more common among contacts of patients treated entirely at home versus those treated in hospital till sputum culture converted negative.[29] Another study in Arkansas showed that the rate of infection (as indicated by conversion of tuberculin skin test) is comparable among contacts of patients treated at home versus those treated in hospital till culture negative.[30] Hospital isolation may, however, be indicated if a large number of vulnerable contacts will otherwise be exposed, e.g. in residential institutions.

Engineering Controls

<u>Room Ventilation</u>

The rate of exchange of contaminated air with clean air within a room is referred to as the ventilation rate, expressed as the number of air changes per hour (ACH). A ventilation rate of one ACH means that the ventilation system delivers a volume of air equal to the room volume each hour. One ACH will reduce the concentration of a given contaminant within a room by 67% in one hour, whereas a

ventilation rate of six ACH will reduce the contaminant concentration by more than 99% in the same period. Increasing from 1 to 6 ACH will result in four to five times more rapid clearing of infectious particles from the air within the room. However, further increases above 6 ACH will have less and less effect, and increases above 12 to 15 ACH will be of little further benefit.[5]

In respiratory isolation rooms, at least 6 ACH is needed.[11] Some authorities recommend that newly constructed isolation rooms should have 9 ACH or even 12 ACH.[31] In rooms designated for high-risk activity such as bronchoscopy suites, autopsy rooms, or rooms where sputum induction or nebulisation therapy is conducted, a higher rate of at least 15 ACH is recommended.[31]

Apart from rate of ventilation, attention should also be paid to the direction of air flow. Air should flow from clean to non-clean areas. To prevent escape of infectious droplet nuclei from TB isolation rooms, they should be kept under negative pressure. Some authorities recommended that 10% negative pressure is probably acceptable and affordable for an isolation room with suitable design.[32]

In places where the setup is not using central air conditioning, "maximising natural ventilation through open windows" as stated in WHO's guidelines[33] is a practical and inexpensive way to dilute the infectious particles. This was how the TB sanatorium was designed. Together with other factors like high ceiling, large windows, widely separated bed space, and vigilant precautionary measures like judicious use of surgical masks, the sanatorium design has stood the test of time. A recent study demonstrated the efficacy of natural ventilation in achieving high ACH.[34]

Regarding ventilation design of health care facilities, the medical personnel should work in consultation and collaboration with the engineering experts. In addition, other designs such as use of enclosing devices like booths, tents, and hoods may be considered under special circumstances or when performing high-risk and cough-inducing procedures.

<u>High Efficiency Particulate Air (HEPA) Filtration Unit</u>

HEPA filters can provide a minimum particulate removal efficiency of 99.97% for thermally generated smoke particles or equivalent with a diameter of 0.3 micron. It works by the processes of diffusion, interception and inertial impaction. Particles with diameters below 0.3 micron exhibit significant degree of Brownian movement, and thus can be removed effectively through filtration by the diffusion regime. As the estimated size of the airborne infectious droplet is generally around 1 to 5 micron, HEPA filter should be highly efficient in removing these droplet nuclei from contaminated air.[35]

HEPA filters can be used in a number of ways to reduce or eliminate infectious droplet nuclei from room air or exhaust. These methods include placement of HEPA filters in[36]:

1. exhaust ducts to remove droplet nuclei in air from being discharged to the outside, either directly or through ventilation equipment (HEPA filter is not needed if air exchange system of the isolation room uses fresh air and the exit air is disposed of properly.)
2. ducts discharging room air into the general ventilation system
3. fixed or portable room-air cleaners

However HEPA filters increase the resistive load and a more powerful ventilation unit is required. Because mycobacteria can survive in the environment in a potentially virulent state for a long period of time, the used HEPA filters should be regarded as of high-grade biohazard when being disposed.

<u>Ultraviolet Germicidal Irradiation</u>

UV light has been recommended for institutional TB control, because of its efficacy in eradicating airborne pathogens in experimental studies.[37] With a room of 200 ft^3 and 10 ft ceiling, installing a 30 W UV lamp was described as equivalent to adding 20 ACH.[38]

UV light is attractive because the fixtures are relatively cheap, and the maintenance and energy costs are low. Studies have shown that the germicidal effect of UV irradiation varies with relative humidity and intensity of the UV light:

1. Increase in relative humidity reduces the efficacy of UV irradiation.[39] It has been recommended that for optimal efficacy of UV irradiation, the relative humidity should be maintained below 60%.
2. As the lamp gets old or covered with dust, the residence time for air sterilisation increases.[40]

Direct exposure to UV light can result in kerato-conjunctivitis (so-called welder's eye), and prolonged direct exposure is associated with skin cancer. The risk of kerato-conjunctivitis is easily prevented by installing the fixtures within ventilation systems (duct irradiation), or by using wall- or ceiling-mounted fixtures with baffles to block rays directed downward so that only the air in the upper room is irradiated (upper room irradiation). Again, consultation and collaboration with the engineering experts would be desirable. However, due to these potential complications, low penetration power and slow onset of action of UV, the year round high humidity and unproven efficacy in practice, UV light is not so widely used locally.

Ventilation versus HEPA filter and Ultraviolet Irradiation.

Most authorities believe that ACH of 6 to 12 under negative pressure is pivotal for infection control in an isolation room.[41] The most important part of TB control is to get the infectious patient into the isolation room as soon as possible. The other measures such as HEPA filter or UV irradiation are no replacement for a properly maintained respiratory isolation rooms, although they may serve as supplementary measures in selected settings.

Personal Controls

These include education to health care staff on principles of infection control, use of personal respiratory protective device (i.e. face mask), BCG vaccination, tuberculin skin testing and preventive therapy with drugs in particular isoniazid. The importance of education to staff to enhance their knowledge on infection control cannot be overemphasised. As BCG vaccination, and tuberculin skin testing and preventive therapy are discussed elsewhere, this section will focus on the use of personal respiratory protective device only.

Personal Respiratory Protective Device

The use of personal respiratory protective device is to prevent the inhalation of droplet nuclei. Standard surgical masks are effective in preventing larger exhaled droplets from falling onto wounds or mucosal surfaces. However, they have been described as less than 50% effective in filtering the much smaller droplet nuclei (1-5 microns) containing tubercle bacilli that may be inhaled and reach the alveoli.[42] Therefore, higher grades of face mask with better filtering capacity are recommended (filtering 95% of particles of one micron or larger with less than 10% leak[11,43]).

In 1996, the National Institute of Occupational Safety and Health (NIOSH) set up a new system of classification of particulate respirators.[44]
1. It identified three main classes of respirator N, P, R (N stands for "not resistant to oil", P for "oil-proof" and R for "oil-resistant").
2. "N" class intended for protection against non-oil-based aerosols.
3. "R" and "P" for use against oil-based aerosols, which degrade filter material quickly.
4. The filter efficiencies are rated with 0.3 μm mass median aerodynamic diameter particle (MMAD) into three grades: 99.97% (HEPA filter), 99% and 95%.
5. N95 keeps out 95% of particles that have a diameter of 0.3 μm.

In Hong Kong with an endemicity of TB, N95 is recommended for use mainly in circumstances where cough-inducing or high-risk procedures are carried out. If used, N95 should be worn properly, otherwise the infection risk may not be reduced. In situations with low level of exposure, such as TB wards with patients receiving appropriate drug therapy, some authorities recommend the use of surgical masks.[45] A surgical mask is also appropriate when the primary objective is to guard against other respiratory infections which spread mainly through larger droplets.

The efficacies of using surgical masks versus high grade disposable particulate respirators in TB infection programmes had been studied in two large surveys conducted in the United States in the 1990s by examining tuberculin skin test conversion rates among HCW.[46,47] Although the findings might not be specifically related to individual components in the programmes, there was no evidence to suggest any superiority of the particulate respirator over the surgical mask. This probably reflects the importance of the hierarchy of control, with administrative control measures as the more important component. The respirator serves as an adjunctive measure for personal protection in the last line of defence.

It should be noted that the NIOSH classification takes into account only the efficiency of the filter but not the percentage leak. The question of using fit test to detect and minimise leakage has been controversial. Some authorities recommend this practice,[48] while some recommend the use of annual self-assessment health questionnaire to identify workers who need fit testing to replace annual fit testing.[49] On the other hand, some authorities noted that "fit tests can detect only the leakage that occurs at the time of the test and does not account for the variation in fit that occurs in day-to-day use".[50] The Infectious Diseases Society of America (IDSA) commented that "there is no sound evidence to support initial and periodic fit testing, and that well-designed respirators can achieve the desired fit without testing".[50]

Conclusions

In this chapter, the key elements of control against the transmission of TB in health care settings have been reviewed. Among the various measures, early recognition of potentially infectious TB patients remains a crucial step for implementation of appropriate isolation and prompt initiation of treatment.

References

1. TB & Chest Service, Department of Health, Government of the Hong Kong SAR. Annual Report 2003.
2. Riley RL et al. Airborne Infection. New York, Macmillan, 1961
3. Riley RL et al. Infectiousness of air from a tuberculosis ward--ultraviolet irradiation of infected air: Comparative infectiousness of different patients. Am Rev Respir Dis 1962;85:511-25.
4. Riley et al. Airborne spread of measles in a suburban elementary school. Am J Epidemiology 1978;107:421-32.
5. Nardell EA et al. Airborne infection theoretical limits of protection achievable by building ventilation. Am Rev Respir Dis 1991;144:302-6.
6. Catanzaro A et al. Nosocomial tuberculosis. Am Rev Respir Dis 1982;123:559-62.
7. Templeton GL et al. The risk of transmission of mycobacterium tuberculosis at bedside and during autopsy. Ann Intern Med 1995;122:922-925.
8. Small PM, Hopewell PC, Singh SP, et al. The epidemiology of tuberculosis in San Francisco – a population-based study using conventional and molecular methods. N Engl J Med 1994;330:1703-9.
9. Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in household in a high-incidence area. Lancet 2004;363:212-4.
10. Tuberculosis & Chest Service, Hong Kong SAR. Annual Report 2004.
11. Centres for Disease Control. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health care facilities, 1994. MMWR Morb Mortal Wkly Rep 1994;43(RR-13):1–132
12. CDC and the Healthcare Infection Control Practices Advisory committee. Guidelines for environmental infection control in health care facilities. MMWR 2003;52:RR-10.
13. Seto WH. Preventing nosocomial Mycobacterium tuberculosis transmission in international settings. Emerg Infect Dis 2001;7:245-8.
14. Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. Am Rev tubercle 1954;69:724-32.
15. Rose C, Zerbe G, Lantz S, Bailey W. Establishing priority during investigation of tuberculosis contacts. Am Rev Respir Dis 1979;119:603-9.
16. Liipo KK, Kulmala K, et al. Focusing tuberculosis contact tracing by smear grading of index cases. Am Rev Respir Dis 1993;148:235-6.
17. Jindani A, Aber V, Edwards E, Mitchison D. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 1980;121:939–49.
18. Loudon R, Romans W. Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 1969;99:109–11.
19. Noble RC. Infectiousness of pulmonary tuberculosis after starting chemotherapy: review of the available data on an unresolved question. Am J Infect Control 1981;9:6-10.
20. Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet 1999;353:444-9.

21. Hernandez-Garduno E, Cook V, Kunimoto D, Elwood RK, Black WA, FitzGerald JM. Transmission of tuberculosis from smear negative patients: a molecular epidemiology study. Thorax 2004;59:286-90.
22. East African/British Medical Research Council. Controlled clinical trial of short-course (6 month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet 1972;1(7760):1079-85.
23. Singapore Tuberculosis Service, British Medical Research Council. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singapore. Lancet 1975;7945:1105-9.
24. Tousek J, Votruba R. Rifampicin plus isoniazid, rifampicin plus PAS, isoniazid plus PAS in the initial treatment of pulmonary tuberculosis. Chemotherapy 1974;20:183-200.
25. Hutton MD, Stead WW, Cauthen GM etal. Nosocomial transmission of tuberculosis associated with a draining abscess. J Infect Dis 1990;161:286-295.
26. Telzak EE, Fazal BA, Pollard CL, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear-positive tuberculosis. Clin Infect Dis 1997;25:666–70
27. Guidelines for Tuberculosis Control in New Zealand 2003, Chapter 9: Infection Control in Tuberculosis.
28. Hospital Authority Task Force in Infection Control. Control of transmission of TB in healthcare settings in the Hospital Authority, January 2002 (updated 2003).
29. Kamet SR, Daawson JJY, Devadatta S, et al. A controlled study of the influence of segregation of tuberculosis patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Bull WHO 1966;34:517–32.
30. Gunnells JJ, Bates JH, Swindoll H. Infectivity of sputum-positive tuberculous patients on chemotherapy. Am Rev Respir Dis 1974;109:323–30.
31. Tuberculosis Control in Canadian Health Care Institutions. Canadian Tuberculosis Standards 5th Edition 2000.
32. Nicas M, Sprinson JE, Royce SE, Harrison RJ, Macher JM. Isolation room for tuberculosis control. Infect Control Hosp Epidemiol 1993;14:619-22.
33. World Health Organisation. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. 1999. WHO/CDS/TB/99.269.
34. Escombe AR, Oeser CC, Martinez C, et al. Natural ventilation to reduce nosocomial transmission of tuberculosis and other airborne infections. Int J Tuberc Lung Dis 2005;9(Supp 1):S56-7.
35. Rutala WA, Jones SM, Worthington JM, Reist PC, Weber DJ. Efficacy of portable filtration units in reducing aerosolized particles in the size range of Mycobacterium tuberculosis. Infect Control Hosp Epidemiol 1995;16:391-98.
36. Rutala WA, Jones SM, Worthington JM etal. Efficacy of portable filtration units in reducing aerolized particles in the size range of Mycobacterium tubeculosis. Control Hosp Epidemiol 1995;16:391-398.
37. Riley RL, Knight M, Middlebrook G. Ultraviolet susceptibility of BCG and virulent tubercle bacilli. Am Rev Respir Dis 1976;113:413-8.
38. Riley RL et al. Clearing the air: the theory and application of ultraviolet air disinfection. Am Rev Respir Dis 1989;139:1286-1294.
39. Ko G, First MW, Burge HA. Influence of relative humidity on particle size and UV sensitivity of Serratia marcescens and Mycobacterium bovis BCG aerosols. Tuberc Lung Disease 2000;80:217-28.
40. First MW, Nardell EA, Chaisson RE, Riley R. Guidelines for the application of upper-room ultraviolet germicidal irradiation for preventing transmission of airborne contagion - Part 2: design and operation guidance. ASHRAE Transactions: Symposia 1999;105:877-87.
41. Wurtz R. Infection control in public hospitals. Infect Control Hosp Epidemiol 1995;16:642-6.
42. Nicas M, Spear RC. A probability model for assessing exposure among respirator wearers: Part 1. Description of the model. Am Ind Hyg Assoc J 1992;53:411-8.
43. Health Canada. Guidelines for preventing the transmission of tuberculosis in Canadian health care facilities and other institutional settings. CCDR 1996;suppl.1:1-50.
44. USDHHS. NIOSH guide to the selection and use of particulate respirators certified under 42 CFR 84. Washington DC: USDHHS, 1996.
45. Fennelly KP. The role of masks in preventing nosocomial transmission of tuberculosis. Int J Tuberc Lung Dis 1998;2:S103–S109.
46. Fridkin SK, Manangan L, Bolyard E, Jarvis WR. SHEA-CDC TB survey, Part II: Efficacy of TB infection control programs at member hospitals, 1992. Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol 1995;16:135-40.
47. Sinkowitz RL, Fridkin SK, Manangan L, Wenger PN, Jarvis WR. Status of tuberculosis infection control programs at United States hospitals, 1989 to 1992. Association for Professionals in Infection Control and Epidemiology. Am J Infect Control 1996;24:223-5.
48. Jarvis WR, Bolyard EA, Bozzi CJ, et al. Respirators, recommendations, and regulations: the controversy surrounding protection of health care workers from tuberculosis. Ann Intern Med 1995;122:142-6.
49. Sepkowitz KA. Tuberculosis control in the 21st century. Emerg Infect Dis 2001;7:259-62.
50. Stamm WE. Comments on CDC's draft "Guidelines for preventing the transmission of mycobacterium tuberculosis in health care settings, 2005" [FR DOC 04-26710] (letter). Full text available at http://www.idsociety.org/. Accessed on 4 Oct 2005.

CHAPTER 17

AMBULATORY TREATMENT AND PUBLIC HEALTH MEASURES FOR A PATIENT WITH UNCOMPLICATED PULMONARY TUBERCULOSIS

CM Tam, CW Lam, HS Chan

Summary points:

1. There are two main purposes in the management of a case of tuberculosis: to cure the patient, and to contain the spread of the infection. The attending physician has the responsibility to ensure treatment completion.
2. The process of diagnosis follows the usual steps: history, physical examination, and investigations. Chest radiograph and sputum bacteriological examination are the basic diagnostic tools, supplemented by other tests where appropriate.
3. Bacteriological examination and drug susceptibility tests should be done as far as possible in every case of tuberculosis. Susceptibility results provide a good guide to formulation of the drug regime, as well as surveillance data on trend of drug resistance in the community.
4. The standard treatment is the short course regimen given for at least 6 months. Drug prescription should be made after assessment of contraindications and necessary precautions. Biochemical and clinical monitoring are performed where appropriate.
5. DOTS is strongly recommended by the World Health Organisation as the cornerstone of TB treatment.
6. Apart from clinical management, public health measures are also essential. These include infection control measures, notification, contact tracing, and health education.

Introduction

In Hong Kong, there are around 7,000 notified cases of tuberculosis (TB) each year. Ambulatory chemotherapy has been the mainstay of anti-TB treatment. The majority (around 80%) of notified TB cases are managed in the chest clinics of the Tuberculosis & Chest Service (TB&CS) under the administration of the Department of Health (DH). Others are treated at various medical units of the Hospital Authority (HA) and in the private sector. It is a statutory requirement for every case of active TB to be notified to DH according to the Prevention of the Spread of Infectious Diseases Regulations under the Quarantine and Prevention of Disease Ordinance (Cap. 141). Broadly speaking, notification serves two main purposes, namely, epidemiological surveillance and contact investigation. Prompt notification facilitates contact tracing procedures and helps to contain the spread of the infection. Details of the notification procedure can be found in the "Guidance notes for notification of tuberculosis".[1] (See also Chapter 2.)

Today, emphasis is placed on encouraging patients with symptoms suggestive of TB to seek medical attention early, so called "passive case finding", rather than indiscriminate screening of asymptomatic individuals. This Chapter provides a summary and general view of the management of a patient with uncomplicated pulmonary TB. For more details on specific aspects of management, the reader should refer to the relevant Chapters of this Manual.

Management of the Patient with Tuberculosis

Aims

There are two main objectives in managing a TB patient. The first is to cure the individual patient. The

second is to contain the spread of the infection. In this regard, the health care provider has a responsibility to monitor every TB patient for treatment adherence till completion.[2]

History

As TB is endemic in Hong Kong, a high index of suspicion should be maintained, especially for patients presenting with symptoms like persistent cough for over 3 to 4 weeks, blood in sputum, weight loss, persistent fever, or night sweating. In assessing a patient presenting with persistent chest and/ or constitutional symptoms, a full medical history is essential. Particularly important issues in the history include previous history of TB, coexisting medical illnesses, occupational history, contact history, and smoking habit, risk of HIV infection (e.g. venereal exposure, intravenous drug addiction). If a positive culture of *Mycobacterium tuberculosis* (MTB) has been isolated from the sputum of the probable source case, the susceptibility pattern may help in the choice of initial drug regimen for the patient. Any evidence of previous BCG vaccination is to be noted especially if the patient is a child.

Physical examination

Physical examination not uncommonly yields negative findings. Some features may be worth mentioning, including: general condition, cervical lymph node enlargement, features of pleural effusion, and unilateral wheeze related to endobronchial involvement. The physical findings may help in the consideration of differential diagnoses, e.g., a lung nodule is more likely to be a carcinoma than a tuberculoma in the presence of finger clubbing.

Investigation

Chest radiograph and sputum examination for acid fast bacilli (AFB) are essential tools employed for the diagnosis of pulmonary TB. The chest radiograph is a relatively simple and sensitive test. Typical radiographic changes, like apical lesions, tend to have a higher positive predictive value for TB in an endemic area like Hong Kong. However, atypical sites of involvement, e.g. predominant lower lobe changes, may occur in elderly patients with TB. Every effort should be made to trace old chest radiographs for comparison, if available. At times, symptomatic TB patients may have normal findings on chest radiographs at presentation.[3]

Diagnostic sputum samples, preferably collected on two to three consecutive mornings, are sent for direct smear and culture examination. Positive smear results should be reported back to the clinics promptly so that patients can be called back for early commencement of treatment. If direct smears are negative, clinico-radiological correlation is essential in deciding the next step of action. In certain situations, trial of antibiotics, and follow-up chest radiograph examination in one to two weeks may be required to differentiate TB from other types of community-acquired pneumonia. However, care should be exercised to avoid certain antibiotics in particular the fluoroquinolones which may mask the features of TB resulting in delayed diagnosis.[4,5]

The use of radiometric cultures and the more advanced laboratory techniques like molecular and amplification tests can shorten the time required for bacteriological diagnosis and/ or susceptibility tests, though at a higher cost. However, false positive results of nucleic amplification tests may occur, e.g. in cases of treated or inactive TB. In more difficult cases, it may be necessary to resort to further investigations like computerised tomography scan, fibreoptic bronchoscopy, and percutaneous transthoracic fine needle aspirate. Thus, the diagnosis of active pulmonary TB may be based on any combination of clinical, radiological, bacteriological, and sometimes histological grounds.

The use of tuberculin test is rather limited in the local setting, partly as a result of widespread BCG vaccination and revaccination, although the latter has been stopped since September 2000. Despite such limitation, the test may still give useful information in certain clinical situations, especially among the younger age group, and in case assessment for need of treatment of latent TB infection is required.

The TB Reference Laboratory of DH performs TB drug susceptibility tests for the great majority of

health care facilities in the public sector, including TB&CS of DH and chest medical units of HA. Identification and susceptibility tests to the four first-line anti-TB drugs (isoniazid, rifampicin, ethambutol and streptomycin) are regularly preformed for all pretreatment culture isolates which are positive for MTB. Susceptibility tests to second-line drugs are performed, if there is multidrug-resistance (resistant to at least isoniazid and rifampicin), or with other clinical indications. The drug susceptibility test results provide a useful guide to the clinical management of the patient, and also allow epidemiological surveillance of drug resistance rates and evaluation of the local TB control programme. Hence, sputum or other relevant specimens should be sent for bacteriological examination including drug susceptibility tests as far as possible.

Notification

Cases diagnosed as active pulmonary TB should be notified promptly to DH, particularly once the case is put on treatment.[1] If the patient happens to be a health care worker or working in other relevant occupations with increased risk of exposure to TB, notification to the Labour Department is required under the Occupational Safety and Health Ordinance.[6] De-notification is necessary if the case eventually turns out to be non-TB, atypical mycobacterial infections, or other diagnoses. De-notification forms can be downloaded from the TB website (http://www.info.gov.hk/tb_chest). (See also Chapter 2.)

Treatment

"Short course chemotherapy" is the current standard treatment for active pulmonary TB. The regimen consists of a two-month initial phase comprising four drugs, namely, isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin, plus a four-month continuation phase of two drugs, namely, isoniazid and rifampicin, making a total duration of six months.[7,8] (See also Chapter 7.) The drugs can be given either daily or three times weekly at the appropriate dosages (Table 17.1 and Appendix 7). The drugs should, as far as possible, be taken together in one single dose each time and not in split doses in order to achieve optimal therapeutic efficacy. Combined drug preparations (or fixed-dose combinations, e.g. rifater, rifinah) are useful alternatives but have to be given daily. While they help to avoid monotherapy with a single drug, they do not allow flexible dosage adjustment of the individual components of the regimen. TB patients are generally managed as an outpatient for ambulatory care unless there are other indications for hospital admission.

Table 17.1. Standard regimen for anti-tuberculosis treatment

Initial phase (2 months)	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol/Streptomycin
Continuation phase (4 months)	Isoniazid + Rifampicin

Contraindications to the use of the anti-TB drugs should be noted prior to commencement of therapy, in particular: history of major diseases such as liver and renal diseases, visual problem, hearing problem, drug allergy, and concomitant treatment with other medications. Young females are counselled on pregnancy-related issues, especially the reduced efficacy of oral contraceptives due to interaction with rifampicin, and alternative contraceptive methods may have to be recommended. Pretreatment blood tests for liver function, renal function, HBsAg[9] and HIV antibody (after counselling and obtaining patient's consent) are performed. Baseline vision tests for visual acuity and colour perception (e.g., using Snellen chart and Ishihara chart) are also performed if ethambutol is to be started.[10] Studies show that it would be desirable to closely monitor liver function for HBsAg carriers during anti-TB treatment.[9] Health education is given on the nature of the disease, personal hygiene, avoidance of smoking and alcohol, necessity for full adherence with drug treatment, and the possible pharmacological and side effects of the anti-TB drugs (e.g., discoloration of urine, faeces, tear and other body fluids). This is supplemented by written educational materials. Self-reporting of side effects is also advised. The importance of health education on drug-induced hepatotoxicity and ocular toxicity have been emphasised in the two relevant sets of local guidelines.[9,10] (See also Chapters 9 and 10.) The establishment of good rapport with the patient from the very beginning is essential for the success of the treatment programme.

Public health measures

The health nurses will enquire the patient about his/ her close contacts (usually the household members), and contact screening will be conducted where appropriate. (See Chapter 12.) Casual contacts are, in general, not targeted for screening because of the low cost-effectiveness, although this has to be assessed on a case-by-case basis. Contact tracing normally follows the "stone-in-the-pond principle". Under this principle, contact tracing will be limited first to the innermost circle with the highest degree of close contact, and if more cases are found, consideration may be given to screen successively the outer circles with lesser degree of contact. However, examination of contacts should be considered mainly as an adjunctive measure in the overall TB control programme as only a relatively small proportion of TB cases can be found through this route. A more effective approach would be to emphasise on health education and early awareness of suspicious symptoms.

The sputum smear status is a general guide to the infectiousness of the TB patient. Those patients with severe cough, cavitary disease, and positive sputum smear are likely to be highly infectious. Prompt initiation of treatment is crucial as infectiousness rapidly decreases with effective treatment. Health education, personal hygiene measures, maintenance of good indoor ventilation and screening of close contacts are useful adjunctive measures to reduce the risk of transmission. Sick leave may be granted for the period during which infectivity is considered significant on a case-by-case basis. In general, infectivity is reduced significantly after two weeks of effective anti-TB treatment. Particular concern should be paid to infectious patients who are in frequent contacts with susceptible people, such as teachers, staff of homes for the elderly, medical personnel working for debilitated patients, and elderly home infectious residents where more stringent measures may be necessary.

DOTS and other monitoring measures

In the chest clinics, anti-TB medication is given under direct observation by the health nurses to ensure full adherence. Directly observed treatment, short course (DOTS), with five principal elements and implemented through holistic care, is strongly recommended by the World Health Organisation (WHO) as one of the most important TB control measures, and is crucial for the success of the treatment programme. (See Chapter 11.) Directly observed treatment (DOT) is one of the five principal elements of DOTS. DOT by a health care worker also facilitates closer clinical monitoring of adverse drug effects.

During the initial phase of chemotherapy, follow up consultation can be arranged monthly to assess progress, and to reinforce patient adherence. For patients at risk of drug-induced hepatitis, including HBsAg carriers, those with pre-existing liver diseases, the alcoholics, the very old, and the malnourished, it would be desirable to monitor liver function tests once every two weeks during the initial two months of treatment, or more frequently as clinically indicated.[9] In the absence of any risk factors, routine biochemical monitoring may not be necessary, but liver function test should be performed if clinical features suspicious of hepatitis arise, such as fever, nausea, vomiting, anorexia and jaundice. (See also Chapter 9.)

There is controversy about the role of regular follow up visual testing for patients put on ethambutol. This may, however, be considered if ethambutol is to be prescribed to some patients at a higher risk of oculotoxicity, especially when a high dose (e.g., 25 mg/kg/day) is used, treatment is prolonged,[10] or for those with impaired renal function (See also Chapter 10).

A chest radiograph is usually taken at the second or third month to assess progress. If the pretreatment bacteriology is positive, sputum examination after the second month will be done to assess whether there is conversion to negativity. If the bacteriology then is still positive, a further sputum examination after the third month is indicated. Prolongation of the treatment duration has been recommended by some authorities in case the sputum shows slow bacteriological conversion and cavitary disease is present.[2] (See also Chapter 7.)

Treatment defaulters will be approached by the health nurses through various means, including telephone calls, visits, and mail. Adherence is positively enhanced through health education and an assisting approach. The underlying reasons for defaulting should be identified and possible solutions are provided to restore adherence. Through the work of the medical social workers, incentives like nutrition allowance or other forms of social assistance may be introduced for eligible patients to enhance treatment adherence. Minimising non-adherence is vital for the overall success of the TB control programme.

At the end of six months' treatment, the patient is assessed with a repeat chest radiograph and sputum examination. After stopping treatment, further health education is delivered to the patient on issues like maintenance of a healthy lifestyle, and returning for assessment should symptoms suspicious of TB recur. Relapse of TB should be uncommon after adequate chemotherapy and regular follow up is not a necessity in general. However, for the purposes of outcome evaluation, TB patients are preferably followed up periodically for two or more years. In fact, standardised "Programme Forms" (Appendix 12) are being used for continuous evaluation of the service programme in the TB&CS since 1998 and an updated version of the Forms has been introduced since 2001 and extended for use to other health care sectors including the HA and the private sector. Data collected include information on demography, past history of treatment, type of TB (pulmonary or extrapulmonary), extent of disease (if pulmonary), case category (new, relapse, treatment after default and treatment after failure), date of starting treatment (DOS), bacteriological status at certain time points, drug susceptibility test results, and treatment outcome at selected time intervals from DOS. Monitoring of treatment outcome is an essential component of the DOTS strategy advocated by WHO. Surveillance of treatment outcomes are regularly reported in the Annual Reports of TB&CS.[11]

Complicating issues

From time to time, complicating issues may be present, including extensive disease, slow bacteriological conversion, poor general condition, diagnostic dilemma, treatment failure related to poor adherence and drug resistance, concurrent medical diseases, and adverse drug reactions etc. Opinion from experienced physicians in this field has to be sought and hospital admission may be required. Modification of the drug regimen may be necessary, for example, in cases with drug-induced hepatitis.[11] Transient rise of liver enzymes may occur, and it does not, by itself, represent genuine hepatotoxicity. The following cut-off levels are recommended for withholding potentially hepatotoxic anti-TB drugs in patients without symptoms: (i) alanine transaminase rising to three times the upper limit of normal or the baseline; or (ii) bilirubin level rising to two times the upper limit of normal or the baseline. A more cautious approach should be adopted in the presence of symptoms suggestive of hepatitis, in which case anti-TB drugs may have to be stopped before the availability of the test results.

Care should also be taken not to add a single drug to a failing regimen (the addition phenomenon), otherwise resistance to the newly added drug will soon develop. Re-challenging and desensitisation with anti-TB medications may be required with drug-induced hypersensitivity skin rash, but care should be taken not to induce emergence of drug-resistant organisms during this process. TB in children is more difficult to diagnose, and treatment with ethambutol should be avoided especially for those under six years old as they may not be able to report visual symptoms reliably. Thus, childhood TB should be managed by an experienced physician. On the other hand, TB in the elderly may have atypical presentations, and there is a higher incidence of side effects from drugs among this population.

The American Thoracic Society, Centres for Disease Control and Prevention and Infectious Diseases Society of America have issued a joint official statement on the treatment of tuberculosis in 2003.[2] The interested reader may also refer to it for further information.

Conclusions

The most important reason for failure of anti-tuberculous treatment is poor adherence. Studies have shown that there is no good way to predict adherence to drug therapy. DOTS is thus the best

available tool to ensure drug adherence. The cost of DOTS is justified because it avoids the greater cost required for the management of failure cases, relapse cases, complications, late effects and even worse, drug-resistant cases. Furthermore, without an effective treatment programme, the spread of TB would lead to an even higher healthcare and economic burden. The management of a case of TB demands the combination of good professional knowledge in clinical medicine as well as adequate attention on public health measures.

Although the local TB situation has much improved in the past 50 years, it is certainly still a major public health concern. In fact, the notification rate has remained relatively stagnant, staying at around 100 per 100,000, in the past decade. The maintenance of a strong infrastructure for the delivery of anti-TB service is required to combat and prevent the resurgence of this disease. The rate of latent infection in the local population is still high, especially among senior citizens. Many more years of work will be required before elimination of the disease may be considered as a foreseeable goal.

References

1. Leung CC, Tam CM. Guidance notes for notification of tuberculosis. Public Health & Epidemiology Bulletin 1999;8:36-9. Available at http://www.info.gov.hk/tb_chest. Accessed on 1.9.2005.
2. American Thoracic Society/ Centres for Disease Control and Prevention/ Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
3. Marciniuk DD, McNab BD, Martin WT, Hoeppner VH. Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Chest 1999;115:445-52.
4. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. Clin Infect Dis 2002;34:1607-12.
5. Yoon YS, Lee HJ, Yoon HI, et al. Impact of fluoroquinolones on the diagnosis of pulmonary tuberculosis initially treated as bacterial pneumonia. Int J Tuberc Lung Dis 2005;9:1215-9.
6. Notification of tuberculosis. Available at http://www.info.gov.hk/tb_chest. Accessed on 1.9.2005.
7. The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Chemotherapy of tuberculosis in Hong Kong: a consensus statement. Hong Kong Med J 1998;4:315-20.
8. The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Chemotherapy of tuberculosis in Hong Kong – update in 2001: a consensus statement. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2001 (Suppl).
9. The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Monitoring for hepatotoxicity during antituberculosis treatment – general recommendations. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2002(Suppl).
10. Tuberculosis & Chest Service of the Hong Kong Department of Health. Preventive measures against drug-induced ocular toxicity during anti-tuberculosis treatment – internal guidelines. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2002(Suppl).
11. Annual Report 2004. TB & Chest Service of Department of Health of the Government of Hong Kong SAR.

CHAPTER 18

MULTIDRUG-RESISTANT TUBERCULOSIS

CK Chan, WW Yew, TYW Mok

Summary points:

1. Multidrug-resistant tuberculosis is defined as disease caused by bacillary strains showing resistance to at least both isoniazid and rifampicin *in vitro*.
2. Multidrug-resistant tuberculosis presents an increasing threat to global tuberculosis control.
3. A multidrug-resistant tuberculosis registry has been set up within the Tuberculosis and Chest Service of Department of Health.
4. Health care workers are requested to notify multidrug-resistant tuberculosis cases to the Tuberculosis and Chest Service using a standard notification form for this disease.
5. Multidrug-resistant tuberculosis is more difficult to treat when compared to drug-susceptible disease, thus resulting in a significantly lower treatment success rate.
6. The regimen used to treat multidrug-resistant tuberculosis should comprise 5 to 6 drugs to which the organism is or likely to be susceptible for the initial 6 months, and then 3 to 4 drugs subsequently.
7. A single drug should never be added to a failing regimen.
8. Surgical resection of a major pulmonary focus may be a useful adjunct for selected cases with sufficiently localised disease not responding well to drug treatment.
9. Periodic follow up screening may be indicated for multidrug-resistant tuberculosis contacts with normal chest radiograph findings on initial screening.
10. Measures to prevent nosocomial spread of multidrug-resistant tuberculosis include an effective triage system, isolation of infectious patients, minimisation of patients' duration of stay in the health care settings, advice on personal hygiene, and the use of face masks.

Background

Multidrug-resistant tuberculosis (MDR-TB), defined as disease caused by bacillary strains showing resistance to at least both isoniazid and rifampicin *in vitro*, is of increasing concern in tuberculosis (TB) control programmes all over the world.[1] Data from the World Health Organisation (WHO)/ International Union Against Tuberculosis And Lung Diseases (IUATLD) Global Project on Drug Resistance Surveillance have identified several hot spots for MDR-TB.[1] Mathematical modeling suggests that 3.2% of the world's estimated new TB cases were MDR-TB in 2000.[2] Most commonly the development of multidrug-resistance occurs when there is a large bacillary population, when an inadequate drug regimen is prescribed, or when there is a combined failure of both the patient and provider to ensure that an adequate regimen is taken.[3] With appropriate combination chemotherapy that is reliably ingested, clinically significant resistance will not develop.[4] Use of directly observed treatment, short course (DOTS) has been shown to reduce the transmission of TB and the incidence of drug-resistant disease. Efficiently-run TB control programmes based on DOTS policy is essential for preventing the emergence of MDR-TB.

MDR-TB is more difficult to treat when compared to drug-susceptible disease thus resulting in a significantly lower treatment success rate. Treatment cost is also much higher, and patients with MDR-TB may remain infectious for a longer period of time. For the control of MDR-TB, "DOTS-PLUS" strategy is recommended.[5] This strategy incorporates continuous drug-resistance surveillance, culture and drug susceptibility testing for TB patients, and tailoring of individual drug regimen through the use of first and second-line drugs. (See also Chapter 11.)

At present, the rate of TB notification in Hong Kong is still high in comparison with other developed countries, viz around 90 per 100,000. The overall rate of MDR-TB, as noted in the Government TB

and Chest Service (TB&CS)'s annual report, has shown a decreasing trend over recent years[6]; currently it stands at around 1%. Nevertheless, it is necessary for doctors to remain vigilant, and continue to update knowledge and measures for the control of drug-resistant TB.

The Tuberculosis Control Coordinating Committee has published guidelines on the management of patients with TB regarding both clinical and public health aspects.[7-10] The treatment of MDR-TB involves the use of second-line (reserve) drugs which are much more expensive, generally less efficacious, and have potentially more adverse effects than the first-line drugs. Suboptimal management of MDR-TB may result in further drug resistance. Clinical expertise and good laboratory support are essential for the successful management of patients with MDR-TB. It is therefore recommended that MDR-TB be managed solely by, or in close consultation with TB specialists. In this chapter, general recommendation is provided regarding diagnosis, reporting, principles of treatment, contact screening, infection control and preventive measures in MDR-TB. It should be stressed that each case should be managed according to the individual circumstance, with the help of the necessary expertise.

Diagnosis of Multidrug-resistant Tuberculosis

It has been recommended that drug susceptibility testing of all pretreatment positive culture isolates should be done.[1] When the results of drug susceptibility testing are available, diagnosis of drug-resistant TB can be made readily, and the treatment regimen may be modified accordingly as needed.

In addition, early diagnosis of drug-resistant TB, particularly MDR-TB, is highly desirable. Delay in the diagnosis of MDR-TB may result in progressive lung destruction, higher bacillary load, and continuing disease transmission. To enable early diagnosis, a high index of suspicion is required. A history of incomplete treatment for TB, close contact with MDR-TB patients, and migration from an area endemic for drug resistance are some useful clues. Other risk factors for MDR-TB such as HIV infection, drug addiction and alcoholism should also be sought in the history. For re-treatment cases, the number and details of previous treatment lots as well as documentation of non-adherence should be obtained. A careful investigation of prior anti-TB treatment may help in identifying the likely pattern of drug resistance.

The Public Health Laboratory Centre (PHLC) of Department of Health (DH) may be contacted for consideration of drug susceptibility testing for first-line as well as second-line anti-TB drugs. Under appropriate circumstances, PHLC may also be contacted for consideration of either rapid drug susceptibility tests, or drug susceptibility tests concomitantly with mycobacteria identification tests.

Furthermore, about 96% of rifampicin-resistant isolates have been reported to have a mutated *rpo*B gene, and the mutations are concentrated on a short, less than 100-bp stretch of the gene.[11] Thus, genetic testing for rifampicin resistance would be useful, and its positive predictive value for MDR-TB can be high. Hence, when available and in case of high index of suspicion, rapid genetic testing for rifampicin resistance may also be recommended.[1]

Reporting of Multidrug-resistant Tuberculosis Cases

Timely notification of TB cases, drug-susceptible and drug-resistant alike, is crucial to the effective control and prevention of the disease. It is also important for public health surveillance and for initiation of contact screening. In addition to the usual TB notification registry, a MDR-TB registry has been set up within the TB&CS since May 1995 and the procedures have been updated in 2005 (MDR_Flow_protocol0503) (Appendix 13a) to include reporting of MDR-TB cases from sources outside TB&CS. Whenever a currently active and previously unreported case of MDR-TB is diagnosed, health care workers are requested to notify the case to Wanchai Chest Clinic using the MDR-TB notification form (MDR_Noti_Form0503) (Appendix 13b). In order to track progress of patients with MDR-TB, a set of special programme forms have been designed (TB-PFMDR-X(1)/10-2004 and TB-PFMDR-X(2)/10-2004) (Appendix 14). These forms are to be filled in every 6 months after the completion of the usual set of programme record forms (PFA, B1, B2, C and D) (Appendix 12) from 2.5 year to 5 year from date of starting treatment (DOS). The

forms can be downloaded from the DH TB website (http://www.info.gov.hk/tb_chest). [NB: PFA at pretreatment, PFB1 & PFB2 at 6 month, PFBC at 12m, PFBD at 24m, and PFMDR-X at 30m, 36m, 42m, 48m, 54m, and 60m.]

Treatment

For MDR-TB patients with known susceptibility pattern, the treatment regimen should comprise 5 to 6 drugs to which the organism is or is likely to be susceptible for the initial 6 months, followed by 3 to 4 drugs subsequently. The inclusion of an injectable agent for the initial months and a fluoroquinolone all through are generally recommended. Daily regime should be used, except perhaps for the injectables. Drugs showing *in vitro* resistance are generally excluded, with the possible exception of use of isoniazid in cases of low level resistance. The possibility of cross-resistance between drugs should be noted.[4,12]

Apart from first-line anti-TB drugs, available drugs for treatment of MDR-TB include the fluoroquinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (e.g. kanamycin, amikacin), prothionamide/ ethionamide, cycloserine, para-aminosalicylic acid, and clofazimine. (Appendices 7 and 8) These drugs vary in terms of anti-TB activity, convenience of administration, potential toxicity and cross-resistance. Drugs that have not been used to treat the patient before are preferred, and so are bactericidal drugs rather than bacteriostatic drugs.

There is controversy on the best approach in managing MDR-TB patients before drug susceptibility results for the second-line drugs become available. Each case should be judged on individual grounds. Recourse to the empirical use of several second-line drugs is often necessary while waiting for the definitive results. If it is considered necessary to treat a suspected MDR-TB patient before drug susceptibility test results are available, it may be advisable to employ an expanded regimen and give both the essential first-line drugs plus at least three second-line drugs that have not been used previously. A single drug should never be added to a failing regimen, because doing so may select organisms in the bacterial population that are resistant to the newly added drug (Addition Phenomenon). A combination of two or three drugs to which the organism is or is likely to be susceptible should be added.

Admission of patients with MDR-TB to special care centres including Grantham Hospital or Kowloon Hospital for newly diagnosed cases, or to the respective chest hospitals for old cases, is recommended particularly during the initial period. This will facilitate detailed assessment, stabilisation and optimisation of drug regime, reinforcement of health education and treatment adherence during subsequent outpatient follow up after discharge. Arrangement for hospital admission can be made through government chest clinics, or direct telephone/ facsimile contact of the hospital units.

Therapy of all patients with MDR-TB should be delivered by directly observed treatment (DOT) as far as practicable. Failure to comply with treatment is the main cause of poor treatment outcome and emergence of drug-resistant organisms. Therefore every effort should be made to ensure that patients complete the full course of treatment.

For patients who have problems with drug adherence, the reasons for defaulting treatment should be carefully explored and addressed promptly. All efforts should be made to seek co-operation from treatment defaulters. The management of treatment defaulters can be problematic. Team approach is the strategy. Counseling by specially trained TB workers and medical social workers forms an integral part of management of these patients.

Close monitoring of progress during anti-TB treatment is mandatory, in particular the general condition, body weight, chest radiograph and bacteriological status. Sputum specimens should be sent monthly for acid fast bacilli (AFB) smear and culture examination, until they are converted negative for three consecutive months. Sputum tests may be monitored at longer intervals thereafter, say, every three months, depending on the clinical situation.

Caution should be exercised in the interpretation of chest radiograph when initial radiographic

improvement is observed. Sometimes this may be a temporary phenomenon due to control of the drug-susceptible bacterial subpopulation when a suboptimal regimen is employed.

Caution is to be exercised in the use of second-line drugs as they are often associated with significant adverse effects. Renal function should be checked regularly when an aminoglycoside is given. Liver function should be monitored regularly in patients with risk factors for hepatitis. The patient should also be regularly assessed for other potential adverse reactions from the drugs given. Cycloserine should only be used with caution and when its benefit is perceived to outweigh its potential adverse effects.

The total duration of therapy for MDR-TB has not been clearly established; most will recommend a total duration of 18 months at least, or 18 months after culture being converted negative. However, local experience suggests that, with combination drug treatment and the inclusion of fluoroquinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 15 months, or one year after sputum culture conversion.[13] A longer duration may however be required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, extensive drug resistance or extensive radiographic disease.

Surgery

For selected cases of MDR-TB with predominantly localised disease that is not responding well to treatment with an "adequate" chemotherapy regimen, surgical resection of a major pulmonary focus may be a useful adjunct. The remaining lung tissue should be relatively devoid of disease and there should be sufficient drug activity to diminish the mycobacterial burden to facilitate healing of the bronchial stump.[4] The opinion and expertise of thoracic surgeons should be sought under these circumstances.

Contact Screening

Good public health measures are mandatory for the prevention of emergence and transmission of drug-resistant organisms. Contact screening, together with notification, surveillance, health education and infection control are the most important public health measures undertaken by DH. The general principles for screening of close contacts also apply to those of MDR-TB cases.[6,14] In addition, for MDR-TB contacts with normal chest radiograph findings on initial screening, periodic screening afterwards, say every 6 to 12 months may be indicated, depending on the infectiousness of the index case as assessed from the updated findings on chest radiograph and sputum bacteriological status. The contacts should also be educated on symptoms suspicious of TB and advised to return for consultation if such symptoms develop. The health staff of chest clinics may be contacted for arranging contact screening if the latter has not been undertaken by general medical doctors.

If a contact is found to have developed active pulmonary TB, it is important to correlate with the drug susceptibility pattern of the index case. Special public health measures may have to be taken if transmission of MDR-TB among contacts is suspected. To achieve effective public health control of the infection, close communication should be maintained with the relevant parties including DH. Restriction fragment length polymorphism (RFLP) analysis (DNA fingerprinting) may be considered.

Infection Control Measures

The patient should be provided health education on measures to prevent the spread of the disease. For examples, these include (1) good personal hygiene (like no spitting and covering mouth and nose during coughing and sneezing in public area), (2) avoid going to overcrowded areas, and (3) put on surgical masks if there is a need to go to crowded public areas including public transport vehicles.

Measures should be taken to prevent nosocomial spread of MDR-TB in clinics, hospitals and other health care settings. These include an effective triage system, isolation of infectious MDR-TB patients in a negative pressure room until assessed to be non-infectious, minimisation of the MDR-TB patients' duration of stay in the health care settings, advice on personal hygiene and the use of face masks, etc[15-16].

Other Issues

Special management may be necessary for chronic MDR-TB cases not responding well to treatment, and the failure failure cases. Compassionate re-housing may have to be considered. It would be useful to discuss with the patient and his/ her household members on observation of personal hygiene, maintenance of good indoor ventilation, as well as other measures including special arrangement of the home setting and layout of rooms. The use of incentives and enablers may be desirable through liaison with medical social workers. Incentives like special diet allowance should be used with close monitoring to ensure that they are used optimally. The DH staff may be contacted if such arrangement is considered necessary.

Conclusions

MDR-TB presents an increasing threat to global TB control. Treatment success rate for MDR-TB is relatively low. In addition, the cheapest MDR-TB treatment regimen is 100 times more expensive than the best first line regimen. It should be much more cost effective to prevent emergence of MDR-TB in the first place, through implementation of the DOTS strategy. Effective implementation of the DOTS strategy saves lives through decreased TB transmission, decreased risk of emergence of drug resistance, and decreased risk for individual patient of treatment failure, TB relapse, and death. The routine use of DOTS in the treatment of all cases of TB cannot be overemphasised.

Many crucial issues in MDR-TB management remain unresolved. The existing data on MDR-TB treatment come mainly from retrospective cohort analyses.[12] Randomised or controlled clinical trials have not been performed to answer questions concerning best treatment regimens and optimal treatment protocols for patients with various patterns of drug resistance. There is a need for further clinical research on MDR-TB treatment. There is also the need for new anti-TB drugs to be developed and tested. Currently, a number of new drugs as well as new vaccines for TB are under different phases of research and development.[17-19] Fluoroquinolones are currently among the most valuable drugs in the medical treatment of MDR-TB because of their bactericidal and sterilising activities and excellent oral bioavailability.[13,20] As Hong Kong has a relatively high TB prevalence, careful use of fluoroquinolones is highly desirable, not only in the context of TB, but also in other medical conditions including community-acquired pneumonia to prevent escalation of fluoroquinolone resistance. Clearly the loss of this important group of compounds will have adverse consequences on our battle against TB.

To control MDR-TB, specific surveillance programmes like the MDR-TB registry, drug resistance surveillance and treatment outcome monitoring are indispensable. These are all in place in Hong Kong and they should provide useful information for close monitoring, evaluation, and planning of targeted control measures. Today, TB is still an infectious disease of public health importance globally and locally. The control of TB demands long term work. Continuous multi-sectoral co-operation/ collaboration is necessary.

References:

1. World Health Organisation. WHO/HTM/TB/2004.343 Global project on anti-tuberculosis drug resistance surveillance. Third report 2004.
2. Espinal MA. The global situation of MDR-TB. Tuberculosis (Edinb) 2003;83:44-51.
3. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. JAMA 1993;270:65-8.
4. American Thoracic Society/ Centres for Disease Control and Prevention/ Infectious Diseases Society of America. Am J Respir Crit Care Med 2003;167:603-62.
5. Gupta R, Espinal M; Stop TB Working Group on DOTS-Plus for MDR-TB. A prioritized research agenda for DOTS-Plus for multi-drug resistant tuberculosis. Int J Tuberc Lung Dis 2003;7:410-4.
6. TB & Chest Service, Department of Health. Annual Report 2004.
7. Tam CM, Yew WW, Leung CC, Chan HS. Chemotherapy of tuberculosis in Hong Kong: Update in 2001: a consensus statement of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority. Hong Kong: Department of Health and Hospital Authority; 2001 Nov.

8. Tam CM, Yew WW, Leung CC, Chan YC. Monitoring for hepato-toxicity during anti-tuberculosis treatment: general recommendations: A consensus statement of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Hong Kong: Department of Health and Hospital Authority; 2002 April.
9. Tuberculosis & Chest Service of Department of Health, Hong Kong. Preventive measures against drug-induced ocular toxicity during anti-tuberculosis treatment: general recommendations. Annual Report 2002.
10. Tuberculosis & Chest Service of Department of Health, Hong Kong. Ambulatory treatment and public health measures for a patient with uncomplicated pulmonary TB. Annual Report 2004.
11. Telenti A. Genetics of drug resistant tuberculosis. Thorax 1998;53:793-7.
12. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474-81.
13. Yew WW, Chan CK, Leung CC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. Chest 2003;124:1476-81.
14. TB & Chest Service, Department of Health. Guidelines on tuberculin testing and treatment of latent TB infection among immunocompetent household contacts of smear-positive pulmonary TB patients in Hong Kong. Annual Report 2004.
15. HA Task Force in Infection Control. Control of transmission of tuberculosis in the healthcare settings in the Hospital Authority (Updated 2003 Jan).
16. Infection Control Committee of Department of Health. Guidelines on infection control practice in the clinic setting. 2004 August (revised).
17. Davies PD, Yew WW. Recent developments in the treatment of tuberculosis. Expert Opin Investig Drugs 2003;12:1297-312.
18. Gupta P, Hameed S, Jain R. Ring-substituted imidazoles as a new class of anti-tuberculosis agents. Eur J Med Chem 2004;39:805-14.
19. Morgan J, Haritakul R, Keller PA. Anilinopyrimidines as novel anti-tuberculosis agents. Bioorg Med Chem Lett. 2003;13:1755-7.
20. Yew WW, Chau CH. Utility of fluoroquinolnes in multidrug-resistant tuberculosis - a balanced view? Int J Tuberc Lung Dis 2002;6:174-5.

CHAPTER 19

TUBERCULOSIS RESOURCE MATERIALS

(A) Tuberculosis website <http://www.info.gov.hk/tb_chest>: sitemap
(B) Tuberculosis telephone hotline [(852)25726024]: topics
(C) Tuberculosis services in Hong Kong: list of historical reviews
(D) List of journal publications related to tuberculosis in Hong Kong

(A) Tuberculosis website <http://www.info.gov.hk/tb_chest>: sitemap (accessed on 1 January 2006)

Information on TB
- **History of TB**
  - Historical Perspective
  - History of TB Treatment
  - Historical Summary of TB and Services in Hong Kong
- **Knowledge on TB**
  - What is tuberculosis?
  - Is TB a common disease?
  - TB is a world-wide problem
  - How is the disease transmitted?
  - What happens after infection with the tubercle bacilli?
  - What are the symptoms of TB?
  - How can TB be diagnosed?
  - What is the treatment for TB?
  - Adverse reactions to anti-TB drugs
  - DOT (directly observed treatment)
  - What is BCG vaccination?
  - How can TB be prevented?
  - Guidelines on handling of TB cases
  - Publicity for TB
  - Some common misunderstandings about TB
  - Frequently Asked Questions on TB
- **Other related information**
  - Guidelines on prevention of communicable diseases in child care centers / kindergartens / schools
  - Guidelines on prevention of communicable diseases in residential care homes for the elderly and people with disabilities

Statistics on Tuberculosis
- **TB - statistical data in Hong Kong**
  - Notification and death rate of TB (All forms), 1947 - 2004
  - Graphical presentation: Notification rate of tuberculosis (all forms)
  - TB notification (all forms) & rate by age & sex, 1995 - 2004
  - TB death (all forms) & death rate by age & sex, 1995 - 2004
  - Statistics on notifiable Infectious Diseases (including TB)

How to notify tuberculosis?
- To notify TB under the Quarantine & Prevention of Disease Ordinance
  - Guidance notes
  - Notification form
  - TB denotification form
- To notify TB under the Occupational Safety and Health Ordinance
  - Guidance notes on the Diagnosis of Notifiable Occupational Diseases
  - Notification form

BCG vaccination
  - Information on BCG vaccination
  - Programme of Immunization

Information for doctors
  - Disclaimer
- **Laws related to TB**
  - Quarantine & Prevention of Disease Ordinance (Cap. 141) (Cap. 141B Prevention of the Spread of Infectious Diseases Regulations)
  - Occupational Safety and Health Ordinance (Cap. 509) (Cap 509 s 15 Medical practitioner to notify occupational disease to Commissioner)
- **How to notify tuberculosis?**
  - To notify TB under the Quarantine & Prevention of Disease Ordinance
    - Guidance notes
    - Notification form
    - TB denotification form

- To notify TB under the Occupational Safety and Health Ordinance
    - Guidance notes on the Diagnosis of Notifiable Occupational Diseases
    - Notification form
- **Use of 'Programme Forms' for monitoring progress and outcome of TB patients**
    - Explanatory letter
    - To download the 'Programme Forms'
- **BCG vaccination practice in Hong Kong**
    - Programme of immunization
    - Letter to doctors on cessation of BCG re-vaccination programme for primary school children
    - BCG reaction care
- **Annual report of TB & Chest Service, Department of Health**
    - 1991 to 2003 Annual Report
- **List of journal publications related to tuberculosis in Hong Kong**
- **Other useful local publications / materials**
    - Tuberculosis Manual 2006
    - Guidelines on the management of patients with multidrug-resistant tuberculosis in Hong Kong. March 2005
    - Guidelines on tuberculin testing and treatment of latent TB infection among immuocompetent household contacts (aged 1-34) of smear-positive pulmonary tuberculosis patients in Hong Kong(2005)
    - Guidelines on tuberculin testing and treatment of latent TB infection among silicotic patients in Hong Kong (2004)
    - Ambulatory treatment and public health measures for a patient with uncomplicated pulmonary tuberculosis (Update 2004)
    - Control of transmission of TB in healthcare settings in the Hospital Authority (Source: HA Task Force in Infection Control)
    - Preventive measures against drug-induced ocular toxicity during antituberculosis treatment (2002)
    - Monitoring for hepatotoxicity during antituberculosis treatment - general recommendations (2002)
    - Recommendations on the treatment of latent TB infection in HIV positive persons in Hong Kong (2002) *(Source: website of AIDS Unit, Department of Health)*
    - Flow chart for the management of household contacts age below 5(2001)
    - Chemotherapy of tuberculosis in Hong Kong - Update in 2001
    - Tuberculosis control in Hong Kong (2000)
    - Slide set on "Management of TB patient in Hong Kong" (power point format)
    - Cessation of the BCG revaccination programme for primary school children in Hong Kong. Public Health & Epidemiology Bulletin 2000;9(3):25-27.
    - Ambulatory treatment and public health measures for a patient with uncomplicated pulmonary tuberculosis (1999)
    - Guidance notes for notification of tuberculosis. Public Health & Epidemiology Bulletin 1999;8(4):36-9.
    - Prevention and management of tuberculosis in HIV infected patients in Hong Kong - An information paper (1995) *(Source: website of AIDS Unit, Department of Health)*.

Major public services for TB

- **Department of Health**
    - Tuberculosis & Chest Service
    - Tuberculosis Reference Laboratory
- **Hospital Authority**
    - Grantham Hospital
    - Haven of Hope Hospital
    - Kowloon Hospital
    - Ruttonjee Hospital
    - TWGHs Wong Tai Sin Hospital

Video, Publications & Pamphlets

- Prevention of tuberculosis
- Prevention of tuberculosis(institutions)
- BCG reaction care
- Information for patients on anti-TB drug treatment
- BCG vaccination
- TB & Chest Service (Information leaflet)
- Poster on health education for tuberculosis
- Slide set on health education for tuberculosis
- Exhibition Boards
- Video

Useful links

- **Local**
    - Department of Health
    - Hospital Authority
    - The Hong Kong Tuberculosis, Chest and Heart Diseases Association
    - Hong Kong Thoracic Society
    - American College of Chest Physicians (Hong Kong & Macau Chapter)
    - Hong Kong Lung Foundation
    - AIDS Unit, Department of Health
- **International**
    - World Health Organization Global TB Programme
    - WHO Western Pacific Region Stop TB Programme
    - WHO: Strategy & Operations, Monitoring & Evaluation
    - International Union Against Tuberculosis & Lung diseases
    - The International Journal of Tuberculosis and Lung Disease
    - CDC Division of TB Elimination
    - CDC Division of TB Elimination: major guidelines

(B) Tuberculosis telephone hotline [(852)25726024]: topics (1 October 2005)

- Full-time chest clinics
- Part-time chest clinics
- Scope of services of TB & Chest Service
- Knowledge on tuberculosis
- BCG Vaccination
- Pneumoconiosis Clinic

(C) Tuberculosis services in Hong Kong: list of historical reviews

1. Tuberculosis services in Hong Kong and their future development (Heaf FRG) 1962
2. Tuberculosis in Hong Kong: present position and future planning of methods of control and treatment (Scadding JG, Fox W) 1975
3. The present status of tuberculosis and its management in Hong Kong and the future development of the tuberculosis and chest services (Fox W) 1990
4. Report of Working Group Examining the Fox Report (Gabriel M) 1990
5. Services for the treatment of patients with tuberculosis in Hong Kong (Hedley AJ et al.) 2000
6. Evaluation of tuberculosis and its management in Hong Kong. (Chan MMW et al) 2000
7. A report on the review of services and strategies for control of tuberculosis in Hong Kong (The Ad Hoc Working Group on Control of Tuberculosis) 2000

(D) List of journal publications related to tuberculosis in Hong Kong

(Note: The list below is for quick and easy reference only, and cannot meant to be comprehensive.)

2005

- Ichikawa M, Nakahara S, Wakai S. Lowered tuberculosis notifications and deterred health care seeking during the SARS epidemic in Hong Kong. Am J Public Health 2005;95:933-4.
- Yew WW, Leung CC. Are some people not safer after successful treatment of tuberculosis? Am J Respir Crit Care med 2005;171:1324-5.
- Tso HW, Ip WK, Chong WP, Tam CM, Chiang AKS, Lau YL. Association of interferon gamma and interleukin 10 genes with tuberculosis in Hong Kong Chinese. Genes Immun 2005;6:358-63.
- Mok CC. Consensus statements on the indications and monitoring of anti-tumour necrosis factor (TNF) therapy for rheumatic diseases in Hong Kong. Hong Kong Bull Rhemat Dis 2005;5:1-7.
- Leung CC, Yew WW, Chan TY, Tam CM, Chan CY, Chan CK, Tang N, Chang KC, Law WS. Seasonal pattern of tuberculosis in Hong Kong. Int J Epidemiol 2005;34:924-30.
- Leung CC, Chan CK, Tam CM, Yew WW, Kam KM, Au KF, Tai LB, Leung SM, Ng J. Chest radiograph screening for tuberculosis in a Hong Kong prison. Int J Tuberc Lung Dis 2005;9:627-32.
- Wong MY, Leung CC, Tam CM, Lee SN. Directly observed treatment of tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2005;9:443-9.
- Kam KM, Yip CW, Tse LW, Wong KL, Lam TK, Kremer K, Au BK, van Soolingen D. Utility of mycobacterial interspersed repetitive unit typing for differentiating multidrug-resistant Mycobacterium tuberculosis isolates of the Beijing family. J Clin Microbiol 2005;43:306-13.
- Kremer K, Au BK, Yip PC, Skuce R, Supply P, Kam KM, van Soolingen D. Use of variable-number tandem-repeat typing to differentiate Mycobacterium tuberculosis Beijing family isolates from hong Kong and comparison with IS6110 restriction fragment length polymorphism typing and spoligotyping. J Clin Microbiol 2005;43:314-20.
- Leung CC, Chang KC, Law WS, Yew WW, Tam CM, Chan CK, Wong MY. Determinants of spirometric abnormalities among silicotic patients in Hong Kong. Occup Med 2005;55:490-3.
- Law WS, Tam CM, Leung CC. How do we tackle latent tuberculosis infection in immunocompetent persons? Public Health & Epidemiology Bulletin 2005;14(3)36-40.
- Wong PC. Management of tuberculous pleuritis: can we do better? Respirology 2005;10:144-8.
- Moore Gillon J. Tuberculin testing, BCG, and tuberculosis today (ed). Thorax 2005;60:90-1.
- Leung CC, Yew WW, Tam CM, Chan CK, Chang KC, Law WS, Lee SN, Wong MY, Au KF. Tuberculin response in BCG vaccinated schoolchildren and the estimation of annual risk of infection in Hong Kong. Thorax 2005;60:124-9.

2004

- Leung CC, Li T, Lam TH, Yew WW, Law WS, Tam CM, Chan WM, Chan CK, Ho KS, Chang KC. Smoking and tuberculosis among the elderly in Hong Kong. Am J Respir Crit Care Med 2004;170:1027-33.
- Vernon AA, Iademarco MF. In the treatment of TB, you get what you pay for (ed). Am Rev Respir Crit Care Med 2004;170:040-2.
- Chang KC, Leung CC, Yew WW, Ho SC, Tam CM. A nested case-control study on treatment-related risk factors for early relapse of tuberculosis. Am J Respir Crit Care Med 2004;170:1124-30.
- Leung CC, Chan CK, Yew WW. Side effects of antituberculosis therapy. Am J Respir Crit Care Med 2004;169:1168-9; author reply 1169.
- Chan CY, Au-Yeang C, Yew WW, Leung CC, Cheng AF. In vitro postantibiotic effects of rifapentine, isoniazid, and moxifloxacin against Mycobacterium tuberculosis. Antimicrob Agents Chemother 2004;48:340-3.
- Cheng AF, Yew WW, Chan EW, Chin ML, Hui MM, Chan RC. Multiplex PCR amplimer conformation analysis for rapid detection of gyrA mutations in fluoroquinolone-resistant Mycobacterium tuberculosis clinical isolates. Antimicrob Agents Chemother 2004;48:596-601.
- Chen ML, Yu WC, Lam CW, Au KM, Kong FY, Chan AY. Diagnostic value of pleural fluid adenosine deaminase activity in tuberculosis pleurisy. Clin Chim Acta 2004;341:101-7.
- Yam WC, Cheng VC, Hui WT, Wang LN, Seto WH, Yuen KY. Direct detection of Mycobacterium tuberculosis in clinical

specimens using single-tube biotinylated nested polymerase chain reaction-enzyme linked immunoassay (PCR-ELISA). Diagn Microbiol Infect Dis 2004;48:271-5.

- Kam KM, Yip CW. Surveillance of Mycobacterium tuberculosis susceptibility to second-line drugs in Hong Kong 1995-2002 after the implementation of DOTS-plus. Int J Tuberc Lung Dis 2004;8:760-6.
- Leung CC, Yew WW, Tam CM, Chan CK, Chang KC, Law WS, Wong MY, Au KF. Socio-economic factors and tuberculosis: a district-based ecological analysis in Hong Kong. Int J Tuberc Lung Dis 2004;8:958-64.
- Kim SJ, Espinal MA, Abe C, Bai GH, Boulahbal F, Fattorin L, Gilpin C, Hoffner S, Kam KM, Martin-Casabona N, Rigouts L, Vincent V. Is second-line anti-tuberculosis drug susceptibility testing reliable? Int J Tuberc Lung Dis 2004;8:1157-8.
- Chang KC, Leung CC, Tam CM. Risk factors for defaulting from anti-tuberculosis treatment under directly observed treatment in Hong Kong. Int J Tuberc Lung Dis 2004;8:1492-8.
- Chu CM, Woo PC, Chong KT, Leung WS, Chan VL, Yuen KY. Association of presence of Aspergillus antibodies with hemoptysis in patients with old tuberculosis or bronchiectasis but no radiologically visible mycetoma. J Clin Microbiol 2004;42:665-9.
- Yam WC, Tam CM, Leung CC, Tong HL, Chan KH, Leung ET, Wong KC, Yew WW, Seto WH, Yuen KY, Ho PL. Direct detection of rifampin-resistant mycobacterium tuberculosis in respiratory specimens by PCR-DNA sequencing. J Clin Microbiol 2004;42:4438-43.
- Cheng VC, Yam WC, Hung IF, Woo PC, Lau SK, Tang BS, Yuen KY. Clinical evaluation of the polymerase chain reaction for the rapid diagnosis of tuberculosis. J Clin Pathol 2004;57:281-5.
- Tso HW, Lau YL, Tam CM, Wong HS, Chiang AK. Associations between IL12B polymorphisms and tuberculosis in the Hong Kong Chinese population. J Infect Dis 2004;190:913-9.
- Chomej P, Bauer K, Bitterlich N, Hui DSC, Chan KS, Gosse H, Schauer J, Hoheisel g, Sack U. Differential diagnosis of pleural effusions by fuzzy-logic-based analysis of cytokines. Respir Med 2004;98:308-17.

2003

- Au WY, Cheng VC, Ho PL, Yuen KY, Hung I, Ma SY, Lie AK, Liang R, Kwong YL. Nontuberculous mycobacterial infections in Chinese hematopoietic stem cell transplantation recipients. Bone Marrow Transplant 2003;32:709-14.
- Leung CC, Law WS, Chang KC, Tam CM, Yew WW, Chan CK, Wong MY. Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. Chest 2003;124:2112-8.
- Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, Lee J. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. Chest 2003;124:1476-81.
- Wong DA, Yip PC, Tse DL, Tung VW, Cheung DT, Kam KM. Routine use of a simple low-cost genotypic assay for the identification of mycobacteria in a high throughput laboratory. Diagn Microbiol Infect Dis 2003;47:421-6.
- Cheng VC, Woo PC, Lau SK, Cheung CH, Yung RW, Yam LY, Yuen KY. Peripartum tuberculosis as a form of immunorestitution disease. Eur J Clin Microbiol Infect Dis. 2003;22:313-7. Review.
- Cheng VC, Yam WC, Woo PC, Lau SK, Hung IF, Wong SP, Cheung WC, Yuen KY. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. Eur J Clin Microbiol Infect Dis 2003;22:597-602.
- Davies PD, Yew WW. Recent developments in the treatment of tuberculosis. Expert Opin Investig Drugs 2003;12:1297-312.
- So SY. The continued threat of tuberculosis. Hong Kong Med J 2003;9:77.
- Tam CM, Leung CC, Noertjojo K, Chan SL, Chan-Yeung M. Tuberculosis in Hong Kong – patient characteristics and treatment outcome. Hong Kong Med J 2003;9:83-90.
- Chan-yeung M, Noertjojo K, Leung CC, Chan SL, Tam CM. Prevalence and predictors of default from tuberculosis treatment in Hong Kong. Hong Kong Med J 2003;9:263-8.
- Chan KH, Ho PL, Cheung RT, Tsang KL, Fong GC, Cheng PW, Ho SL. Tuberculous meningitis with tuberculomata presenting as postpartum pyrexia of unknown origin. Hosp Med 2003;64:306-7.
- Yew WW, Tam CM. DOTS and DOTS-Plus in Hong Kong [letter]. Int J Tuberc Lung Dis 2003;7(1):99-100.
- Yew WW, Leung SK. Prediction of residual pleural thickening in tuberculous pleural effusion. Int J Tuberc Lung Dis 2003;7:199-200.
- Chau CH, Yew WW, Lam FM. Pleural effusion due to Mycobacterium gordonae infection. Int J Tuberc Lung Dis 2003;7:503.
- Leung CC, Yew WW, Chan CK, Tam CM, Lam CW, Chang KC, Chau CH, Lau KS, Law WS. Smoking and tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2003;7:980-6.
- Chan-Yeung M, Tam CM, Wong H, Leung CC, Wang J, Yew WW, Lam CW, Kam KM. Molecular and conventional epidemiology of TB in Hong Kong: a population-based prospective study. J Clin Microb 2003;41:2706-8.
- Lee J, Yew WW, Wong CF, Wong PC, Chiu CS. Multidrug-resistant tuberculosis in a lung transplant recipient. J Heart Lung Transplant 2003;22:1168-73.
- Leung ET, Kam KM, Chiu A, Ho PL, Seto WH, Yuen KY, Yam WC. Detection of katG Ser315Thr substitution in respiratory specimens from patients with isoniazid-resistant Mycobacterium tuberculosis using PCR-RFLP. J Med Microbiol 2003;52(11):999-1003.
- Wong CF, Yew WW, Leung SK, Chan CY, Hui M, Au-Yeang C, Cheng AF. Assay of pleural fluid interleukin-6, tumour necrosis factor-alpha and interferon-gamma in the diagnosis and outcome correlation of tuberculous effusion. Respir Med 2003;97:1289-95.

2002

- Kam KM, Yip CW, Tse LW, Leung OC, Sin LP, Chan MY, Wong WS. Trends in multidrug-resistant Mycobacterium tuberculosis in relation to sputum smear positivity in Hong Kong, 1989-1999. Clin Infect Dis 2002;34:324-9.
- Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. Drug Saf 2002;25:111-33.
- Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, Lau SK, Yuen KY. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21:803-9.
- Yuen KY, Woo PC. Tuberculosis in blood and marrow transplant recipients. Hematol Oncol 2002;20:51-62. Review.
- Chang KC, Leung CC, Tam CM. A clinical approach to tuberculosis. Hong Kong Med Ass CME Bull 2002;1-11.
- Lee WY, Pang KY, Wong CK. Brain tuberculoma in Hong Kong. Hong Kong Med J 2002;8:52-6.
- Leung ECC, Tam CM. Comorbidities among patients with tuberculosis in Hong Kong. Hong Kong Practitioner 2002;24:170-8.
- Vernon A, Burman W, Horsburgh CR. Another step on the path to better TB therapies (ed). Int J Tuberc Lung Dis 2002;6:1-2.

- Tam CM, Chan SL, Kam KM, Goodall RL, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Final report at 5 years: prognostic value of various measures. Int J Tuberc Lung Dis 2002;6:3-10.
- Chan-Yeung M, Noertjojo K, Chan SL, Tam CM. Sex differences in tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2002;6:11-8.
- Noertjojo K, Tam CM, Chan SL, Tan J, Chan-Yeung M. Contact examination for tuberculosis in Hong Kong is useful. Int J Tuberc Lung Dis 2002;6:19-24.
- Yew WW, Chau CH. Utility of fluoroquinolones in multidrug-resistant tuberculosis--a balanced view? Int J Tuberc Lung Dis 2002;6174-5; author reply 175-6.
- Chan-Yeung M, Noertjojo K, Tan J, Chan SL, Tam CM. Tuberculosis in the elderly in Hong Kong. Int J Tuberc Lung Dis 2002;6:771-9.
- Noertjojo K, Tam CM, Chan SL, Chan-Yeung MM. Extra-pulmonary and pulmonary tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2002;6:879-86.
- Yew WW, Chan E, Chan CY, Cheng AF. Genotypic and phenotypic resistance of Mycobacterium tuberculosis to rifamycins and fluoroquinolones. Int J Tuberc Lung Dis 2002;6:936-7.
- Yew WW, Chau CH, Lee J. Superficial fungal infection of the skin during treatment of tuberculosis. Int J Tuberc Lung Dis 2002;6:1132.
- Leung CC, Yew WW, Chan CK, Chau CH, Tam CM, Lam CW, Tam WO, Lau KS, Liu WT. Tuberculosis in older people: a retrospective and comparative study from Hong Kong. J Am Geriatr Soc 2002; 50:1219-26.
- Chang KC, Leung CC, Tam CM. Recent trend of tuberculosis in Hong Kong. Public Health & Epidemiology Bulletin 2002;11:69-75.
- Tam LS, Li EK, Wong SM, Szeto CC. Risk factors and clinical features for tuberculosis among patients with systemic lupus erythematosus in Hong Kong. Scand J Rheumatol. 2002;31:296-300.

2001

- Lui SL, Tang S, Li FK, Choy BY, Chan TM, Lo WK, Lai KN. Tuberculosis infection in Chinese patients undergoing continuous ambulatory peritoneal dialysis. Am J Kidney Dis 2001;38:1055-60.
- Chan CY, Au-Yeang C, Yew WW, Hui M, Cheng AF. Postantibiotic effects of antituberculosis agents alone and in combination. Antimicrob Agents Chemother 2001;45:3631-4.
- Lam TH, Ho SY, Hedley AJ, Mak KH, Peto R. Mortality and smoking in Hong Kong: case-control study of all adult deaths in 1998. BMJ 2001;323:361.
- Yew WW. Therapeutic drug monitoring in antituberculosis chemotherapy: clinical perspectives. Clin Chim Acta 2001;313:31-6.
- Yew WW, Tong SC, Lui KS, Leung SK, Chau CH, Wang EP. Comparison of MB/BacT system and agar proportion method in drug susceptibility testing of Mycobacterium tuberculosis. Diagn Microbiol Infect Dis 2001;39:229-32.
- Seto WH. Preventing nosocomial Mycobacterium tuberculosis transmission in international settings. Emerg Infect Dis 2001;7:245-8.
- Yuen MC, Tung WK. An uncommon cause of foot ulcer: tuberculosis osteomyelitis. Emerg Med J 2001;18:140-1.
- Chan MY, Borgdorff M, Yip CW, de Haas PE, Wong WS, Kam KM, Van Soolingen D. Seventy percent of the Mycobacterium tuberculosis isolates in Hong Kong represent the Beijing genotype. Epidemiol Infect 2001;127:169-71.
- Chan SL, Lee YT, Chan YC, Au YK, Yeung VT. A young male patient with persistent fever due to tuberculous peritonitis. Hong Kong Med J 2001;7:209-12.
- Lee J, Yew WW, Wong PC, Fu KH. Non-hodgkin's pleural lymphoma in long-standing tuberculous pyothorax mimicking suppuration. Int J Infect Dis 2001;5:167-9.
- Yew WW. Risk factors for hepatotoxicity during anti-tuberculosis chemotherapy in Asian populations. Int J Tuberc Lung Dis 2001;5:99-100.
- Chang KC, Leung CC, Tam CM. Tuberculosis risk factors in a silicotic cohort in Hong Kong. Int J Tuberc Lung Dis 2001;5:177-84.
- Yew WW, Wong CF, Chan CY, Cheung SW, Cheng AF. Serological diagnosis of tuberculosis using IgA detection against the mycobacterial kp-90 antigen. Int J Tuberc Lung Dis 2001;5:585-6.
- Leung CC, Tam CM, Chan SL, Chan-Yeung M, Chan CK, Chang KC. Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. Int J Tuberc Lung Dis 2001;5:717-23.
- Espinal MA, Gupta R, Raviglione MC. The future may not be so dark (ed). Int J Tuberc Lung Dis 2001;5:787-8.
- Kam KM, Yip CW. Surveillance of Mycobacterium tuberculosis drug resistance in Hong Kong, 1986-1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001;5:815-23.
- Yew WW, Chau CH, Lee J, Wong PC, Leung CK. Hoarseness due to recurrent laryngeal nerve palsy from intrathoracic mycobacteriosis. Int J Tuberc Lung Dis 2001;5:1074-5.
- Green RA. Efficacy of the BCG revaccination programme in Hong Kong (letter). Int J Tuberc Lung Dis 2001;5(12):1161.
- Fine PEM. Efficacy of the BCG revaccination programme in Hong Kong (letter). Int J Tuberc Lung Dis 2001;5(12):1161-2.
- Wong DA, Yip PC, Cheung DT, Kam KM. Simple and rational approach to the identification of Mycobacterium tuberculosis, Mycobacterium avium complex species, and other commonly isolated mycobacteria. J Clin Microbiol 2001;39:3768-71.
- Hui M, Cheung SW, Chan CY, Cheng AF. Rapid identification of Mycobacterium tuberculosis complex from Bactec 12B broth cultures originating from non-respiratory secretion specimens: comparison between Accuprobe and in-house polymerase chain reaction. Pathology 2001;33:61-5.
- Chu CM, Yung CY, Leung WS, Chan VL, Leung EM. Early unplanned readmission of patients with newly diagnosed tuberculosis discharged from acute hospital to ambulatory treatment. Respirology 2001;6:145-9.
- Wong GWK, Hui DSC, Tam CM, Chan HH, Fok TF, Chan-Yeung M, Lai CKW. Asthma, atopy and tuberculin responses in Chinese schoolchildren in Hong Kong. Thorax 2001;56:770-3.
- Hoheisel G, Sach U, Hui DS, Huse K, Chan KS, Chan KK, Hartwig K, Schuster E, Scholz GH, Schauer J. Occurrence of matrix metalloproteinases and tissue inhibitors of metalloproteinases in tuberculous pleuritis. Tuberculosis (Edinb) 2001;81:203-9.

2000

- Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, Lee J. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000;117:744-51.
- Lau YL, Chan GC, Ha SY, Hui YF, Yuen KY. The role of phagocytic respiratory burst in host defense against Mycobacterium tuberculosis. Clin Infect Dis 1998;26:226-7.
- Wong WM, Wu PC, Yuen MF, Cheng CC, Yew WW, Wong PC, Tam CM, Leung CC, Lai CL. Antituberculosis drug-related liver dysfunction in chronic hepatitis B infection. Hepatology 2000; 31:201-6.
- Lau KK, Yu TS, Chan CK, Tam CM. The use of ethambutol has lowered the 2-year mortality rate in patients with

tuberculous meningitis [letter]. Hong Kong Med J 2000;6:329-30.
- Tam CM, Leung CC. Cessation of the BCG revaccination programme for primary school children in Hong Kong. Public Health & Epidemiology Bulletin Vol. 9 (3), Aug 2000: 25-27.
- Taylor WR, Zumla A. Referral times of Vietnamese refugees with tuberculosis in camps in Hong Kong. Int J Tuberc Lung Dis 2000;4:350-5.
- Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, Baez J, Kochi A, Dye C, Raviglione MC. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA 2000;283:2537-45.
- Sirgel FA, Donald PR, Odhiambo J, Githui W, Umapathy KC, Paramasivan CN, Tam CM, Kam KM, Lam CW, Sole KM, Mitchison DA. A multicentre study of the early bactericidal activity of anti-tuberculosis drugs. J Antimicrob Chemother. 2000;45:859-70.
- Tam CM, Chan SL, Kam KM, Sim E, Staples D, Sole KM, Al-Ghusein H, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Interim report: no activity of isoniazid in the continuation phase. Int J Tuberc Lung Dis 2000;4:262-7.
- Dye C, Williams BG. Criteria for the control of drug-resistant tuberculosis.Proc Natl Acad Sci 2000;97:8180-5.
- Chan CK, Leung SM, Lee KC, Li R, Tam CM, Leung CC, Law WS. An unusual case of double tuberculous broncho-oesophageal fistulas in an adult. Respirology 2000;5:397-401.
- Ho PL, Chim CS, Yuen KY. Isolated splenic tuberculosis presenting with pyrexia of unknown origin. Scand J Infect Dis 2000;32:700-1.

1999
- Kam KM, Yip CW, Chan MY, Mok CY, Wong WS. IS6110 dot blot hybridization for the identification of Mycobacterium tuberculosis complex. Diagn Microbiol Infect Dis 1999;33:13-8.
- Yew WW, Chau CH, Lee J, Leung CK. Is inhaled corticosteroid useful as adjunctive management in tuberculous pyrexia? Drugs Exp Clin Res 1999;25:179-84.
- Yew WW, Cheung SW, Chau CH, Chan CY, Leung CK, Cheng AF, Wong CF. Serum pharmacokinetics of antimycobacterial drugs in patients with multidrug-resistant tuberculosis during therapy. Int J Clin Pharmacol Res 1999;19:65-71.
- Ho TTY, Wong KH, Lee SS. Low yield of chest radiography in screening for active pulmonary tuberculosis in HIV-infected patients in Hong Kong. Int J STD AIDS 1999;10:409-12.
- Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
- Leung CC, Tam CM. Guidance notes for notification of tuberculosis. Public Health & Epidemiology Bulletin 1999;8:36-9.
- Chan TY. Seasonal variations in vitamin D status and the incidence of tuberculosis in different countries. Respiration 1999;66:196.
- Cheng AF, Tai VH, Li MS, Chan CH, Wong CF, Yew WW, Hui M, Chan CY, Lee JC. Improved recovery of Mycobacterium tuberculosis from pleural aspirates: bedside inoculation, heparinized containers and liquid culture media. Scand J Infect Dis 1999;31:485-7.

1998
- Tocque K, Bellis MA, Tam CM, Chan SL, Syed Q, Remmington T, Davies PD. Long-term trends in tuberculosis. Comparison of age-cohort data between Hong Kong and England and Wales. Am J Respir Crit Care Med 1998;158:484-8.
- Tam CM, Chan SL, Lam CW, Leung CC, Kam KM, Morris JS, Mitchison DA. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. Am J Respir Crit Care Med 1998;157:1726-33.
- Chan CY, Tsang DS, Chan TL, Yew WW, Cheung SW, Cheng AF. Detection of fluoroquinolones in urinary specimens from patients undergoing anti-tuberculous therapy. Chemotherapy 1998;44:7-11. Erratum in: Chemotherapy 1998;44:180.
- Wong CF, Yew WW, Wong PC, Lee J. A case of concomitant tuberculosis and sarcoidosis with mycobacterial DNA present in the sarcoid lesion. Chest 1998;114:626-9.
- Yam WC, Yuen KY, Seto WH. Direct detection of Mycobacterium tuberculosis in respiratory specimens using an automated DNA amplification assay and a single tube nested polymerase chain reaction (PCR). Clin Chem Lab Med 1998;36:597-9.
- Tam CM. Rifapentine – a viewpoint. Drugs 1998;56:617.
- The Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hospital Authority, Hong Kong. Chemotherapy of tuberculosis in Hong Kong: a consensus statement. Hong Kong Med J 1998;4:315-20.
- Mak W, Cheung RTF, Ho SL, Tsang KL, Fong GCY. Tuberculous meningitis in Hong Kong: experience in a regional hospital. Int J Tuberc Lung Dis 1998;2:1040-3.
- Yew WW, Chau CH. Fluoroquinolones and tuberculosis. Int J Tuberc Lung Dis 1998;2:1050-2.
- Wong CF, Yew WW, Chan CY, Au LY, Cheung SW, Cheng AF. Rapid diagnosis of smear-negative pulmonary tuberculosis via fibreoptic bronchoscopy: utility of polymerase chain reaction in bronchial aspirates as an adjunct to transbronchial biopsies. Respir Med 1998;92:815-9.
- Yew WW. Therapeutic drug monitoring in antituberculosis chemotherapy. Ther Drug Monit 1998;20:469-72.

1997
- Yew WW, Chau CH Future directions in the development of new antitubercular drugs. Where do we go from here? Drugs Aging 1997;10:405-10.
- Yew WW, Au KF, Lee J, Chau CH . Levofloxacin in the treatment of drug-resistant tuberculosis. Int J Tuberc Lung Dis 1997;1:89.
- Tam CM, Chan SL, Lam CW, Dickinson JM, Mitchison DA. Bioavailability of Chinese rifapentine during a clinical trial in Hong Kong. Int J Tuberc Lung Dis 1997;1:411-6.
- Ho YI, Chan CY, Cheng AF. In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. J Antimicrob Chemother 1997;40:27-32.
- Yuen KY, Yam WC, Wong LP, Seto WH. Comparison of two automated DNA amplification systems with a manual one-tube nested PCR assay for diagnosis of pulmonary tuberculosis. J Clin Microbiol 1997;35:1385-9.
- Yuen KY, Chan KS, Chan CM, Ho PL, Ng MH. Monitoring the therapy of pulmonary tuberculosis by nested polymerase chain reaction assay. J Infect 1997;34:29-33.
- Sun RY, Senok AC, Ho A, Oppenheimer SJ, Davies DP. Meningitis in Hong Kong children, with special reference to the infrequency of haemophilus and meningococcal infection. J Paediatr Child Health 1997;33:296-9.
- Yuen AP, Wong SH, Tam CM, Chan SL, Wei WI, Lau SK. Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. Otolaryngol Head Neck Surg 1997;116:189-92.

1996
- Yew WW, Chau CH, Leung S. Anti-tuberculosis drugs and liver toxicity. Eur Respir J 1996;9:389-90.
- Woo J, Chan HS, Hazlett CB, Ho SC, Chan R, Sham A, Davies PD. Tuberculosis among elderly Chinese in residential homes: tuberculin reactivity and estimated prevalence. Gerontology 1996;42:155-62.
- Lau KK, Yuen H. Paradoxical development of brainstem tuberculoma during treatment for tuberculous meningitis. Hong Kong Med J 1996;2:211-2.
- Chan CM, Yuen KY, Chan KS, Yam WC, Yim KHM, Ng WF, Ng MH. Single-tube nested polymerase chain reaction in the diagnosis of tuberculosis. J Clin Pathol 1996;49:290-4.
- Yew WW, Chau CH. New antimycobacterial agents. Monaldi Arch Chest Dis 1996;51:394-404.
- Tam CM. Tuberculosis in Hong Kong. Public Health & Epidemiology Bulletin 1996;5(4):25-8.
- Yew WW. Pefloxacin and pulmonary tuberculosis. Tuberc Lung Dis 1996;77:194.

1995
- Kapur V, Li LL, Hamrick MR, Plikaytis BB, Shinnick TM, Telenti A, Jacobs WR Jr, Banerjee A, Cole S, Yuen KY, et al. Rapid Mycobacterium species assignment and unambiguous identification of mutations associated with antimicrobial resistance in Mycobacterium tuberculosis by automated DNA sequencing. Arch Pathol Lab Med 1995;119:131-8.
- Yew WW, Chau CH, Wong PC, Lee J, Wong CF, Cheung SW, Chan CY, Cheng AF. Ciprofloxacin in the management of pulmonary tuberculosis in the face of hepatic dysfunction. Drugs Exp Clin Res 1995;21:79-83.
- Chan CH, Lai CK, Leung JC, Ho AS, Lai KN. Elevated interleukin-2 receptor level in patients with active pulmonary tuberculosis and the changes following anti-tuberculosis chemotherapy. Eur Respir J 1995;8:70-3.
- Wong PC, Yew WW, Wong CF, Choi HY. Ethambutol-induced pulmonary infiltrates with eosinophilia and skin involvement. Eur Respir J 1995;8:866-8.
- Yew WW, Chau CH. Drug-resistant tuberculosis in the 1990s. Eur Respir J 1995;8:1184-92.
- Dai DLK, LeeYC. Usefulness of the Mantoux test in screening for active pulmonary tuberculosis in the Hong Kong elderly. Hong Kong Med J 1995;1:195-200.
- Chong LY, Lo KK. Cutaneous tuberculosis in Hong Kong: a 10-year retrospective study. Int J Dermat 1995;34:26-9.
- Yuen KY, Chan CM, Chan KS, Yam WC, Ho PL, Chau PY. IS6110 based amplityping assay and RFLP fingerprinting of clinical isolates of Mycobacterium tuberculosis. J Clin Pathol 1995;48:924-8.
- Chan CH, Or KK, Cheung W, Woo J. Adverse drug reactions and outcome of elderly patients on antituberculosis chemotherapy with and without rifampicin. J Med 1995;26:43-52.
- Woo J, Chan C, Chan R, Cheung W, Or K, Chan K. Correlation between steady-state plasma concentration of antituberculous drugs and age, inclusion of rifampicin in the treatment regimen, adverse drug reactions and other clinical parameters. J Med 1995;26:279-94.
- Hosker HSR, Lam CW, Ng TK, Ma HK, Chan SL. The prevalence and clinical significance of pulmonary infection due to non-tuberculous mycobacteria in Hong Kong. Respir Med 1995;89:3-8.
- Ip MS, Yuen KY, Chiu EK, Chan JC, Lam WK, Chan TK. Pulmonary infections in bone marrow transplantation: the Hong Kong experience. Respiration 1995;62:80-3.
- Yew WW, Wong CF, Lee J, Wong PC, Chau CH. Do beta-lactam-beta-lactamase inhibitor combinations have a place in the treatment of multidrug-resistant pulmonary tuberculosis? Tuberc Lung Dis 1995;76:90-2.
- Yew WW, Chau CH, Wong PC, Choi HY. Ciprofloxacin-induced renal dysfunction in patients with mycobacterial lung infections. Tuberc Lung Dis 1995;76:173-5.
- Yew WW, Lee J. Pathogenesis of cervical tuberculous lymphadenitis: pathways to anatomic localization. Tuber Lung Dis 1995;76:275-6.
- Chan CH, Woo J, Or KK, Chan RC, Cheung W. The effect of age on the presentation of patients with tuberculosis. Tuberc Lung Dis 1995;76:290-4.

1994
- Yew WW, Wong PC, Lee J, Chau CH. Ofloxacin and pulmonary tuberculosis. Chest 1994;105:1624.
- Yew WW, Wong PC, Lee J, Wong CF. Rapid diagnosis of smear-negative pulmonary tuberculosis. Chest 1994;106:326-7.
- Wong CF, Yew WW. Ethambutol-induced neutropenia and eosinophilia. Chest 1994;106:1638-9.
- Yew WW, Chau CH, Lee J, Leung CW. Cholestatic hepatitis in a patient who received clarithromycin therapy for a Mycobacterium chelonae lung infection. Clin Infect Dis 1994;18:1025-6.
- Yew WW, Chau CH, Tse LS. Does hospitalizing patients with tuberculosis ensure compliance with drug regimens? Clin Infect Dis 1994;19:554-5.
- Chan SL, Yew WW, Porter JHD, McAdam KPWJ, Allen BW, Dickinson JM, Ellard GA, Mitchison DA. Comparison of Chinese and Western rifapentines and improvement of bioavailability by prior taking of various meals. Int J Antimicrob Agents 1994;3:267-74.
- Yew WW, Piddock LJ, Li MS, Lyon D, Chan CY, Cheng AF. In-vitro activity of quinolones and macrolides against mycobacteria. J Antimicrob Chemother 1994;34:343-51.
- Cheng AF, Li MS, Chan CY, Chan CH, Lyon D, Wise R, Lee JC. Evaluation of three culture media and their combinations for the isolation of Mycobacterium tuberculosis from pleural aspirates of patients with tuberculous pleurisy. J Trop Med Hyg 1994;97:249-53.
- Hoheisel G, Chan KM, Chan HS, Chan KS, Teschler H, Costobel U. Endobronchial tuberculosis: diagnostic features and therapeutic outcome. Respir Med 1994;88:593-7.
- Chan SL, Wong PC, Tam CM. 4-, 5- and 6-month regimens containing isoniazid, rifampicin, pyrazinamide and streptomycin for treatment of pulmonary tuberculosis under program conditions in Hong Kong. Tuberc Lung Dis 1994;75:245-50.
- Chan KL, Chan HS, Lui SF, Lai KN. Recurrent acute pancreatitis induced by isoniazid. Tuberc Lung Dis 1994;75:383-5.

1993
- Tsui SY, Yew WW, Li MS, Chan CY, Cheng AF. Postantibiotic effects of amikacin and ofloxacin on Mycobacterium fortuitum. Antimicrob Agents Chemother 1993;37:1001-3.
- Yew WW, Wong CF, Wong PC, Lee J, Chau CH. Adverse neurological reactions in patients with multidrug-resistant pulmonary tuberculosis after coadministration of cycloserine and ofloxacin. Clin Infect Dis 1993;17:288-9.
- Yew WW, Wong PC, Woo HS, Yip CW, Chan CY, Cheng FB. Characterization of Mycobacterium fortuitum isolates from sternotomy wounds by antimicrobial susceptibilities, plasmid profiles, and ribosomal ribonucleic acid gene restriction patterns. Diagn Microbiol Infect Dis 1993;17:111-7.
- Chan SL. Update on chemotherapy for tuberculosis. Hong Kong Pract 1993;15:2448-53.
- Yew WW, Tam CM, Chan CY, Li MS, Cheng AF. Lack of activities of amikacin and sulphamethoxazole against Mycobacterium avium-intracellulare. Int J Clin Pharmacol Res 1993;13:65-8.

- Yuen KY, Chan KS, Chan CM, Ho BS, Dai LK, Chau PY, Ng MH. Use of PCR in routine diagnosis of treated and untreated pulmonary tuberculosis. J Clin Path 1993;46:318-22.
- Das S, Chan SL, Allen BW, Mitchison DA, Lowrie DB. Application of DNA fingerprinting with IS986 to sequential mycobacterial isolates obtained from pulmonary tuberculosis patients in Hong Kong before, during and after short-course chemotherapy. Tuberc Lung Disease 1993;74:47-5.

1992

- Woo J, Chan HS. Therapeutic problems in the management of elderly patients with tuberculosis. Adverse Drug React Toxicol Rev 1992;11:13-8.
- Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992;145:36-41.
- Yew WW, Lee J. Drug treatment of chronic tuberculous empyema. Chest 1992;101:1741-2.
- Yew WW, Lau KS, Tse WK, Wong CF. Imipenem in the treatment of lung infections due to Mycobacterium fortuitum and Mycobacterium chelonae: further experience. Clin Infect Dis 1992;15:1046-7.
- Yew WW, Lee J, Wong PC, Kwan SY. Tolerance of ofloxacin in the treatment of pulmonary tuberculosis in presence of hepatic dysfunction. Int J Clin Pharmacol Res 1992;12:173-8.
- Woo J, Chan CH, Walubo A, Chan KK. Hydrazine--a possible cause of isoniazid--induced hepatic necrosis. J Med 1992;23:51-9.
- Chan SL, Yew WW, Ma WK, Girling DJ, Aber VR, Felmingham D, Allen BW, Mitchison DA. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. Tuberc Lung Dis 1992;73:33-8.
- Hong Kong Chest Service/ British Medical Research Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. Tuberc Lung Dis 1992;73:59-67.

1991

- Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. Am Rev Respir Dis 1991;143:262-7.
- Hong Kong Chest Service/ British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampicin, and pyrazinamide. Results at 30 months. Am Rev Respir Dis 1991;143:700-6.
- Yew WW, Lee J, Chan CY, Cheung SW, Wong PC, Kwan SY. Ofloxacin penetration into tuberculous pleural effusion. Antimicrob Agents Chemother 1991;35:2159-60.
- Lau SK, Wei WI, Kwan S, Yew WW. Combined use of fine-needle aspiration cytologic examination and tuberculin skin test in the diagnosis of cervical tuberculous lymphadenitis. A prospective study. Arch Otolaryngol Head Neck Surg 1991;117:87-90.
- Yew WW, Chan CY, Kwan SY, Cheung SW, French GL. Diagnosis of tuberculous pleural effusion by the detection of tuberculostearic acid in pleural aspirates. Chest 1991;100:1261-3.
- Chan SL. Advances in the Diagnosis of Tuberculosis. JAMA SE Asia 1991;7:11-2.
- Yew WW, Kwan SY, Wong PC, Fu KH. Percutaneous transthoracic needle biopsies in the rapid diagnosis of pulmonary tuberculosis. Lung 1991;169:285-9.
- Walubo A, Chan K, Woo J, Chan HS, Wong CL. The disposition of antituberculous drugs in plasma of elderly patients I. Isoniazid and hydrazine metabolite. Methods Find Exp Clin Pharmacol 1991;13:545-50.
- Walubo A, Chan K, Woo J, Chan HS, Wong CL. The disposition of antituberculous drugs in plasma of elderly patients II. Isoniazid, rifampicin and pyrazinamide. Methods Find Exp Clin Pharmacol 1991;13:551-6.
- Chan CH, Arnold M, Chan CY, Mak TW, Hoheisel GB. Clinical and pathological features of tuberculous pleural effusion and its long-term consequences. Respiration 1991;58:171-5.
- Yew WW, Lau KS, Ling MH. Phenytoin toxicity in a patient with isoniazid-induced hepatitis. Tubercle 1991;72:309-10.

1990

- Chan SL, Reggiardo Z, Daniel TM, Girling DJ, Mitchison DA. Serodiagnosis of tuberculosis using an ELISA with antigen 5 and a hemagglutination assay with glycolipid antigens – results in patients with newly diagnosed pulmonary tuberculosis ranging in extent of disease from minimal to extensive. Am Rev Respir Dis 1990;142:385-90.
- Chan HS, Pang J. Vasculitis in tuberculous infection. Chest 1990;98:511.
- Kwan SY, Yew WW, Chan SL. Nosocomial tuberculosis in hospital staff. The size of the problem in a Hong Kong chest hospital. Chin Med J (Engl) 1990;103:909-14.
- Wu JC, Lee SD, Yeh PF, Chan CY, Wang YJ, Huang YS, Tsai YT, Lee PY, Ting LP, Lo KJ. Isoniazid-rifampin-induced hepatitis in hepatitis B carriers. Gastroenterology 1990;98:502-4.
- Yew WW, Kwan SY, Ma WK, Lui KS, Suen HC. Ofloxacin therapy of Mycobacterium fortuitum infection: further experience. J Antimicrob Chemother 1990;25:880-1.
- Yew WW, Kwan SY, Ma WK, Khin MA, Chau PY. In-vitro activity of ofloxacin against Mycobacterium tuberculosis and its clinical efficacy in multiply resistant pulmonary tuberculosis. J Antimicrob Chemother. 1990;26:227-36.
- Chan SL. Editorial – Tuberculosis in Hong Kong – update. J Hong Kong Med Ass 1990;42:1.
- Chan HS, Sun AJ, Hoheisel GB. Bronchoscopic aspiration and bronchoalveolar lavage in the diagnosis of sputum smear-negative pulmonary tuberculosis. Lung 1990;168:215-20.
- Chan SL. Short course chemotherapy of tuberculosis. Medical Progress 1990;March:7-10.
- Chan HS, Sun A, Hoheisel GB. Endobronchial tuberculosis--is corticosteroid treatment useful? A report of 8 cases and review of the literature. Postgrad Med J 1990;66:822-6.
- Yew WW, Kwan SY, Wong PC, Lee J. Ofloxacin and imipenem in the treatment of Mycobacterium fortuitum and Mycobacterium chelonae lung infections. Tubercle 1990;71:131-3.
- Humphries MJ, Teoh R, Lau J, Gabriel M. Factors of prognostic significance in Chinese children with tuberculous meningitis. Tubercle 1990;71:161-8.
- Yew WW, Kwan SY, Ma WK, Lui KS .Minimal bactericidal and inhibitory concentrations of ofloxacin on Mycobacterium fortuitum at pH 7 and 5: therapeutic implications. Tubercle 1990;71:205-8.

1989

- A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. Am Rev Respir Dis 1989;139:871-6.

- Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Hong Kong Chest Service/ British Medical Research Council. Am Rev Respir Dis 1989;140:1618-22.
- Pang JA, Chan HS, Chan CY, Cheung SW, French GL. A tuberculostearic acid assay in the diagnosis of sputum smear-negative pulmonary tuberculosis. A prospective study of bronchoscopic aspirate and lavage specimens. Ann Intern Med 1989;111(8):650-4.
- Yew WW, Kwan SY, Ma WK, Khin MA, Mok CK. Single daily-dose ofloxacin monotherapy for Mycobacterium fortuitum sternotomy infection. Chest 1989;96:1150-2.
- Chan HS, Pang JA. Effect of corticosteroids on deterioration of endobronchial tuberculosis during chemotherapy. Chest 1989;96:1195-6.
- Chan HS, Pang J. Isolated giant tuberculomata of the liver detected by computed tomography. Gastrointest Radiol 1989;14:305-7.

1988

- Hawkins BR, Higgins DA, Chan SL, Lowrie DB, Mitchison DA, Girling DJ. HLA typing in the Hong Kong Chest Service/ British Medical Research Council study of factors associated with the breakdown to active tuberculosis of inactive pulmonary lesions. Am Rev Respir Dis 1988;138:1616-21.
- Anti-TB regimens of chemotherapy – Recommendations from the Committee on treatment of the International Union against TB and lung disease. Bulletin of the International Union Against TB and Lung Disease (June 1988);63:60-64.
- Woo J, Leung A, Chan K, Lai KN, Teoh R. Pyrazinamide and rifampicin regimens for patients on maintenance dialysis. Int J Artif Organs 1988;11:181-5.
- Arnold M, Chan CY, Cheung SW, Van Hasselt CA, French GL. Diagnosis of nasopharyngeal tuberculosis by detection of tuberculostearic acid in formalin fixed, paraffin wax embedded tissue biopsy specimens. J Clin Pathol 1988;41:1334-6.

1987

- Five-year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. Hong Kong Chest Service/ British Medical Research Council. Am Rev Respir Dis 1987;136:1339-42.
- Woo J, Wong CL, Teoh R, Chan K. Liquid chromatographic assay for the simultaneous determination of pyrazinamide and rifampicin in serum samples from patients with tuberculous meningitis. J Chromatogr. 1987;420:73-80.
- French GL, Chan CY, Cheung SW, Oo KT. Diagnosis of pulmonary tuberculosis by detection of tuberculostearic acid in sputum by using gas chromatography-mass spectrometry with selected ion monitoring. J Infect Dis 1987;156:356-62.
- French GL, Teoh R, Chan CY, Humphries MJ, Cheung SW, O'Mahony G. Diagnosis of tuberculous meningitis by detection of tuberculostearic acid in cerebrospinal fluid. Lancet 1987;2:117-9.

1986

- Ellard GA, Ellard DR, Allen BW, Girling DJ, Nunn AJ, Teo SK, Tan TH, Ng HK, Chan SL. The bioavailability of isoniazid, rifampin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. Am Rev Respir Dis 1986;133:1076-80.
- Yuen WC, Chan YF, Loke SL, Seto WH, Poon GP, Wong KK. Chronic lymphadenopathy caused by Penicillium marneffei: a condition mimicking tuberculous lymphadenopathy. Br J Surg 1986;73:1007-8.
- A controlled trial of six-month and nine-month regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. Tenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. Tubercle 1986;67:243-59.

1984

- Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British medical Research Council. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60months. Am Rev Respir Dis 1984;130:23-8.
- Wong SH, Lau WY, Ho KK, Fan ST, Yiu TF, Chan SL. The management of urinary tuberculosis--a logical approach. Br J Urol 1984;56:349-53.
- Wong SH, Lau WY, Poon GP, Fan ST, Ho KK, Yiu TF, Chan SL. The treatment of urinary tuberculosis. J Urol 1984;131:297-301
- Hong Kong Chest Service/ BMRC. Study of a fully supervised programme of chemotherapy for pulmonary tuberculosis given once weekly in the continuation phase in the rural areas of Hong Kong. Tubercle 1984;65:5-15.
- Survey of the previous investigation and treatment by private practitioners of patients with pulmonary tuberculosis attending government chest clinics in Hong Kong. Hong Kong Chest Service/ British Medical Research Council. Tubercle 1984;65:161-71.
- Survey of patients presenting to the government chest service in Hong Kong and the effects of active tuberculosis case-finding by publicity campaigns. Hong Kong Chest Service/ British Medical Research Council. Tubercle 1984;65:173-84
- Hong Kong Chest Service/ BMRC Survey of deaths in Hong Kong attributed to tuberculosis during a five-year period. Tubercle 1984;65:253-61

1983

- Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis-I. Br Med J (Clin Res Ed). 1983 Jul 2;287(6384):33-5.
- Allen BW, Mitchison DA, Darbyshire J, Chew WW, Gabriel M. Examination of operation specimens from patients with spinal tuberculosis for tubercle bacilli. J Clin Pathol. 1983 Jun;36(6):662-6.
- Allen BW, Mitchison DA, Chan YC, Yew WW, Allan WG, Girling DJ. Amikacin in the treatment of pulmonary tuberculosis. Tubercle 1983;64:111-8.

1982

- A 10-year assessment of a controlled trial comparing debridement and anterior spinal fusion in the management of tuberculosis of the spine in patients on standard chemotherapy in Hong Kong. Eighth Report of the Medical Research Council Working Party on Tuberculosis of the Spine.
  J Bone Joint Surg Br 1982;64:393-8.
- Controlled trial of 4 three-times-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Hong Kong Chest Service/ British Medical Research Council. Tubercle 1982;63:89-98.

1981

- A controlled trial of a 2-month, 3-month, and 12-month regimens of chemotherapy for sputum smear-negative pulmonary tuberculosis: the results at 30 months. Hong Kong Chest Service/ Tuberculosis Research Centre, Madras/ British Medical Research Council. Am Rev Respir Dis 1981;124:138-42.

- Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet 1981;1(8213):171-4.
- Allan WG, Snell NJ, Hill LE, Fayers PM, Scadding JG, Fox W. A survey of deaths in Hong Kong attributed to tuberculosis. Tubercle 1981;62:1-11.
- Hong Kong Chest Service/ TB Research Centre, Madras/ BMRC. A study of the characteristics and course of sputum smear-negative pulmonary tuberculosis. Tubercle 1981;62:155-67.
- Jenner PJ, Ellard GA, Allan WG, Singh D, Girling DJ, Nunn AJ. Serum uric acid concentrations and arthralgia among patients treated with pyrazinamide-containing regimens in Hong Kong and Singapore. Tubercle 1981;62:175-9.

1980

- A service program of antituberculosis chemotherapy with five drugs for four months in the treatment of drug addicts and prisoners with pulmonary tuberculosis in Hong Kong. Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis 1980;122:417-24.

1979

- Horsfall PA, Plummer J, Allan WG, Girling DJ, Nunn AJ, Fox W. Double blind controlled comparison of aspirin, allopurinol and placebo in the management of arthralgia during pyrazinamide administration. Tubercle. 1979 Mar;60(1):13-24.
- Hong Kong Chest Service/ BMRC. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24months. Tubercle 1979;60:201-10.
- Allan WG, Girling DJ, Fayers PM, Fox W. The symptoms of newly diagnosed pulmonary tuberculosis and patients' attitudes to the disease and to its treatment in Hong Kong. Tubercle.1979;60:211-23.

1978

- Hong Kong Chest Service/ BMRC. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. First report. Am Rev Respir Dis 1978;118:219-28.
- Five-year assessments of controlled trials of ambulatory treatment, debridement and anterior spinal fusion in the management of tuberculosis of the spine. Studies in Bulawayo (Rhodesia) and in Hong Kong. Sixth report of the Medical Research Council Working Party on Tuberculosis of the Spine. J Bone Joint Surg Br 1978;60:163-77.

1977

- Allan WG. Hong Kong tuberculosis treatment services/ British Medical Research Council Study of 6- and 9-month regimens of daily and intermittent streptomycin, isoniazid and pyrazinamide for pulmonary tuberculosis. Bull Int Union Tuberc 1976;51:91-3.
- Dickinson JM, Mitchison DA, Lee SK, Ong YY, O'Mahoney MG, Girling DJ, Nunn AJ. Serum rifampicin concentration related to dose size and to the incidence of the 'flu' syndrome during intermittent rifampicin administration. J Antimicrob Chemother 1977;3:445-52.

1976

- Allan WG. Hong Kong tuberculosis treatment services/ British Medical Research Council Study of 6- and 9-month regimens of daily and intermittent streptomycin, isoniazid and pyrazinamide for pulmonary tuberculosis. Bull Int Union Tuberc 1976;51:91-3.
- Allan WG. A study of BCG at birth in Hong Kong. Bull Int Union Tuberc 1976;51:239-42.
- Hong Kong TB Treatment Services, Singapore TB Service, Royal Postgraduate Medical School, Brompton Hospital, BMRC. Lack of association between rifampicin-dependent antibodies and bacteriological response during intermittent rifampicin treatment. J Antimicrob Chemother 1976;2:265-70.
- Hong Kong TB Treatment Services and East African and BMRC. First-line chemotherapy in the retreatment of bacteriological relapses of pulmonary tuberculosis following a shortcourse regimen. Lancet 1976;1:162-3.
- Hong Kong TB Treatment Services/ BMRC. Adverse reactions to short-course regimens containing streptomycin, isoniazid, pyrazinamide and rifampicin in Hong Kong. Tubercle 1976;57:81-95.

1975

- Hong Kong TB Treatment Services/ BMRC Investigation. Investigations of allergic status and blood counts in Chinese patients receiving daily or iintermittent rifampicin in Hong Kong. Clin Allergy 1975;5:189-99.
- Hong Kong TB Treatment Services/ BMRC. Controlled trial of 6- and 9-month regimens of daily and intermittent streptomycin plus isoniazid plus pyrazinamide for pulmonary tuberculosis in Hong Kong. Tubercle 1975;56:81-96.
- The influence of age and sex on the incidence of the ‘flu’ syndrome and rifampicin dependent antibodies in patients on intermittent rifampicin for tuberculosis. Hong Kong TB Treatment Services/ BMRC. Tubercle 1975;56:173-8.
- Hong Kong TB Treatment Services/ Brompton Hospital/ BMRC. A controlled trial of daily and intermittent rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis: results up to 30 months. Tubercle 1975;56:179-89.

1974

- A controlled trial of anterior spinal fusion and debridement in the surgical management of tuberculosis of the spine in patients on standard chemotherapy: a study in Hong Kong. Br J Surg 1974;61:853-66.
- A controlled clinical trial of small daily doses of rifampicin in the prevention of adverse reactions to the drug in a once-weekly regimen of chemotherapy. A Hong Kong Tuberculosis Treatment Services-British Medical Research Council Investigation. Clin Allergy 1974;4:1-12.
- Allan WG. Practical policies in the control of tuberculosis in Hong Kong. Trop Doct 1974;4:178-83.
- A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis in Hong Kong. A Hong Kong Tuberculosis Treatment Services/ Brompton Hospital/ British Medical Research Council investigation. Tubercle 1974;55:1-27.
- A study in Hong Kong to evaluate the role of pretreatment susceptibility tests in the selection of regimens of chemotherapy for pulmonary tuberculosis—second report. A Hong Kong Tuberculosis Treatment Services/British Medical Research Council Investigation. Tubercle 1974;55:169-92.
- Mitchison DA, Allen BW, Gabriel M, Nunn AJ. Sensitive microbiological method for the detection of rifampicin in urine. Tubercle 1974;55:245-8.

1973

- Hong Kong Treatment Services-Royal Postgraduate Medical School-British Medical Research Council co-operative study of rifampicin plus ethambutol in daily and intermittent regimens. Clinical observations on adverse reactions. Scand J Respir Dis Suppl 1973;84:119-24.
- Allan WG. Tuberculosis in Hong Kong ten years later. Tubercle 1973;54:234-46.

1972

- A study in Hong Kong to evaluate the role of pretreatment susceptibility tests in the selection of regiments of chemotherapy for pulmonary tuberculosis. Hong Kong Tuberculosis Treatment Services-British Medical Research Council Investigation. Am Rev Respir Dis 1972;106:1-22.

- Aquinas M, Allan WG, Horsfall PA, Jenkins PK, Hung-Yan W, Girling D, Tall R, Fox W. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. Br Med J 1972;1:765-71.

1971

- Aquinas M, Allan WG, Horsfall PA, Jenkins PK, Hung-Yan W, Girling D, Tall R, Fox W. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. Br Med J 1972;1:765-71.
- Allan WG, Tanaka A. A comparative study of different techniques of giving BCG vaccination to newborn infants in Hong Kong. Tubercle 1971;52:247-57.

1970

- Mitchison DA, Allen BW, Miller AB. Detection of rifampicin in urine by a simple microbiological assay. Tubercle 1970;51:300-4.

1968

- Hong Kong Anti-TB Association and Government TB Service/ BMRC investigation. A controlled comparison of thiacetazone (thioacetazone) plus isoniazid with PAS plus isoniazid in Hong Kong. Tubercle 1968;49:243-80.

1967

- Moodie AS. Mass ambulatory chemotherapy in the treatment of tuberculosis in a predominantly urban community. Am Rev Respir Dis 1967;95:384-97.

1964

- Pines A, Richardson RJ. Drug-resistance in patients with pulmonary tuberculosis presenting at chest clinics in Hong Kong. Tubercle 1964;45:77-95.
- A report from the Research Committee of the British TB Association and the TB Treatment Services in Hong Kong. A controlled trial of ethionamide with isoniazid in the treatment of pulmonary tuberculosis in Hong Kong. Tubercle 1964;45:299-320.
- Mitchison DA, Lloyd J. Comparison of the sensitivity to thiacetazone of tubercle bacilli from patients in Britain, east Africa, south India and Hong Kong. Tubercle 1964;45:360-9.

1963

- Moodie AS. Tuberculosis in Hong Kong. Tubercle 1963;44:334-45.

1951

- Moodie AS. Analysis and evaluation of tuberculosis in the British Crown Colony of Hong Kong. WHO/TBC/44;1951: P1-37.

1950

- Lee HL. BCG vaccination against tuberculosis. Bull Hong Kong Chinese Med Ass 1950;43-8.

CHAPTER 20

APPENDICES

Surveillance

Appendix 1	Surveillance case definition for tuberculosis
Appendix 2	Notifiable occupational diseases – tuberculosis (extracted from Second Schedule to Occupational Safety And Health Ordinance (Cap. 509))
Appendix 3	Occupational diseases – tuberculosis (extracted from Second Schedule to Employees' Compensation Ordinance (Cap. 282))
Appendix 4	Tuberculosis notification form (dh1a) (Quarantine and Prevention of Disease Ordinance)
Appendix 5	Tuberculosis notification form (ld483) (Occupational Safety and Health Ordinance)
Appendix 6	De-notification of previously notified TB cases

Treatment of active tuberculosis disease

Appendix 7	Table 1 – Usual dosages of conventional antituberculosis drugs Table 2 – Usual dosages of second-line antituberculosis drugs in the treatment of multidrug-resistant tuberculosis
Appendix 8	Adverse reactions to antituberculosis drugs

Treatment of latent tuberculosis infection

Appendix 9	Tuberculin testing and treatment of latent tuberculosis infection among immunocompetent household contacts aged under 35 of smear positive pulmonary tuberculosis patients
Appendix 10	Algorithm on the treatment of latent tuberculosis infection in HIV-infected persons in Hong Kong

Programme form and outcome evaluation

Appendix 11	Definitions of some terms on treatment outcomes and performance indicators
Appendix 12	Programme forms (PFA, PFB1, PFB2, PFC, PFD)

Management of multidrug-resistant tuberculosis and programme forms

Appendix 13a	Protocol for the management flow and reporting of multidrug-resistant TB (MDR-TB) cases to an MDR-TB Registry
Appendix 13b	Form for notification of case to MDR-TB registry at Wanchai Chest Clinic
Appendix 14	Supplementary programme forms for MDR-TB patients

Surveillance Case Definition for Tuberculosis

Clinical description

Tuberculosis (TB) is a chronic bacterial infection characterized pathologically by the formation of granulomas, most common site of infection is the lungs, but other organs may be involved:

- **Pulmonary TB:** Classical symptoms including persistent cough, haemoptysis, afternoon fever, night sweating and weight loss.
- **Extrapulmonary TB:** Clinical features referable to the respective organ/ system and general well-being affected.

Clinical case definition

A case that meets the following criteria:

- Signs and symptoms compatible with active TB; and
- Supporting evidence from relevant and clinically indicated diagnostic evaluation (e.g., abnormal, unstable [i.e., worsening or improving] chest radiographs) and
- The attending physician forms the opinion that treatment for active TB with a combination of anti-TB medications is required.

Laboratory criteria

Any of the following:

- Isolation of *Mycobacterium tuberculosis complex* from a clinical specimen (through culture and identification tests)
- Demonstration of *Mycobacterium tuberculosis* from a clinical specimen by nucleic acid amplification test (e.g., polymerase chain reaction together with species-specific probe)
- Demonstration of acid-fast bacilli in a clinical specimen (e.g., histological examination)

Confirmed case

A clinically compatible illness that is laboratory confirmed, or in the absence of laboratory confirmation, a case meeting the clinical case definition and showing an appropriate response to treatment

Probable case

- All cases meeting either the clinical case definition or laboratory criteria, but not the full set of criteria for a confirmed case.

Special footnotes:

- *If there is strong clinical suspicion of active TB, notify the case even before all the criteria for clinical case definition are met*
- *Notification should be made for suspected or confirmed cases even after their death*
- *When a fresh episode of active TB, such as relapse of pulmonary TB, occurs in the same patient*
- *Notification is not necessary for the following conditions when there is no evidence of active TB:*
    i. *Persons who are found to have old TB scars on chest radiographs*
    ii. *Recent conversion of tuberculin skin test from negative to positive without supportive clinical or radiographic evidences of active disease*
    iii. *Cases given medications for treatment of latent TB infection only (or "TB chemoprophylaxis")*
    iv. *Cases diagnosed as having disease caused by non-tuberculous mycobacteria*

Notifiable Occupational Diseases – Tuberculosis

(Extracted from Second Schedule to
Occupational Safety And Health Ordinance (Cap. 509))[#]

Disease	Occupation
Tuberculosis	Any occupation involving close and frequent contact with a source of tuberculosis infection that is attributable to employment: (a) in the medical treatment or nursing of a person or persons suffering from tuberculosis, or in a service ancillary to that treatment or nursing; or (b) in attending to a person suffering from tuberculosis, where the need for attendance arises because of the person's physical or mental infirmity; or (c) as a research worker engaged in research in connection with tuberculosis; or (d) as a laboratory worker, pathologist or post-mortem worker, where the employment involves working with materials that are a source of TB infection; or (e) in any occupation ancillary to employment in an occupation specified in paragraph (d).

[#] Full text available at http://www.legislation.gov.hk/eng/index.htm. Accessed on 1.9.2005

Occupational Diseases – Tuberculosis

(Extracted from Second Schedule to
Employees' Compensation Ordinance (Cap. 282))[#]

Description of occupational disease	Nature of trade, industry or process	Prescribed period[@]
Tuberculosis	Any occupation involving close and frequent contacts with a source or sources of tuberculosis infection by reason of employment – (a) in the medical treatment or nursing of a person or persons suffering from tuberculosis, or in a service ancillary to such treatment or nursing; (b) in attendance upon a person or persons suffering from tuberculosis, where the need for such attendance arises by reason of physical or mental infirmity; (c) as a research worker engaged in research in connection with tuberculosis; (d) as a laboratory worker, pathologist, or post-mortem worker, where the occupation involves working with materials which are a source of tuberculosis infection, or in any occupation ancillary to such employment.	6 months

[#] Full text available at <http://www.legislation.gov.hk/eng/index.htm>. Accessed on 1.9.2005.
[@] The objective of prescribing occupational diseases for compensation purpose is to facilitate the application of the principle of presumption of occupational origin of a disease in compensation claims. The incapacitated employee will be relieved from the legal complications of having to prove that a certain disease is of occupational origin. Compensation process is hence expedited.

FORM 1

QUARANTINE AND PREVENTION OF DISEASE ORDINANCE

(Cap. 141)

TUBERCULOSIS NOTIFICATION

Particulars of Infected Person

<table>
<tr><td colspan="3">Name in English</td><td colspan="2">Name in Chinese</td><td colspan="2">Age/Sex:</td><td>I.D. Card/Passport No.</td></tr>
<tr><td colspan="7">Address:</td><td>Telephone Number:</td></tr>
<tr><td colspan="7">Place of Work/
School Attended:</td><td>Telephone Number:</td></tr>
<tr><td colspan="2">Site of TB</td><td colspan="3">Sputum</td><td colspan="2">Disposal</td><td rowspan="5">Hospital/Clinic sent to (if any):</td></tr>
<tr><td>Resp. System</td><td></td><td></td><td>Smear</td><td>Culture</td><td>On Treatment</td><td></td></tr>
<tr><td>Meninges</td><td></td><td>Positive</td><td></td><td></td><td>On Observation</td><td></td></tr>
<tr><td>Bone & Joint</td><td></td><td>Negative</td><td></td><td></td><td>Referred</td><td></td><td rowspan="2">Hospital No.:</td></tr>
<tr><td>Other(s)</td><td></td><td>Unknown</td><td></td><td></td><td>Died</td><td></td></tr>
<tr><td colspan="8">Duration of stay in Hong Kong: _____ Years
Does patient have a history of past treatment for tuberculosis? __Yes __No
If yes, please state the YEAR in which he first received treatment: _____</td></tr>
</table>

Notified under the Prevention of the Spread of Infectious Diseases Regulations by

Dr. _____ on _____ / _____ / _____
(Full Name in BLOCK Letters) (Date)

Telephone Number: _____ _____
(Signature)

(Please DELETE whichever is not applicable)

"I will arrange for examination of contacts myself."

"Please arrange for examination of contacts to be done by the Government Chest Service."

Further Remarks:

DH 1A(s)(Rev.99)

OCCUPATIONAL SAFETY AND HEALTH ORDINANCE
NOTIFICATION OF OCCUPATIONAL DISEASES

To : Commissioner for Labour

PARTICULARS OF PATIENT

Name: _____ HKID/Passport no.: _____

Male/Female* Date of birth: ____ /___ /____ Occupation: _____

Home address: _____

_____

Telephone no. (Home) _____ (Office) _____ (Pager/Mobile) _____

Name and address of employer: _____

_____ Telephone no. (Employer) _____

Workplace address (if different from employer's address): _____

_____

For Internal use:

Code: _____
Code: _____

Code: _____
Code: _____

NOTIFIABLE OCCUPATIONAL DISEASES (*Please put a tick in* □)

□1	Radiation Illness	□18	Lead Poisoning	□35	Chrome Ulceration
□2	Heat Cataract	□19	Manganese Poisoning	□36	Urinary Tract Cancer
□3	Compressed Air Illness	□20	Phosphorus Poisoning	□37	Peripheral Polyneuropathy
□4	Cramp of Hand or Forearm	□21	Arsenic Poisoning	□38	Localised Papillomatous or Keratotic New Skin Growth
□5	Beat Hand	□22	Mercury Poisoning	□39	Occupational Vitiligo
□6	Beat Knee	□23	Carbon Bisulphide Poisoning	□40	Occupational Dermatitis
□7	Beat Elbow	□24	Benzene Poisoning	□41	Chemical Induced Upper Respiratory Tract Inflammation
□8	Tenosynovitis of Hand or Forearm	□25	Poisoning by Nitro-, Amino-, or Chloro- Derivatives of Benzene	□42	Nasal or Paranasal Sinus Cancer
□9	Anthrax	□26	Dinitrophenol Poisoning	□43	Byssinosis
□10	Glanders	□27	Poisoning by Halogen Derivatives of Hydrocarbons	□44	Occupational Asthma
□11	Leptospirosis	□28	Diethylene Dioxide Poisoning	□45	Silicosis
□12	Extrinsic Allergic Alveolitis	□29	Chlorinated Naphthalene Poisoning	□46	Asbestos-Related Diseases
□13	Brucellosis	□30	Poisoning by Oxides of Nitrogen	□47	Occupational Deafness
□14	Tuberculosis in health care workers	□31	Beryllium Poisoning	□48	Carpal Tunnel Syndrome
□15	Parenterally Contracted Viral Hepatitis in health care workers	□32	Cadmium Poisoning	□49	Legionnaires' Disease
□16	Streptococcus suis Infection	□33	Dystrophy of the Cornea	□50	Severe Acute Respiratory Syndrome
□17	Avian Chlamydiosis	□34	Skin Cancer	□51	Avian Influenza A

Diagnosis: Confirm/Suspect* Date of onset of illness: _____ / _____ / _____

Follow-up of patient: Treated/Referred to hospital/Others(specify)*: _____

Other relevant information: _____

Name of notifying medical practitioner: _____

Address of notifying medical practitioner: _____

_____

Telephone no. of notifying medical practitioner: _____

Fax no. of notifying medical practitioner: _____

Date: _____ Signature: _____

**Delete whichever is inapplicable*

*Please return this form by **fax (no. 25812049)** or by **mail** to Occupational Health Service, Labour Department, 15/F Harbour Building, 38 Pier Road, Central, Hong Kong.*
For details of Notifiable Occupational Diseases and their related occupations, please refer to Schedule 2 of the Occupational Safety & Health Ordinance and to the Labour Department publication "Guidance Notes on the Diagnosis of Notifiable Occupational Diseases". Enquiry telephone no. : 2852 4041.

LD483 (Rev. 8.2.2005)

To: Statistics Unit, Wanchai Chest Clinic
99 Kennedy Road, Hong Kong
(Fax: 28346627)

Date:

De-notification of previously notified TB cases

Clinic/ Hospital: _____

Name: _____

HKID no.: _____ Clinic/ Hospital no.: _____

Date notified: _____

Revised diagnosis: _____

Smear: positive / negative / unknown

Culture: positive / negative / unknown

De-notification requested by: _____

****

To Statistics Unit: Please confirm receiving TB de-notification form of the following patient:

Name: _____ Clinic no.: _____

HKID no.: _____ Chest Clinic: _____

It is confirmed that the TB de-notification form of the above named has been received by the Statistics Unit, TB & Chest Service, Department of Health.

Chop or signature: _____ Date: _____

(Form TBCS/DE/0405)

Table 1. Usual dosages of conventional anti-tuberculosis drugs

Drug	Daily dosage			Intermittent dosage (3 times/week)		
	Adults and children (mg/kg)	Adults		Adults and children (mg/kg)	Adults	
		Weight (kg)	Dose		Weight (kg)	Dose
Isoniazid * @	5	–	300 mg #	10	–	–
Rifampicin *	10	<50	450 mg	10-12	–	600 mg
		≥50	600 mg			
Streptomycin *^						
Age ≤50	12-15	<50	500 mg (5 times/week)	12-15	<50	500-750 mg
		≥50	750 mg (5 times/ week)		≥50	750-1000 mg
Age 50-70			500 mg (5 times/week)			500-750 mg
Age ≥70			-			500-750 mg
Pyrazinamide	25-30	<50	1.0-1.5 g	30-40	<50	1.5-2.0 g
		≥50	1.5-2.0 g		≥50	2-2.5 g
Ethambutol §	15	–		30	–	–
Thiacetazone *	2.5	–	150 mg	–	–	–
Rifater		per 10 kg	1 tablet			
		>50 kg	5 tablets			

* *Some authorities recommend higher dosages (per kg body weight) of isoniazid, rifampicin, streptomycin, and thiacetazone for children.*

\# *Some elderly and/or malnourished patients can only tolerate isoniazid 200 mg daily.*

@ *Pyridoxine supplement should be considered for those with malnutrition or at risk of neuropathy, e.g. pregnancy, diabetes mellitus, alcoholism, chronic renal failure, and HIV infection.*

^ *Dosage of streptomycin is adjusted according to age (Reference: American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997;156:S1-25.)*

§ *Even if the renal function is normal, it is prudent not to exceed 2400 mg for thrice-weekly regimens, and 1200 mg for daily regimens. It may also be advisable to use the lean body weight (see Chapter 10) for prescription when the patient is excessively overweight or underweight.*

Table 2. Usual dosages of second-line anti-tuberculosis drugs in the treatment of multidrug-resistant tuberculosis

Drug	Daily dosage			
	Adults and children (mg/kg)	Adults		
		Weight (kg)	Dosage	
Amikacin *	15		750 mg	3 to 5 times/week
Kanamycin *	15		750 mg	
Capreomycin *	15		750 mg	
Ofloxacin			600-800 mg	
Levofloxacin			500-600 mg	
Ciprofloxacin			750-1500 mg	
Ethionamide	15 (adults)	<50	500 mg	
Prothionamide		≥50	750 mg	
Cycloserine	15 (adults)	<50	500 mg	
		≥50	750 mg	
Clofazimine			50-100 mg	
Para-aminosalicylic acid	2 g/10 kg		8-12 g	

* Dosages may be adjusted downward to 500 mg for elderly subjects.

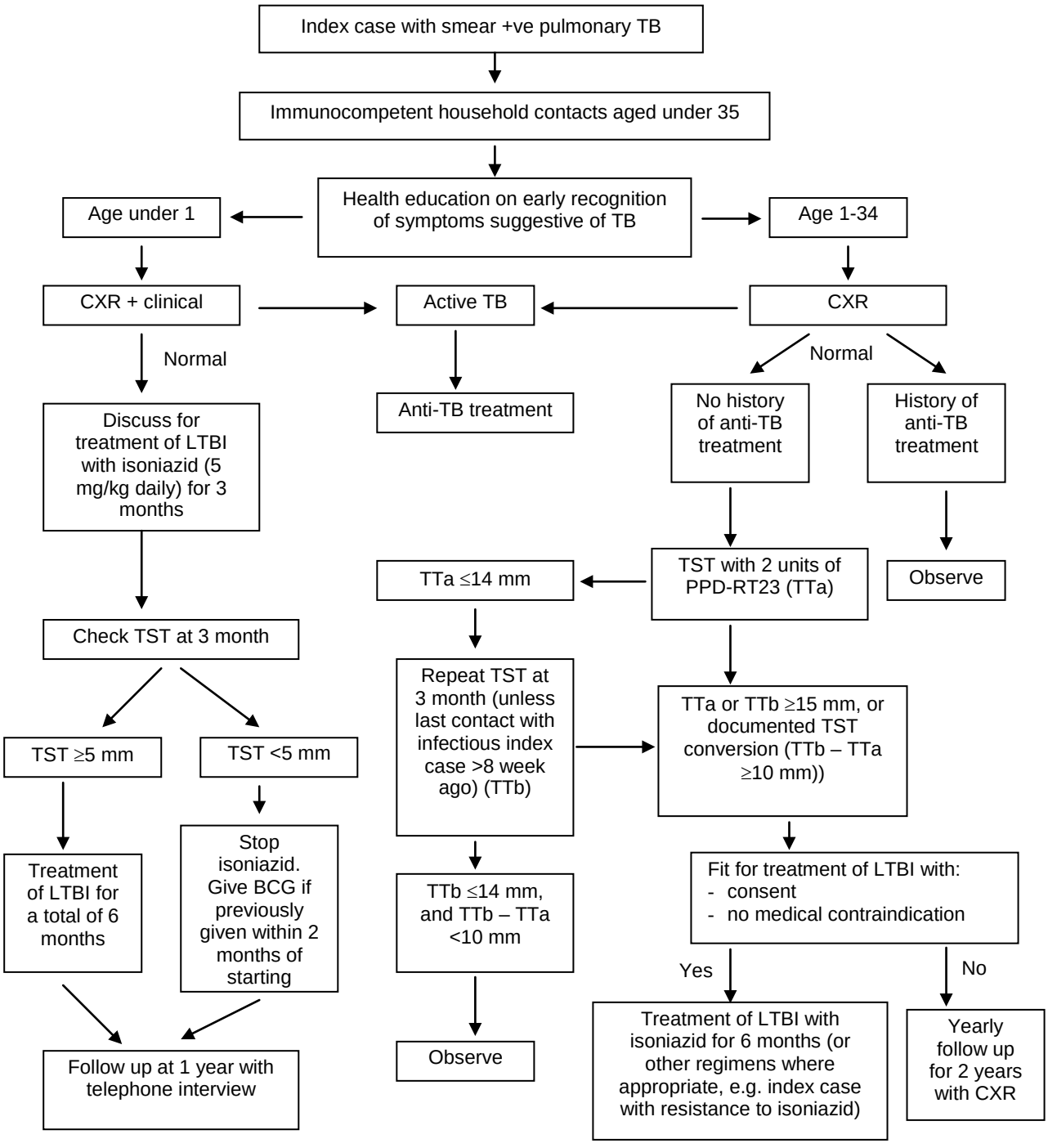
Adverse reactions to anti-tuberculosis drugs

Drug	Reactions		
	Common	**Uncommon**	**Rare**
Isoniazid		Hepatitis Cutaneous hypersensitivity Peripheral neuropathy	Giddiness Convulsion Optic neuritis Mental symptoms Haemolytic anaemia Aplastic anaemia Lupoid reactions Arthralgia Gynaecomastia
Rifampicin		Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura Febrile reactions "Flu syndrome"	Shortness of breath Shock Haemolytic anaemia Acute renal failure
Pyrazinamide	Anorexia Nausea Flushing	Hepatitis Vomiting Arthralgia Cutaneous reaction	Sideroblastic anaemia
Ethambutol		Retrobulbar neuritis Arthralgia	Cutaneous reaction Peripheral neuropathy
Streptomycin	Cutaneous hypersensitivity Giddiness Numbness Tinnitus	Vertigo Ataxia Deafness	Renal damage Aplastic anaemia
Thiacetazone	Gastrointestinal reactions Cutaneous hypersensitivity Vertigo Conjunctivitis	Hepatitis Erythema multiforme Exfoliative dermatitis Haemolytic anaemia	Agranulocytosis

Amikacin Kanamycin Capreomycin	Ototoxicity: hearing damage, vestibular disturbance Nephrotoxicity: deranged renal function test	Clinical renal failure	
Ofloxacin Ciprofloxacin	Gastrointestinal reactions Insomnia	Anxiety Dizziness Headache Tremor	Convulsion Haemolytic anaemia in G6PD deficiency*
Ethionamide Prothionamide	Gastrointestinal reactions	Hepatitis Cutaneous reactions Peripheral neuropathy	Convulsion Mental symptoms Impotence Gynaecomastia
Cycloserine	Dizziness Headache Depression Memory loss	Psychosis Convulsion	Sideroblastic anaemia
Clofazimine	Nausea Giddiness Discolouration of skin (dose-related) and urine Dryness of skin	Eye irritation Diarrhoea with high doses	Taste disorder
Para-aminosalicylic acid	Gastrointestinal reactions	Hepatitis Drug fever	Hypothyroidism Haematological reactions

* Special caution is required in the use of fluoroquinolones among patients with G6PD deficiency.

Tuberculin Testing (TST) And Treatment Of Latent Tuberculosis Infection (LTBI) Among Immunocompetent Household Contacts Aged Under 35 Of Smear-positive Pulmonary Tuberculosis (TB) Patients *

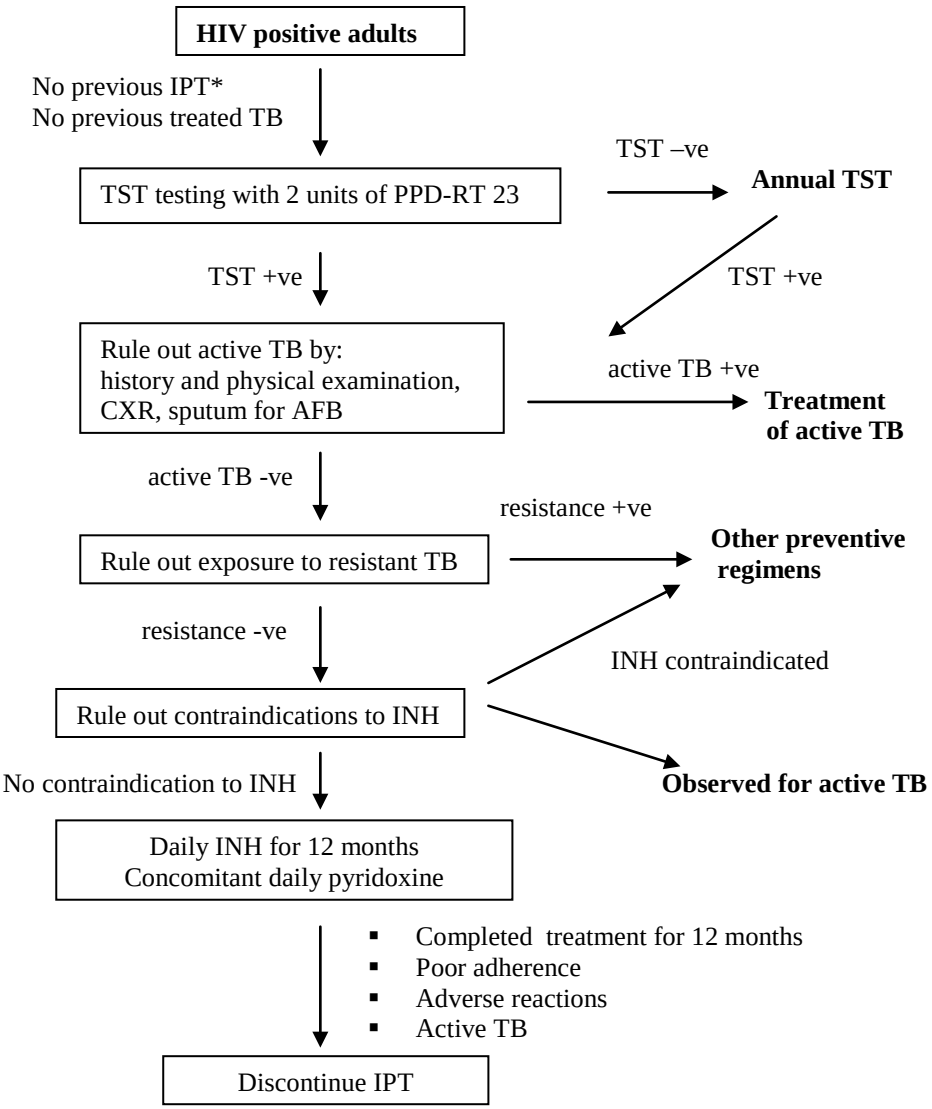


* After finding an index case with smear-positive pulmonary TB, tuberculin testing should be arranged for immunocompetent household contacts aged under 35. All of them should receive health education on early recognition of symptoms suggestive of TB in addition to chest X-ray examination. If active TB is likely, consider anti-TB treatment. If chest X-ray is normal, further management depends on the age.

For infants (aged under 1) with normal chest X-ray, if clinical assessment is also normal, discuss for treatment of latent TB infection with isoniazid 5 mg per kg daily for three months. Tuberculin skin test (TST) is to be done at 3 months. A TST response of 5 mm or more indicates that treatment of latent TB infection should be given for a total of 6 months. If TST response is below 5 mm, stop isoniazid. Additionally, repeat BCG vaccination if it has been given within 2 months before starting isoniazid. All infants are followed up at one year by telephone interview.

For contacts aged 1-34 with normal chest X-ray, consider observation in the presence of a history of anti-TB treatment. In the absence of such a history, arrange TST with 2 units of PPD-RT23 (TTa). If response to TTa is 14 mm or less, repeat TST 3 months later (TTb) unless TTa is done more than 8 weeks after the last contact with the infectious index case. If response to TTb is 14 mm or less, or the difference between TTb and TTa is less than 10 mm, consider observation. On the other hand, if response to TTa or TTb is at least 15 mm, or TST conversion is documented with a difference of at least 10 mm between TTb and TTa, consider treatment of latent TB infection with isoniazid for 6 months, after obtaining consent and excluding medical contraindications. Other alternative preventive treatment regimens may also be given where appropriate, for example, presence of bacillary resistance to isoniazid in the index case. If the contact is unfit for preventive treatment, arrange yearly follow up with chest X-ray for two years.

Algorithm on the treatment of LTBI in HIV-infected persons in Hong Kong



* IPT = isoniazid (INH) preventive treatment

(Reference: Scientific Committee on AIDS of Hong Kong Advisory Council on AIDS. 2002: Recommendations on the treatment of latent TB infection in HIV-positive persons in Hong Kong. Available at http://www.info.gov.hk/aids. Accessed on 1 Oct 2005.)

HIV-positive adults with neither previous isoniazid preventive treatment nor treatment of tuberculosis are eligible for tuberculin skin testing with two units of PPD-RT 23.

If tuberculin skin test is negative, consider annual tuberculin skin testing.

If the tuberculin skin test is positive, consider daily isoniazid preventive treatment for 12 months with pyridoxine, after excluding active tuberculosis, isoniazid-resistant TB, and contraindications for isoniazid. Isoniazid preventive treatment can be discontinued when treatment for 12 months has completed, adherence is poor, adverse reactions occur, or active tuberculosis develops.

If active tuberculosis is present, treat active tuberculosis instead. If isoniazid is contraindicated because of exposure to isoniazid-resistant tuberculosis or other reasons, consider either other preventive regimens or observation.

The above algorithm is based on recommendations on the treatment of latent TB infection in HIV-positive persons in Hong Kong, which were prepared by the Scientific Committee on AIDS of Hong Kong Advisory Council on AIDS in 2002, and accessed on 1 Oct 2005 at http://www.info.gov.hk/aids.

Definitions

Treatment outcomes

Cured	A patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion.
Completed treatment	A patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
Treatment success	The sum of patients who are cured and those who have completed treatment.
Died	A patient who dies for any reason during the course of treatment.
Failure	A patient who, while undergoing treatment, is sputum smear-positive at five months or later during the course of treatment.
Defaulted	A patient who has interrupted treatment for two consecutive months or more.
Transferred out	A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.
Not evaluated	Patients who did not have the treatment outcome evaluated.

Performance indicators

Cure rate (%)	Proportion of cured cases out of all cases registered in a certain period.
Treatment success rate (%)	The sum of the proportion of patients who were cured and patients who completed treatment out of all cases registered in a certain period.
Case detection rate (%)	$\frac{\text{Annual new smear-positive notifications}}{\text{Estimated annual new smear-positive incidence}}$
DOTS detection rate (%)	$\frac{\text{Annual new smear-positive notifications under DOTS}}{\text{Estimated annual new smear-positive incidence}}$

Reference: WHO, IUATLD, KNCV. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis 2001;5:213-5.

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

PFA - To be completed at around DOS (for TB patients) *[DOS = date of starting treatment (or, if patient defaulted>2 months before starting anti-TB treatment, put down the date of diagnosis)]*

Part (A) Basic information

TB notified: N / Y : Date: _ _ / _ _ / _ _ _ _ Sex: M / F Age: _ _ years Date of birth : _ _ / _ _ / _ _ _ _

Marital status: 1.single/ 2.married/ 3.separated/ 4.divorce/ 5.widowed Smoking status: 1.never/ 2.ex-smoker/ 3.current smokers

Institution-related: N / Y : 1.Client / 2.Staff Type: 1.Old age home/ 2.School/ 3. Hospital/ 4.Handicapped/ 5.Prison/ 6.Others

Name of institution: _____

Living situation: 1.street-sleeper/ 2.cubicle bed space/ 3.institution/ 4.work quarter/ 5.alone (but not 1. to 4.)/ 6.with friends/ 7.with family

Resident status: 1.PermanentResident/ 2.ChineseNewImmigrant(inHK<7yr)/ 3.ImportedWorker/ 4.Tourist-2wayPermitChinese/ 5.OtherTourist/ 6.Vietnamese/ 7.IllegalImmigrants

Place of birth: 1.Hong Kong / 2.Mainland/ 3.Others _____

Ethnicity: 1.Chinese/ 2.Other Asian/ 3.Caucasian/ 4.Other _____

Previous BCG history: N / Y / Unknown BCG scar: N / Y

Employment status (including self-employment) at DOS: 1.Full-time/ 2.Part-time/ 3.Retired/ 4.Unemployed/ 5.Housewife/ 6.Student

Occupation (current or last): 1.Blue collar/ 2.White collar/ 3.Medical/ 4.Nursing/ 5.Paramedical/ 6.Supporting health staff/ 7.Not applicable

Job title: _____

Part (B) Information on this episode of TB:

First presentation to: 1. Private doctor / 2.Private Hospital / 3.GOPC / 4.Chest Clinic / 5.Other DH Clinic / 6 .HA Clinic / 7. HA Hospital / 8. Mainland / 9.Overseas

Symptomatic on presentation: N / Y: 1.Chest symptoms / 2.Systemic Symptoms / 3.Other site-specific symptoms

Reason for presentation: 1. Symptom / 2.Contact Screening / 3. Pre-employment / 4.Pre-emigration/ 5.Other body check / 6. Incidental to other illness / 7. Others: _____

Contact with TB patients: N / Y: 1.Household / 2.Work / 3.Casual
1. within 2 year / 2. over 2 year

Previous chemoprophylaxis: N / Y : reason: 1. Contact / 2. Silicosis / 3. HIV / 4. Old scar on CXR / 5. Others _____

Drugs & duration: _____

Part (C) Case category (choose 1 item only):

1. New case (<1m previous Rx)
2. Relapse case.
3. Treatment after default.
4. Failure of previous treatment.

Date of last treatment (mm/yyyy): _ _ / _ _ _ _ Duration of last treatment: _ _ months

5. Others, specify: _____

Part (D) Disease classification: (please circle ≥1 item)

1. Pulmonary tuberculosis
   Extent of disease: 1minimal (total area< RUL)/ 2moderate (> RUL)/ 3advanced (> 1 lung) Cavity: N / Y

Extra-pulmonary tuberculosis:

2. Pleura
3. Lymph node
4. Meninges
5. Miliary
6. Abdomen
7. Bone and joint (other than spine)
8. Spine
9. Genito-urinary tract
10. Naso/oro-pharynx
11. Larynx
12. Pericardium
13. Skin
14. Other site(1), specify _____
15. Other site(2), specify _____
16. Other site(3), specify _____

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1.Chest Clinic/ 2.Chest Hospital/ 3.General Hospital/ 4.Private Practice. ; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)
(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.)

TB-PFA/1-2001

DH2417A

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

PFB1 – To be completed at 6 month from DOS (for TB patients)

Part (E) Mode of TB diagnosis: 1. Bacteriological/ 2.Histological/ 3.Clinical-radiological/ 4.Clinical only (choose 1 item, priority from left to right)

Bacteriological examination for MTB: P (positive), N (negative) , U (not done), NTM (Non-tuberculous Mycobacteria)

	Sputum			**Other type of specimen:** 1.gastric aspirate/ 2.pleural fluid/ 3.bronchial washing/ 4.urine/ 5.biopsy or others, specify: _____		
	Pre-treatment	2 months	3 months	Pre-treatment	2 months	3 months
Smear	P / N / U	P / N / U	P / N / U	P / N / U	P / N / U	P / N / U
Culture	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM

- Histological result from (site) _____: 1 Typical (with caseation) / 2.Granulomatous inflammation / 3.other
  Ziehl-Neelzen staining: P / N / U
- **If pre-treatment culture is positive for MTB, is the ST favourable? (i.e., sensitive to HRES)**: N / Y / U (ST not done)

If unfavourable ST, please mark S (sensitive) or R (resistant) for all ST done:

Isoniazid (H)	: S / R	Pyrazinamide	: S / R	Cycloserine	: S / R
Rifampicin (R)	: S / R	Ofloxacin	: S / R	Other (1) _____	: S / R
Ethambutol (E)	: S / R	Ethionamide	: S / R	Other (2) _____	: S / R
Streptomycin (S)	: S / R	Kanamycin	: S / R		

Part (F) Risk factors for TB: N / Y (If Y, please circle whichever applicable)

1. Diabetes mellitus
2. Lung cancer
3. Other malignancies
4. On cytotoxic drugs
5. On steroid
6. Chronic renal failure
7. HIV
8. Silicosis
9. Alcoholism
10. Drug abuser
11. Gastrectomy
12. General debilitation (e.g., due to old age, immobility, stroke, etc.)
13. Other(1), specify_____
14. Other(2), specify_____
15. Other(3), specify_____

Part (G) Factors affecting treatment choices: N / Y (If Y, please circle whichever applicable)

1. Hepatitis-B carrier
2. Chronic active hepatitis
3. Impaired renal function
4. Chronic renal failure (require dialysis, etc.)
5. Impaired vision
6. Impaired hearing
7. Known drug reaction
8. Known drug resistance
9. Gout
10. Idiopathic thrombocytopenic purpura
11. Other(1), specify_____
12. Other(2), specify_____
13. Other(3), specify_____

Part (H) Other co-morbidities: N / Y : 1. _____ 2. _____ 3. _____

Part (I) Treatment regimen:

6-month short course treatment: N / Y: 1. [2HRZE+4HR] / 2. [2HRZS+4HR]

If neither of the above 2 regimens, please complete the following two questions:

Other standard regimens based on HRZES (at least HRZ in initial and HR in continuation phase): N / Y

Drugs that have been used (for at least over 1 month): 1 Isoniazid (H) / 2 Rifampicin (R) / 3 Ethambutol (E) / 4 Streptomycin (S) / 5 Pyrazinamide (Z) / 6 Ofloxacin / 7 Levofloxacin / 8 Ethionamide / 9 Prothionamide / 10 Kanamycin / 11 Cycloserine / 12 PAS /

12 Other(1) _____ / 13 Other(2) _____ / 14 Other (3) _____

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1 Chest Clinic/ 2 Chest Hospital/ 3 General Hospital/ 4 Private Practice. ; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)
(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.)

TB-PFB1/1-2001

DH2417B1

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

PFB2 – To be completed at 6 month from DOS (for TB patients)

Part (J) Treatment side effects: N / Y (If Y, please circle)

1.GI upset/ 2.skin rash/ 3.visual/ 4.transient rise of liver enzyme/ 5. hepatitis/ 6.vestibular/ 7.arthropathy/ 8.fever-chill/ 9.dizziness/ 10.thrombocytopenia/ 11.leucopenia/ 12.flush face/ 13.other(1) _____ / 14.other(2) _____ /15.other(3) _____

Treatment temporarily withheld for side effects: N / Y

Desensitisation or drug trial required: N / Y

Change in dosage or frequency required: N / Y

Change of drugs required: N / Y

Part (K) Treatment Supervision:

Proportion of doses:	Initial 2 month	Subsequent 4 months (up to 6 month from DOS)
Under DOT at chest clinic, hospital, CNS or other health staff	>90% >75% >50% >25% ≤25%	>90% >75% >50% >25% ≤25%
Under supervison by relatives	>90% >75% >50% >25% ≤25%	>90% >75% >50% >25% ≤25%
Supplied for unsupervised treatment	<5% <10% <15% < 25% <50% ≥50%	<5% <10% <15% < 25% <50% ≥50%
Defaulted	<5% <10% <15% < 25% <50% ≥50%	<5% <10% <15% < 25% <50% ≥50%

Part (L) Outcome at 6 months (please √, circle and/ or fill in the spaces provided as appropriate)

(1) Cured/ treatment completed — Date treatment stopped (mm/yyyy): ____/_____

Status at completion:

- Bacteriological conversion
- Radiological improvement
- Other clinical improvement
- No available evidence of response

(2) Treatment incomplete

- Still on treatment, reason: 1.retreatment/ 2.extrapulm./ 3.extensive/ 4.interrupted treatment/ 5.drug resistance/ 6.poor response/ 7.others, specify: _____
- Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown — Date of death (mm/yyyy): ____/_____

(3) Transferred to: 1.GP/ 2.Chest Clinic/ 3.Hospital/ 4.Outside HK — Details: _____ Last treatment date (mm/yyyy): ____/_____

(4) Defaulted (defaulted treatment for a continuous period > 2m)

- Never found — Last visit date (mm/yyyy): ____/_____
- Retreated after default — Date treatment re-started (mm/yyyy): ____/_____
- Treatment stopped by doctor — Last treatment date (mm/yyyy): ____/_____

(5) Failure (persistent positive bacteriology and treatment stopped)

(6) Wrong/ revised diagnosis — Last treatment date (mm/yyyy): ____/_____

- New diagnosis: _____

(7) Others , specify: _____

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1.Chest Clinic/ 2.Chest Hospital/ 3.General Hospital/ 4.Private Practice; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)
(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.)

TB-PFB2/1-2001

DH2417B2

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

PFC – To be completed at 12 month from DOS (for TB patients)

Part (M) Bacteriological examination for MTB: P (positive), N (negative) , U (not done), NTM (Non-tuberculous Mycobacteria)

	Sputum		**Other type of specimen:** 1.gastric aspirate/ 2.pleural fluid/ 3.bronchial washing/ 4.urine/ 5.biopsy or others, specify: _____	
	5-6 months	7-12 months	5-6 months	7-12 months
Smear	P / N / U	P / N / U	P / N / U	P / N / U
Culture	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM

Part (N) Outcome at 12 months (please √, circle and/ or fill in the spaces provided as appropriate)

(1) Cured/ treatment completed — Date treatment completed (mm/yyyy): ____/_____

(a) Status at completion:
- Bacteriological conversion
- Radiological improvement
- Other clinical improvement
- No available evidence of response

(b) After treatment completed:

No relapse

Loss to follow-up — Last visit date (mm/yyyy): ____/_____

Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown — Date of death (mm/yyyy): ____/_____

Relapse — Date relapse (mm/yyyy): ____/_____

- 1.Bacteriological / 2.Histological / 3.Clinical-radiological (choose 1 item, priority from left to right)

(2) Treatment incomplete (including death while on treatment)
- Still on treatment, reason: 1.retreatment/ 2.extrapulm./ 3.extensive/ 4.interrupted treatment/ 5.drug resistance/ 6.poor response/ 7.others, specify: _____
- Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown — Date of death (mm/yyyy): ____/_____

(3) Transferred to: 1.GP/ 2.Chest Clinic/ 3.Hospital/ 4.Outside HK — Details: _____

Last treatment date (mm/yyyy): ____/_____

(4) Defaulted (defaulted treatment for a continuous period > 2m)
- Never found — Last visit date (mm/yyyy): ____/_____
- Retreated after default — Date treatment re-started (mm/yyyy): ____/_____
- Treatment stopped by doctor — Last treatment date (mm/yyyy): ____/_____

(5) Failure (persistent positive bacteriology and treatment stopped)

(6) Wrong/ revised diagnosis — Last treatment date (mm/yyyy): ____/_____
- New diagnosis: _____

(7) Others , specify: _____

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1.Chest Clinic/ 2.Chest Hospital/ 3.General Hospital/ 4.Private Practice; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)
(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.)

TB-PFC/1-2001

DH2417C

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

PFD – To be completed at 24 month from DOS (for TB patients)

Part (O) Outcome at 24 months (please √, circle and/ or fill in the spaces provided as appropriate)

(1) Cured/ treatment completed — Date treatment completed (mm/yyyy): ____/_____

(a) Status at completion:

- Bacteriological conversion
- Radiological improvement
- Other clinical improvement
- No available evidence of response

(b) After treatment completed:

No relapse

Loss to follow-up — Last visit date (mm/yyyy): ____/_____

Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown — Date of death (mm/yyyy): ____/_____

Relapse — Date relapse (mm/yyyy): ____/_____

- 1.Bacteriological / 2.Histological / 3.Clinical-radiological / 4.Clinical only (choose 1 item, priority from left to right)

(2) Treatment incomplete (including death while on treatment)

- Still on treatment, reason: 1.retreatment/ 2.extrapulm./ 3.extensive/ 4.interrupted treatment/ 5.drug resistance/ 6.poor response/ 7.others, specify: _____
- Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown — Date of death (mm/yyyy): ____/_____

(3) Transferred to: 1.GP/ 2.Chest Clinic/ 3.Hospital/ 4.Outside HK — Details: _____

Last treatment date (mm/yyyy): ____/_____

(4) Defaulted (defaulted treatment for a continuous period > 2m)

- Never found — Last visit date (mm/yyyy): ____/_____
- Retreated after default — Date treatment re-started (mm/yyyy): ____/_____
- Treatment stopped by doctor — Last treatment date (mm/yyyy): ____/_____

(5) Failure (persistent positive bacteriology and treatment stopped)

(6) Wrong/ revised diagnosis — Last treatment date (mm/yyyy): ____/_____

- New diagnosis: _____

(7) Others , specify: _____

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1.Chest Clinic/ 2.Chest Hospital/ 3.General Hospital/ 4.Private Practice; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)
(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.)

TB-PFD/1-2001

DH2417D

Protocol for the management flow and reporting of multidrug-resistant TB (MDR-TB) cases to an MDR-TB Registry

The purpose of setting up an MDR-TB registry is to keep close surveillance of this high risk group of patients for assessment, management and evaluation of control measures.

1. Chest Clinics
   - If a case is newly diagnosed as having MDR-TB in the Chest Clinics, the case should be notified to Consultant Chest Physician i/c at Wanchai Chest Clinic (WCC) using the MDR-TB notification form (MDR_Noti_Form0503).
   - Under most circumstances, the case of MDR-TB will be admitted to hospital for management. For newly diagnosed cases from Kowloon Chest Clinic, Shek Kip Mei Chest Clinic, and Yaumatei Chest Clinic, they should be admitted to Kowloon Hospital (KH). For cases from other chest clinics, they should be admitted to Grantham Hospital (GH). MDR-TB cases which are old cases of certain chest hospitals will in general be admitted to the same hospital for management if admission is required.

2. General Hospitals and Chest Hospitals other than Grantham Hospital (GH) and Kowloon Hospital (KH)
   - If a case is diagnosed as having MDR-TB in these hospitals, the case should be transferred to GH or KH for further management and GH and KH will be responsible for reporting the case to the MDR-TB registry at WCC.
   - However, if somehow the case is not to be transferred to GH or KH, but is to be managed in the respective hospital or is to be discharged, the case should be notified to the MDR-TB registry at WCC. Even if the case is to be discharged and referred to chest clinics, it should still be notified to WCC as the patient may default for follow up at chest clinic.

3. GH and KH
   - If a case of MDR-TB is diagnosed in GH or KH, or recently diagnosed and transferred to GH or KH but has not yet been notified to the MDR-TB registry at WCC, the case should be notified to WCC using MDR_Noti_Form0503.

4. TB Reference Laboratory of Department of Health
   - When a new case has been found to have specimen with drug susceptibility tests showing MDR-TB by the TB Reference Laboratory, the case should be notified to WCC together with the information on the source of care requesting the bacteriological examination. Upon receiving the information, WCC will see whether the case has been notified or not to the MDR-TB Registry, and if not, will trace the source of care for any necessary reporting.

Note:
After notifying the MDR-TB case to WCC (using the form MDR_Noti_Form0503), a copy of the form should be filed in the hospital record (as well as filing with discharge summary upon transferring case to chest clinic) or chest clinic record for future reference and to avoid duplicate notification. There is no need for re-notification of the case even if a new episode of treatment is to be initiated for the same patient again.

MEMO

From	*To* Consultant Chest Physician i/c
Ref. *in*	*(Attn.:* Statistics Unit, Wanchai Chest Clinic *)*
Tel. No.	*Your Ref.* *in*
Fax. No.	*dated* *Fax. No.* 28346627
Date	*Total Pages*

Notification of case to MDR-TB Registry at Wanchai Chest Clinic

I would like to notify a case of Multi-drug Resistant TB as follows:

Name: _____

Sex: M / F Age: _____

ID Number: _____

Clinic number: _____

Date when MDR-TB was first documented: / /

Pretreatment ST pattern:

	(S)	(R)		(S)	(R)
H			E		
R			S		

Date of start of second line treatment for this episode: / /

Case referred to (if applicable): Chest Clinic (name): _____

Grantham / Kowloon / Other Chest Hospital: _____

Other HA Hospital: _____

Others: _____

Remarks:

Signature: _____

Name of doctor: _____

A copy of this form should preferably be filed in the patient's medical record for future reference. *MDR_Noti_Form0503*

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

Date of start of 2nd line anti-TB treatment: _ _/_ _/_ _ _ _

PF-MDR(X), supplementary record forms for MDRTB patients (Page 1 of 2)

(X = multiples of 6, ranging from 30 to 60) (That is, this form is to be completed for MDR-TB patients every 6 months from 2½ year to 5 year of DOS)

PF-MDR (_____) [That is, this form has been completed at (_____) months from DOS]

A. Treatment outcome (please √, circle and/ or fill in the spaces provided as appropriate)

(1) Cured/ treatment completed Date treatment completed (mm/yyyy): ____/_____

(a) Status at completion:

- Bacteriological conversion
- Radiological improvement
- Other clinical improvement
- No available evidence of response

(b) After treatment completed:

No relapse

Loss to follow-up Last visit date (mm/yyyy): ____/_____

Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown Date of death (mm/yyyy): ____/_____

Relapse Date relapse (mm/yyyy): ____/_____

- 1.Bacteriological / 2.Histological / 3.Clinical-radiological (choose 1 item, priority from left to right)

(2) Treatment incomplete (including death while on treatment)

- Still on treatment (including those whose treatment only temporarily withheld, e.g., due to side effects), reason: 1.retreatment/ 2.extrapulm./ 3.extensive/ 4.interrupted treatment/ 5.drug resistance/ 6.poor response/ 7.others (specify): _____
- Died Cause: 1.TB-related/ 2.Not TB-related/ 3.Unknown Date of death (mm/yyyy): ____/_____

(3) Transferred to: 1.GP/ 2..Chest Clinic/ 3.Hospital/ 4.Outside HK Details: _____

Last treatment date (mm/yyyy): ____/_____

(4) Defaulted (defaulted treatment for a continuous period > 2m)

- Never found Last visit date (mm/yyyy): ____/_____
- Retreated after default Date treatment re-started (mm/yyyy): ____/_____
- Treatment stopped by doctor Last treatment date (mm/yyyy): ____/_____
- Reason(s) for defaulting treatment in the last 6 months (if applicable):
  1 No reason/ 2 Denial of disease/ 3 Seeking treatment from others/ 4 Treatment side effect/
  5 Frequent travel outside Hong Kong/ 6 Other reason (1): _____ /
  7 Other reason (2): _____

(5) Failure- failure (persistent positive bacteriology despite treatment with 2nd line drugs and treatment stopped; cases with treatment stopped and planned not to be given again despite disease not yet cured are included in this category)

B. Bacteriological examination in the past 6 months: P (positive), N (negative) , U (not done), NTM (Non-tuberculous Mycobacteria)

	Sputum		**Other type of specimen:** 1.gastric aspirate/ 2.pleural fluid/ 3.bronchial washing/ 4.urine/ 5.biopsy/ 6.others: _____	
	First 3 months	Subsequent 3 months	First 3 months	Subsequent 3 months
Smear	P / N / U	P / N / U	P / N / U	P / N / U
Culture	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM	P / N / U / NTM

C. Was treatment given in the past 6 months: Yes / No / Unknown If yes:

1. Drugs that have been used (for at least over 1 month): 1 Ethambutol (E) / 2 Pyrazinamide (Z) / 3 Ofloxacin / 4 Levofloxacin / 5 Ethionamide / 6 Prothionamide / 7 Kanamycin / 8 Cycloserine / 9 PAS / 10 Other (1) _____ / 11 Other (2) _____ / 12 Other (3) _____
2. Was treatment temporarily withheld for side effects: N / Y

D. Treatment side effects in the past 6 months: N / Y (If Y, please circle one or more of the followings:)

1.GI upset/ 2.skin rash/ 3.visual/ 4.transient rise of liver enzyme/ 5. hepatitis/ 6.vestibular/ 7.arthropathy/ 8.fever-chill/ 9.dizziness/ 10.thrombocytopenia/ 11.leucopenia/ 12.flush face/ 13.suicidal ideation/ 14.sleep disturbance/ 15.depression/ 16.psychotic reaction/ 17.renal function impairment/ 18.other (1) _____ /19.other (2) _____

HKID/ Passport/ Birth certificate no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Clinic/ Hospital no.: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Name: _ DOS: _ _/_ _/_ _ _ _

Date of start of 2nd line anti-TB treatment: _ _/_ _/_ _ _ _

PF-MDR (X), supplementary record forms for MDRTB patients (Page 2 of 2)

(X = multiples of 6, ranging from 30 to 60) (That is, this form is to be completed for MDR-TB patients every 6 months from 2½ year to 5 year of DOS)

PF-MDR (_____) [That is, this form has been completed at (_____) months from DOS]

E. Treatment supervision in the past 6 months *(no need to be completed if no treatment given)***:**

Category	Proportion of doses:
Under DOT at chest clinic, hospital, CNS or other health staff	>90% >75% >50% >25% ≤25%
Under supervision by relatives	>90% >75% >50% >25% ≤25%
Supplied for unsupervised treatment	<5% <10% <15% < 25% <50% ≥50%
Defaulted	<5% <10% <15% < 25% <50% ≥50%

F. Home and working environment in the past 6 months *(no need to be completed if treatment success)***:**

		Home	**Workplace**
Is the patient living alone?		Yes/ No	Not applicable
Total number of close contacts	examined:		
	not examined:		
Total number of close contacts aged <5	examined:		
	not examined:		
Among the above, number of close contacts with immunocompromised condition and state the condition (s)		Number: Condition:	Number: Condition:
Result of active case finding in the last six months		NA/ ND/ positive/ negative	NA/ ND/ positive/ negative
Does the patient have a single room?		Yes/ No	Yes/ No

(*NA= not applicable; ND= Not done; positive=active TB case detected during contact examination; negative=no active case detected)*

G. Hospitalization for management of MDRTB in the past 6 months

Episode	Period (dd/mm/yy – dd/mm/yy)	Duration (weeks)	Hospital	Indication(s)* (Please refer to key)
1				
2				
3				
4				

**Key: (more than one option can be chosen)*

1. Establishment of 2nd line drug regimen

2. Treatment complication: a. hepatitis; b. skin reaction; c. psychiatric symptom; d. others (please state)

3. Disease complication: a. Haemoptysis; b. pneumothorax; c. chronic respiratory failure; d. others (please state)

4. Other comorbidities: a. poor DM control; b. concomitant pneumonia; c. acute exacerbation of COPD; d. others (please state)

5. Modification of 2nd line drug regimen

6. Poor compliance

7. Other public health or social reasons

H. Public financial assistance and special housing needs in the past 6 months *(no need to be completed if treatment success)*

1. Is the patient receiving public financial assistance? Yes / No / Unknown

2. Which of the following forms of financial assistance is the patient receiving? (If applicable)
   CSSA Diet allowance Normal disability allowance High disability allowance
   Special grant for renting Special grant for rehousing to a public housing unit for one person
   Special grant for rehousing to a bigger housing unit with provision of a single room for the patient

Completed by: _____ (name) Tel: _____ Fax: _____

Institution: 1.Chest Clinic/ 2.Chest Hospital/ 3.General Hospital/ 4.Private Practice; Name (and ward) of institution: _____

(After completion, this form should be sent to Consultant Chest Physician i/c, Wanchai Chest Clinic, 99 Kennedy Road, Hong Kong. Fax: (852) 28346627)

(If patient is transferred, a copy of this completed form should also be sent to the new source of care for information.