Taiwan Epidemiology Bulletin

September 18 , 2012/ Vol.28 / No.18

Original Article

Evolution of MDR-TB Control Strategy in Taiwan

Su-Hua Huang, Kwei-Feng Wang, Pei-Chun Chan, Chin-Hui Yang, Chang-Hsun Chen

The third division, Centers for disease control, Taiwan

Abstract

Tuberculosis (TB) is the most serious communicable disease in Taiwan, with about 13000 newly identified cases yearly. A long period of treatment and the side effects of the drugs very often make TB patients take their drugs irregularly, and eventually lead to the development of drug-resistant tuberculosis.

The World Health Organization alerted in 2007 that the spread of drug-resistant TB is a major public health problem with potential global threats and called for countries in the world to adopt the directly observed treatment, short-course, plus (DOTS-plus) strategy to effectively control the multi-drug resistant TB.

The DOTS program was first implemented in Taiwan in 2006, with hired observers to monitor the patient in compliance with TB treatment. In December 2006, the Taiwan CDC began monitoring the anti-TB drugs which TB strains have developed resistance and use of the second-line anti-TB drugs. Later, the MDR-TB Health Care System was established in May 2007, five contract health care teams were funded and required to strictly follow the WHO guideline to administer the management and treatment of MDR-TB patients and conduct community-based DOTS-plus activities, providing patients with complete and non-stop care. In July 2007, the MDR-TB was added to the list of the Category 2 notifiable communicable diseases and, in August, the Taiwan CDC started to collaborate with the National Health Insurance to perform the control of the fluoroquinolone drug class. Moreover, in May 2008, which required health care facilities nationwide are required to send the isolated TB strains from the notified MDR-TB patients to the Research and Diagnostic Center at Taiwan CDC for confirmation. In addition, in order to shorten the time of diagnosis, the rapid genotyping test for high risk population was provided in September 2009. Through a series of control programs and the enforcement of DOTS strategy in Taiwan, the patient who in compliance with TB treatment was promoted, the probability of development of MDR-TB in these patients was decreased, the occurrence

of MDR-TB was timely updated, and the number of MDR-TB patients to be treated has decreased from 440 cases in May 2007 to 245 cases in April 2012.

Introduction

From the bacteriological point of view, the emergence of drug-resistant tuberculosis is usually the result of the genetic mutation in tubercle bacteria. However, the probability of genetic mutations occurring spontaneously is extremely low. For example, the probability of developing resistance to isoniazid (INH) due to spontaneous genetic mutations is only approximately 1 in 10^6 tubercle bacilli and that is even lower to rifampicin (RMP), only about 1 in 10^8 tubercle bacilli. This means that the probability of occurring resistance to INH and RMP simultaneously through spontaneous genetic mutation is 1 in 10^{14}, which is considerably low [1]. Therefore, the occurrence of multidrug resistant tuberculosis (MDR-TB) is generally considered to be the man-made results [2]. If patients take their medicine irregularly or the physicians prescribe a drug regimen inappropriately for TB therapy, the resistant mutants in the patients will be selected and will have the opportunity to largely proliferate. As a result, the resistant strains become the dominant strains within the body.

The treatment of tuberculosis (TB) was entering the era of a nine-month short course treatment regimen containing INH and RMP in 1970s, and evolved into a six-month short course treatment regimen in 1980s that started with two months of INH + RMP + Pyrazimide (PZA) treatment, followed by four months of INH + RMP treatments [3-4]. However, over the past ten years, the TB epidemic has been on an increasing trend again in many regions of the world. Therefore, the World Health Organization (WHO) declared in 1993 that TB was a global emergency and began actively promoting its remedial DOTS (Directly Observed Treatment, Short-course) strategy [5]. In 1997, the WHO and the International Union against Tuberculosis and Lung Disease– (IUATLD) jointly released a report about the investigation of resistance to anti-tuberculosis drugs in 35 countries around the globe since 1994. The report indicated that the strains of tubercle bacilli resistant to antimicrobial drugs were very common in these countries, e.g., the average rate for primary MDR-TB strains was 1.4% (range 0 - 14.4%) and the average rate for secondary MDR-TB strains was 13% (range 0 - 54.4%), especially in the former Soviet regions [6]. Apparently the DOTS strategy currently employing a short course standard treatment regimen has been unable to sufficiently deal with the drug-resistance problems. Therefore, the WHO established the Working Group on DOTS-Plus for MDR-TB in 1999 to assist countries to evaluate the feasibility of implementing DOTS-Plus strategy [7].

In addition, the treatments of MDR-TB not only take a longer time but also are often less effective. The 1993 report published by the National Jewish Health, the center for treatment of the MDR-TB patients in the United States, stated that 134 of the 171 MDR-TB patients have provided complete data set, and 47 (35%) of the 134 cases finished the initial treatments had no response to the treatment, with positive sputum culture results; 87 (65%) of

them had a good response to the initial treatment. However, 12 of the 87 cases reoccurred, so the overall response rate was 56%. Four years later, 63 (37%) of 171 cases died, and 37 (22%) of them died from TB [8]. The National Jewish Health published another paper eleven years after the last report documenting the treatment and outcome analysis of 205 MDR-TB patients. The paper indicated that a remarkable progress in terms of the treatments was observed as compared with those obtained in the previous research, which the percentage of patients with good response to the treatment increased from 65% to 85%, the long-term success rate elevated from 56% to 75%, and the mortality rate decreased from 22% to 12%. The surgical resection and fluoroquinolone therapy were the main factors contributed to the improvements of treatment outcomes [9].

Based on data published by the WHO in 2011, around 0.29 million MDR-TB cases have been reported from all over the world in 2010, only less than 5% of newly diagnosed TB cases have received screening test for MDR-TB strains in most of the countries, the MDR-TB cases undergoing treatment were only 16% [10], and only 1.2% of the MDR-TB patients receiving treatment have been treated by following the standard MDR-TB treatment regimens recommended by the WHO. These situations indicated that the control of TB epidemic have become even more difficult. Although 50% of the MDR-TB cases in the world aggregated in China and India, the WHO has also alerted European countries in response to the startling increase in the number of MDR-TB cases and emphasized that the number of MDR-TB cases has grown two times in London areas, United Kingdom, during 2005-2009. The WHO, therefore, called for countries facing up to the problems squarely and constituting strategies to solve them [11].

Monitoring of drug resistance and construction of health care systems for patients with MDR-TB

The investigation conducted by the Taiwan Chronic Disease Control Bureau in northern areas showed that the average rate of primary INH-resistant TB was about 10% [12-13]. The report published by the National Taiwan University Hospital indicated that 30.5% of *Mycobacterium tuberculosis* strains have developed resistance to any one of the first-line anti-TB drugs and 5.1% to multiple drugs [14]. The investigation by the Buddhist Tzu Chi General Hospital in eastern Taiwan during 2004-2008 revealed that the rate for primary MDR-TB cases was 4.0% and that for secondary MDR-TB cases was 17.6% [15]. These indicated that the occurrence of drug-resistant TB strains in Taiwan has been a very serious problem. In order to understand the status of anti-TB drug resistance in TB strains in this country and, in turn, to formulate control strategy, Taiwan CDC began monitoring the anti-TB drugs strains and use of the second-line drugs. Data from hospitals through the operation of the Central Infectious Disease Follow-up and Management System were collected from December 2006. This was the first step in initiating the nationwide drug resistance monitoring activities in Taiwan.

Based on the surveillance data, there were around 440 MDR-TB patients nationwide. Currently, these patients were treated by hospitals that most of them did not have the capability of dealing with this type of patients and the current National Health Insurance (NHI) payment system was disadvantageous to hospitals that take care of the MDR-TB patients and thus these hospitals have a lower willingness in providing health care to these patients. These problems will definitely influence on the effectiveness of TB control if they cannot be solved appropriately. Therefore, Taiwan CDC made the efforts to construct MDR-TB Health Care System in May 2007 through the process of openly calling for projects of caring for MDR-TB patients and providing funds for the projects. As a result, five projects representing five health care teams were granted. The amount of funds provided for each of the projects was calculated based on the service offered. In order to establish a specialized and concentrated health care system, the health care teams were required to strictly follow the WHO guideline to administer the management and treatment of MDR-TB patients, and were given one million New Taiwan Dollar (TWD) a year with a maximum of two million TWD for a maximum two year period, including cost for treatment of TB patient within the period but excluding cost for anti-TB drugs, and the amount of funds was reduced to 0.8 million a year and a maximum of 1.6 million for a two-year period after reviewing the actual cost for implementation in 2009 for every single MDR-TB patient by Taiwan CDC. The health care teams could use the funds flexibly. In practice, the health care teams were performing the health care services in a patient-centered way and should continually provide two years of active treatment for each patient they enrolled.

Except providing clinical therapy, the health care teams will leave the confines of current TB control guideline and hire observers to conduct community-based DOTS-plus activities, for providing patients with complete and non-stop care. Starting from the time when the patients were enrolled by the health care teams, a special case manager and an observer will be assigned to provide services related to the disease for the patients at all times until the patients have completed 18 months to 2 years of therapy. These services include making appointment for patients to revisit clinic, accompanying the patients to revisit clinic for examination and picking up drugs from the pharmacy, and sending drugs to patients' hand five days per week. These approaches will be able to overcome the difficulty that the clinical practice could not be smoothly connected with public health practice in TB control, and will be able to solve the problems about the health care of MDR-TB patients when they return to community after discharge from hospitals. In order to provide services for TB patients scattered in different geographical areas, the health care teams have specially organized a fleet of vehicles to send drugs for them. Moreover, the vehicles were equipped with a professional nurse to provide services to MDR-TB patients who required long-term injection therapy. For completing the missions of successfully sending drugs to TB patients, the health workers equipped in the fleet of

vehicles have been working very hard from the coast to the mountains, no matter how rough the environmental conditions might be. In addition, for patients with difficulty in getting access to health care services due to economy reason or single patients living alone and lack of care from others, the health care teams will make efforts to provided assistance to them. Through the DOTS observers hired by the health care teams, the physicians responsible for clinical treatment of the TB patients are more clearly understand the progress of treatment of patient in the community, and the level of compliance and treatment success rate of the MDR-TB patients are enhanced.

Starting 2008, a seminar is held on a seasonal basis to review data of the hard-to-treat TB patients together with health workers in local health bureaus and to evaluate the effectiveness of treatment provided by the health care teams. During the same period, several well-known international experts were invited to undertake an on-site evaluation and make recommendations on the implementation of TB control, including Dr. Peter Cegielski, editor-in-chief of WHO Guidelines for the programmatic management of drug-resistant tuberculosis and chief *of MDR-TB Team*, Division of Tuberculosis Elimination, US CDC, and Dr. Charles L. Daley, Professor of Medicine, National Jewish Medical and Research Center and University of Colorado Health Sciences Center. Over the last five years, the health care teams have enrolled a total of 879 patients with MDR-TB. The sputum smear conversion rate after two months of DOTS therapy was 38.2%, the sputum culture conversion rate at six months following DOTS treatment was 70.9%, and the treatment success rate at the end of 24 months of DOTS therapy reached as high as 75.8% (Figure 1) which has surpassed the treatment success rate, 69.9%, obtained in five regions adopting DOTS-plus program supported by the Green Light Committee for the WHO European Region [16]. The DOTS model implemented by the health care teams has built up a new milestone in caring for MDR-TB patients in Taiwan, beside that it has assisted the patients to eliminate the threats of MDR-TB to their families. In addition, the analysis of the time interval from the date that the specimens confirmed to be positive of MDR-TB strain were collected to the date that the patients were enrolled by the health care teams shows that the percentage of the patients who were enrolled into the DOTS program in a time interval of more than four months has reduced from 43% in 2007 to 10% in 2011 (Table 1). This means that most of MDR-TB patients have been referred to the health care teams for professional treatment at an earlier time than before and the probability of being successfully treated has been largely elevated. Apparently, these situations have been different from what it was before the operation of the health care teams. At that time, the patients might take a long time to shop around for their medical services and eventually might become a patient with extensively drug-resistant tuberculosis (XDR-TB), and continually spread the disease to others in the community and hospitals. Therefore, the progress in the treatment of MDR-TB patients is a fact that makes patients, hospitals, and community residents be worthy of being happy.

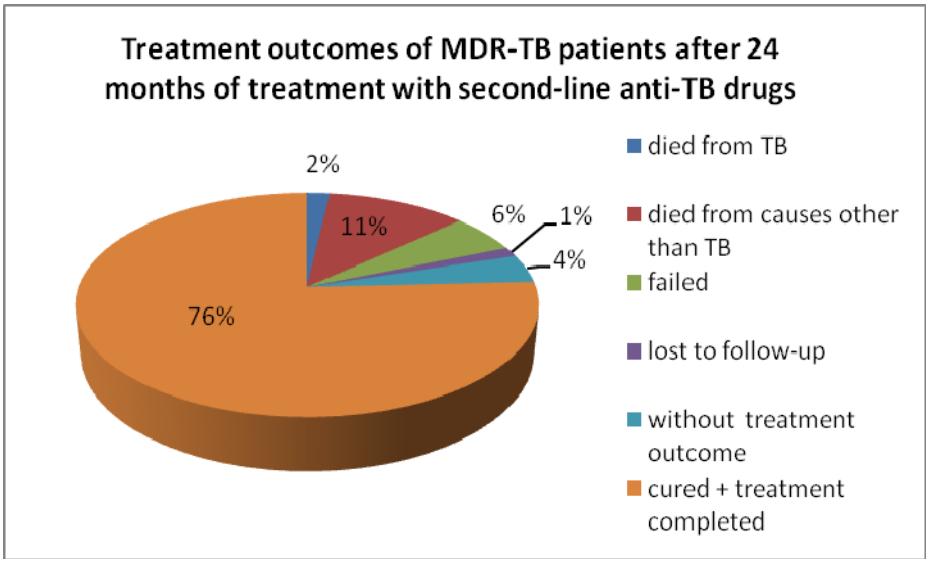

Figure 1. Pie chart of treatment outcomes of MDR-TB patients after 24 months of treatment with second-line anti-TB drugs

Table 1. Percentage of MDR-TB patients referred to health care teams in a prolonged delay time, by year

	2007	2008	2009	2010	2011
Percentage of patients referred in a prolonged delay time* (%)	43	30	22	16	10

*Patients referred in a prolonged delay time are defined as patients who were referred to the health care teams in a time interval of more than four months from the date that the specimens confirmed as MDR-TB were collected.

Notification and pushing policy on rapid screening test

In July 2007, the MDR-TB was added to the list of the Category 2 communicable diseases which the health care facilities are mandatory to report to health authorities within 24 hours after a suspected diagnosis is made by the physician, based on the Communicable Disease Control Act. This policy has largely shortened the time gap for updating epidemic information. Afterwards, the Taiwan CDC made further regulations in May 2008, which required health care facilities nationwide to send the MDR-TB strains isolated to the Research and Diagnostic Center at Taiwan CDC for confirmation. In addition, in order to shorten the time of waiting for confirmation, September 2009 the Taiwan CDC has provided rapid genotyping test for contacts of lost, failed, or relapsed TB patients or MDR-TB patients, and patients from three mountain villages of Hua-lien County. Any sputum specimens have been treated with digestion and decontamination procedures can be directly sent to the Taiwan CDC and the test reports will be issued within 3-7 days. Moreover, as long as the patients meet the conditions mentioned previously and the two genotyping tests indicated that a resistance to INH and RMP has developed, they can be confirmed to be MDR-TB cases, and the actions on patient treatment and infection control can be taken earlier.

Sufficient supply and control of second-line drugs

To ensure sufficient supply of quality-assured second-line anti-TB drugs for health care facilities nationwide and to control the use of these drugs to avoid misusing, these drugs were totally provided by the Taiwan CDC. Health care facilities demands for the second-line anti-TB drugs will have to submit an application for reviewing before they can get these drugs. Six types of anti-TB drugs were first offered in 2006, and the types of anti-TB drugs were increased to nine. In 2008, an additional four types of anti-TB drugs (to be prescribed only for patients enrolled by the health care teams) that have not been officially licensed in this country were imported for special project, to increase the choices of drugs for clinical description.

Promotion of health care quality

There is a proverb which says that “prevention is better than treatment.” Therefore, except conducting a series of control procedures for existing MDR-TB patients, the Taiwan CDC has been continually monitoring and improving the implementation of DOTS strategies, which includes expanding the areas for DOTS activities and, in particular, focusing on the monitoring of the quality of DOTS implementation. These were done through uninterrupted inspection and follow-up of cohort review in critical areas to make sure that all TB cases have completed their treatment courses and in turn to reduce treatment failure. In addition, the Taiwan CDC was continuing to review medical records randomly taken from TB cases by cooperating with the NHI. The analysis of medical records sampled in 2010 and 2011 shows that the percentage of those with inappropriate prescriptions has decreased from 39% to 15%. Although the problem has been largely minimized, there is still room for further improvements. Therefore, starting from 2011, the Taiwan CDC conducts the Health Care Quality Promotion Plan for TB Patients in collaboration with the Infectious Diseases Society of Taiwan (IDST) and the Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM), which 20 hospitals that have notified more than 50 TB patients during the previous year and have outside consultation needs were selected by the Taiwan CDC and then experienced professional physicians from the IDST and TSPCCM will assist them to hold seminar on TB and give them second opinions regarding prescriptions of TB treatments. Through the consultation and seminar, we can timely find inappropriate prescribing practices, reduce the occurrence of ineffective treatment, and prevent TB patients developing drug-resistant TB. A total of 530 seminars and 6039 person-times of prescription review have been completed for the 20 hospitals through the Health Care Quality Promotion Plan for TB Patients.

Surgical treatment of MDR-TB and control of fluoroquinolone class of drugs

Studies conducted by the National Jewish Health indicated that the key factors contributed to the large increase of treatment success rate in TB were surgical resection and the use of the fluoroquinolone class of drugs [9]. Therefore, the Taiwan CDC requested the five health care teams to conduct assessment for pulmonary resection surgery for MDR-TB cases if their

sputum culture did not convert to negative after 8 months of therapy in 2009. The analysis on patients enrolled by the health care team shows that the time interval between the date of starting the use of second-line anti-TB drugs to the date of conducting assessment for resection surgery has been shortened from 14.2 months in 2009 to 3.9 months in 2010. The statistics show that 40 patients have received surgical resection as of March 2012, and 26 of them were successfully treated, 3 died of non-TB disease, 6 failed treatments, and 5 were still under treatment, as shown in Figure 2. Since the analysis indicated that the sputum culture-negative conversion rate of the TB cases changed slightly after 3 months of therapy, the Taiwan CDC required the health care teams to move the time point of completing the assessment for pulmonary resection surgery forward to within 5 months after treatments. Moreover, due to that the extensive abusing of fluoroquinolone class of drugs in clinical treatments had seriously influenced on the effectiveness of TB treatment, the Taiwan CDC started to cooperate with the NHI in August 2007 to perform the control of the fluoroquinolone drug class. All the use of fluoroquinolone for treatment of patients with TB are required to submit an application for reviewing and getting permission in order to improve the problems of abusing of fluoroquinolone drug class and high incidence of anti-TB drug resistance. The data analysis shows that, after several years of control of the fluoroquinolone, the percentage of the 115 patients diagnosed with MDR-TB and having developed resistance to fluoroquinolone has largely decreased from 56.4% in 2007 to 17% of 109 patients in 2011, as shown in Table 2. The results supports that the control procedures are really effective.

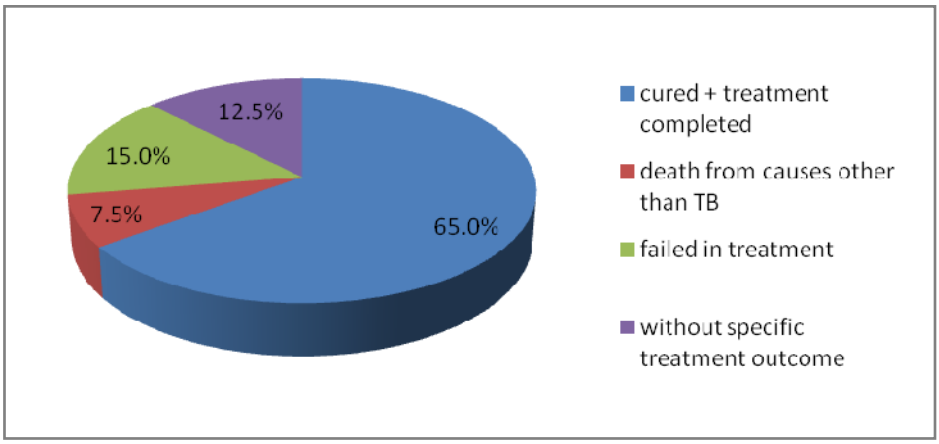

Figure 2. Treatment results of MDR-TB patients receiving surgical resection (N=40)

Table 2. Percentage of patients developing resistance to fluoroquinolone, by year of diagnosis

Year of diagnosis	Percentage of patients developing resistance to fluoroquinolone (%)	No. of MDR-TB patients (N)
before 2007	56.4	115
2007	25.7	157
2008	16.9	183
2009	21.4	147
2010	18.8	129
2011	17.0	109

Conclusions

The WHO recommended that a successful implementation of DOTS-plus strategy for control of MDR-TB will largely depend on the effective implementation of DOTS strategy that include five components: 1) political commitment for TB control; 2) quality-assured system for TB diagnosis; 3) standardized treatment with supervision and patient support; 4) sufficient supply of second-line anti-TB drugs; 5) standardized registration and notification system. Moreover, the DOTS-plus activities shall pay more consideration on the issues of diagnosis of MDR-TB and the use of second-line anti-TB drugs [17]. Although the MDR-TB control activities in Taiwan have never received any assistance from the WHO and its subordinate organizations or from the World Bank as they did for other countries, we have done our best to fulfill the five major strategies recommended by the WHO by using the very limited available resources. Because of the above mentioned intervention performed in recent years, the number of MDR-TB patients in Taiwan has decreased yearly, from 440 cases in May 2007 to 245 cases at present. The percentage of MDR-TB patients was 1% in the newly identified TB cases and 6% in patients being retreated for TB. Both of them were lower than those in the neighboring countries. These results demonstrate that the MDR-TB control strategies have been effectively implemented in Taiwan. Based on the estimates produced by the WHO, the medical expense for curing one MDR-TB patients is about one hundred times higher than that for general TB cases. Therefore, a series of control strategies systematically implemented by the Taiwan CDC not only has saved more resources for this country but also has provided citizens a healthier living environment.

References

1. WHO. Frieden T. Toman's Tuberculosis: Case Detection, Treatment, and Monitoring. 2nded.（WHO/HTM/TB/2004.334）.
2. WHO. Guidelines for the management of drug-resistant tuberculosis. Geneva, WHO, 1996 (WHO/TB/96.210(Rev.1)).
3. Amearican Thoracic Society, CDC, and the Infectious Disease Society of Amearica. Treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
4. Taiwan CDC. Guideline for Tuberculosis Diagnosis. 2006.
5. Tuberculosis. Available at:http://www.who.int/mediacentre/factsheets/fs104/en/
6. WHO. Anti-tuberculosis drug resistance in the world. First global report. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, 1994--1997. Geneva, World Health Prganization,1997 (WHO/TB/97.229).
7. The Global plan to stop TB, 2006-2015: actions for life-toward a world free of tuberculosis. Available at: http://www.stoptb.org/globalplan/assets/documents/GlobalPlanFinal.pdf.
8. Goble M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993;3288:527-32.
9. Chan ED, Laurel V, Strand MJ, et al. Treatment and Outcome Analysis of 205 Patients

with Multidrug-resistant Tuberculosis. Am J Respir Crit Care Med 2004;169:1103-9.
10. WHO. Global tuberculosis control 2011. Geneva, Switzerland: WHO, 2011(WHO/HTM /TB/2011.368).
11. Taiwan CDC. Tuberculosis news. Available at http://www.cdc.gov.tw/ct.asp?xItem= 35677&ctNode=1515&mp=230 Accessed 1 November, 2011.
12. Yu MC, Suo J, Chiang CY, et al. Initial drug resistance of Mycobacterium tuberculosis in Taiwan. J Formos Med Assoc 1997;96:890-4.
13. Chiang IH, Yu MC, Bai KJ, et al. Drug resistance patterns of tuberculosis in Taiwan. J Formos Med Assoc 1998;97:581-3.
14. Liaw YS, Hsueh PR, Yu CJ, et al. Drug resistance pattern of Mycobacterium Tuberculosis in a university hospital in Taiwan, 1998-2002. J Formos Med Assoc 2004; 103:671-7.
15. Chen YT, Lee JJ, et al. Effective Interventions and Decline of Anti-tuberculosis Drug Resistance in Eastern Taiwan, 2004-2008. PLoS ONE 7(2):e31531
16. Nathanson E, et al. Multidrug-resistant tuberculosis management in resource-limited settings. Emerg Infect Dis 2006;12(9):1389-97.
17. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva,（WHO,2006;WHO/HTM/TB/2006.361）.

Quality Management of Mycobacteriology Laboratory in Taiwan: Current Status and Future Perspectives

Ting-Fang Wang, Ruwen Jou

Research and Diagnostic Center, Centers for Diseases Control, Taiwan

Abstract

Among the National Notifiable Communicable Diseases in Taiwan, tuberculosis has the highest annual mortality and incidence. It is always a big challenge for public health authorities to control the epidemic and to integrate laboratory examination, clinical management, and public health resources. Taiwan Centers for Diseases Control (Taiwan CDC) has launched a campaign - Mobilization Plan to Halve Tuberculosis Incidence in Ten Years. Since bacteriological examinations are associated with finding of case, evaluating the treatment response, and investigating the transmission, it is important to improve the quality management system of a laboratory. Accordingly, an external quality assessment program has been established for acid-fast bacilli smear microscopy, culture, identification and drug susceptibility testing. Clinical laboratories are also encouraged to

set up an internal quality control system. Currently, Taiwan CDC is developing a web-based laboratory management system, standardizing a training program, and implementing a certification mechanism for laboratories and medical technologists. To achieve a better tuberculosis control, we should be able to offer an accessible and professional service based on a well-established mycobacterial laboratory examination network.

Keywords: tuberculosis, laboratory, quality of laboratory examinations

Introduction

Taiwan has implemented National Tuberculosis Program for more than 50 years. Despite the drastic decline in prevalence and mortality, many new tuberculosis (TB) cases are notified every year. Thus, TB remains a major public health concern in Taiwan [1]. Bacteriological examinations can provide scientific evidences for making sound TB control policies and strategies. In addition, clinicians also rely on correct laboratory results to confirm TB cases and to evaluate the treatment responses. Competence, quality, and efficiency of laboratory services are therefore vital to achieve early diagnosis and adequate treatment, as well as a good overall disease control.

Current status of laboratory diagnosis

Taiwan CDC has evaluated the capacities of all mycobacterial laboratories in Taiwan in 2009. At least 102 laboratories can perform acid-fast bacilli (AFB) smear microscopy, 46 laboratories can perform mycobacterial culture, and 36 laboratories can perform identification and drug susceptibility testing (Table 1). In addition, according to data collected in 2009, the estimated number of specimens ordered for AFB-smear microscopy was over 800,000 in 2011. Current laboratory methodologies for TB diagnosis include many manual steps. Therefore, daily workloads, techniques of medical technologists, standard operating procedures and algorithm of work flow have great impact on quality of laboratory examinations.

Table 1.Level of mycobacterial laboratories and their services in Taiwan, 2009

Level of mycobacterial laboratories (Number of laboratory)	Bacteriological examination			
	AFB-smear microscopy	Culture	Identification	Drug susceptibility testing
Medical Centers	21	19	17	17
Regional Hospitals	49	19	13	13
District Hospitals	10	4	3	3
Private clinics	2	2	1	1
Commercial laboratories	11	2	2	2
Total	102	46	36	36

Infrastructure of laboratory network

A well-established laboratory examination network can steadily provide a good quality of service. There are three levels of mycobacterial laboratories: the National Reference laboratory, certified laboratory (including regional reference laboratories and Taiwan CDC-contracted laboratories), and other laboratories. To establish a comprehensive TB laboratory service network, Taiwan CDC conducted a pilot program in designated six contract laboratories to provide referral laboratory service in 2001. Since then, mycobacterial laboratory examinations were more accessible and more reliable. By 2003, 10 contract laboratories were designated. In 2004, Taiwan CDC established the National Reference Laboratory (NRL) of Mycobacteriology, which was responsible to formulate standard operating procedures, assess and regulate quality control programs, conduct operational studies or confirm discordant test results, assist public health investigation, and assist clinical laboratories by offering technical supports and consultations. Subsequently, 32 mycobacterial laboratories have been authorized by Taiwan CDC since January 2009 according to the Enforcement Rules of the Communicable Diseases (Table 2). In order to offer quality-assured examinations, certified laboratories should follow the “Operational Regulations on Quality Assurance of Infectious Diseases Laboratories” guideline to execute internal quality management. Furthermore, Taiwan CDC also strictly conducts documents review, on-site visit, and evaluates external quality control. In 2012, three regional reference laboratories were designated to assist the NRL in improving the quality of the certified laboratories.

Table 2.Authorized clinical mycobacterial laboratories in Taiwan, by region, 2012

Region	Number of laboratory	Name List
Northern	13	Tao-Yuan General Hospital, Shin-Jong Wu Ho-Su Memorial Hospital, Linsen Branch of Taipei City Hospital, Wan-Fang Hospital of Taipei Medical University, Super Laboratory Corporation, Tamshui Branch of Mackay Memorial Hospital, National Taiwan University Hospital, Far Eastern Memorial Hospital, Tingjhou Branch of Tri-Service General Hospital, Linkou Branch of Chang Gung Medical Foundation, Sijhih Cathay General Hospital, Taipei Veterans General Hospital
Central	7	Taichung Veterans General Hospital, China Medical University Hospital, Chung Shan Medical University Hospital, Changhua Christian Hospital, Chung-Hua Hospital of Department of Health, Reference Medical Laboratory, Taichung Hospital of Department of Health
Southern	11	Chest Hospital of Department of Health, Kaohsiung Veterans General Hospital, Kaohsiung Branch of Chang Gung Medical Foundation, National Cheng Kung University Hospital, Chia-Yi Christian Hospital of Ditmanson Medical Foundation, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung Municipal Min-Sheng Hospital, Dalin Branch of Buddhist Tzu-Chi General Hospital, E-Da University Hospital, Chia-Yi Branch of Chang Gung Medical Foundation, Chi Mei Medical Center
Eastern	1	Buddhist Tzu-Chi General Hospital

Laboratory diagnosis of *Mycobacterium tuberculosis*

Routine laboratory diagnoses of *Mycobacterium tuberculosis* include four tests: acid-fast bacilli smear microscopy, mycobacterial culture, identification, and drug susceptibility testing [2].

A. Acid-fast bacilli smear microscopy

This method can provide preliminary diagnosis of suspected infection and effective monitoring of treatment response. Acid-fast bacilli in the concentrated sputum samples were stained using Ziehl-Neelsen method or Kinyoun method or fluorescence microscope method including light-emitting diodes.

B. Mycobacterial culture

Mycobacterial culture is critical in differential diagnosis, subsequent drug susceptibility testing, and genotyping. Commercial culture media include solid culture media, such as egg-based Lowenstein-Jensen media and synthetic Middlebrook 7H10 or 7H11 media, and liquid culture media, such as BacT/ALERT 3D (bioMerieux, France) and BACTEC™MGIT™ System (Becton and Dickinson, USA).

C. Identification

In addition to morphology and growth rate of the bacterial colonies, biochemical tests, molecular assays, and immunochromatographic test (ICT) can be applied to identify *M. tuberculosis* [3].

D. Drug susceptibility testing

Results of drug susceptibility tests are crucial for prescribing adequate treatment. Well-adopted methods include agar-based or egg-based method, and the liquid-based BACTEC™MGIT™ System. In addition, molecular techniques, such as a liner-probe assay for detecting mutations conferring drug resistance including the GenoType® MTBDR and MTBDRplus (Hain Lifescience GmbH, Germany), INNO-LiPA Rif.TB (Innogenetics NV, Belgium). A fully automated machine Cepheid GeneXpert is adopted in clinical use.

External quality control

Currently, there is no organization provides a comprehensive external quality program for mycobacterial laboratory examinations, including specimen processing and the aforementioned 4 laboratory diagnostics. Taiwan CDC has conducted proficiency testing on drug susceptibility testing since 2006 and nucleic acid amplification tests for mycobacteria in 2009-2010. In addition, more than 100 clinical laboratories purchased panels of AFB smears from Taiwan Society of Laboratory Medicine annually as part of their quality control program. Furthermore, some mycobacteriology laboratories also participated in a proficiency testing offered by the College of American Pathologists. In addition, in a World Health Organization (WHO) manual, External Quality Assessment for AFB Smear Microscopy, indicating that on-site evaluation, panel testing, and blinded rechecking should all be included

in an external quality assessment program [4]. Current status of external quality assessment of mycobacterial laboratories conducted by Taiwan CDC is described as below:

A. Quality control projects

1. Blinded rechecking of AFB smear: The quality of AFB smear microscopy depends not only on internal quality assessment of the laboratory, but also needs external blinded rechecking on a regular base. Based on the Lot Quality Assurance System, random sampling strategy, the quality of smear preparation and the accuracy of reading are evaluated [5].
2. Proficiency testing of molecular diagnosis: Molecular techniques have been used for rapid detection, identification and drug susceptibility testing.
   (1). Proficiency testing: Taiwan CDC conducted proficiency testing on molecular diagnosis of mycobacteria in 2009-2010. In 2009, the accuracy of participated mycobacterial laboratories was over 95% except one commercial laboratory, whose accuracy was only 65%. Overall, molecular diagnosis on species identification was not ready to be fully implemented in all levels of clinical mycobacteriology laboratories. Thus, to provide a reliable report, laboratories that adopted molecular techniques in their routine services should be carried out by competent and experienced medical technologists and have a comprehensive internal quality assessment program.
   (2). Results rechecking: For discordant laboratory results that were not compatible with clinical diagnosis, Taiwan CDC offers a confirmation service.
3. Rechecking of mycobacterial culture and species identification: The Reference Laboratory of Mycobacteriology at Taiwan CDC rechecked all the samples with requests for designated tuberculosis control needs. In addition, certain proportion of mycobacteria isolates sent from different laboratories was sampled to check the rate of contamination and to confirm the accuracy of species identification.
4. Proficiency testing of drug susceptibility testing
   (1). Proficiency testing: To improve the quality of drug susceptibility testing on the first-line anti-tuberculosis drugs, a pilot study on external quality assessment of drug susceptibility testing was launched in 2006 by Taiwan CDC [5]. This project has been scaled up to include all mycobacterial laboratories performing the test since 2007. Technical training courses were also arranged.
   (2). Results rechecking: For multidrug-resistant tuberculosis and patients with unsatisfactory treatment response, Taiwan CDC provides rechecking service on drug susceptibilities to both first-line and second-line anti-tuberculosis drugs.

For laboratories that perform only AFB smear microscopy, with or without culture, proficiency testing provided by Taiwan Association of Medical Technologists is recommended, and they should consider incorporating into their internal quality assessment program of bacterial laboratories. Because most of these laboratories use a direct AFB smear method which is not as sensitive as recommended concentration smear method, and might be

the reason of the low smear positive rate among our notified new tuberculosis cases. Furthermore, since quality of specimen and speed of it delivery to the laboratory is crucial to obtain accurate test result, Taiwan CDC implemented a mandatory express delivery policy to ensure specimens arrival within 3-4 days.

B. On-site evaluation

On-site evaluation of operating procedures and algorithms by external experts can improve the quality of laboratory services. Currently, laboratories certified by domestic or oversea organizations have annual external on-site visits; while non-certified laboratories need to maintain strict internal control program and should invite experts to visit and review. Taiwan CDC carried out both regular review of self-check lists, standard operation procedures and mandatory on-site visit to the 32 authorized laboratories. In 2012, on-site visit are executed with the assistance of 3 regional reference laboratories. Laboratories with suboptimal performance are informed, corrective actions are required to be completed within an assigned time frame and close follow-up and necessary consultation are provided. For those laboratories with unsatisfied performance or those with major problems, unscheduled on-site evaluations are done. Furthermore, exchange visits along with seasonal regional or annual national conferences on technical issues and quality system can promote the awareness and improve the quality of laboratory examinations in Taiwan.

C. Training and certification of laboratory technologists

A pilot project on standardization of training modules and assessment of laboratory technologists was initiated in 2011 and implemented in 2012. The goals for this 3-year project include AFB-smear microscopic examination and external quality assessment in 2012, mycobacterial identification in 2013, and drug susceptibility test in 2014. Qualified and certified personnel will be invited to join an expert team, and have the responsibility to implement internal quality control and staff training programs.

D. Indices of quality control

The quality of the laboratory service is directly related to competence of their personnel. Monitoring of the quality index can be used to trace the dynamic change of routine services. Most laboratory examinations for mycobacteria are operated manually. Thus, each specimen could be considered as an independent event in quality control. The quality of examination of each specimen cannot be assessed by singe evaluation and regular evaluation on all indices is necessary. American Clinical and Laboratory Standards Institute has approved standards and guidelines on all mycobacterial laboratory examinations. Following the instructions in the document 48 of A Laboratory Detection and Identification of Mycobacteria, mycobacterial laboratories can regularly monitor the following indices: positive rate of AFB smears, positive rate of culture, proportion of nontuberculous mycobacteria, turnaround time of reporting, rate of contamination, and proportion of samples with negative AFB smear but with positive culture results [6]. Taiwan CDC has suggested indices associated with quality control in mycobacterial examinations to be collected bi-monthly from all authorized

laboratories. Data were analyzed statistically for monitoring any abnormal variation and taking corrective actions. In addition, representative from authorized laboratories can share experiences and comparing their outcomes to one another in bimonthly meeting organized by Taiwan CDC.

Future prospective

According to the Phase II of the Mobilization Plan to Halve Tuberculosis Incidence in Ten Years, improve quality management of laboratory and strengthen levels of laboratory services become mandatory in 2012. Laboratory diagnosis of tuberculosis will be stratified and done by authorized laboratories, regional reference laboratories, and the National Reference laboratory of Mycobacteriology. This infrastructure can provide a better examination service and a more effective monitoring system. Eventually, functions of Taiwan CDC contracted laboratories will be extended to all authorized laboratories gradually and self-management of program will be implemented. In addition, Taiwan CDC encourages all mycobacteriology laboratories to be certified by domestic or foreign accreditation organizations or foundations, and meet the ISO 15189 requirements. By the end of 2011, 22 laboratories have been accredited by the aforementioned four examinations; and by 2015, all of the Taiwan CDC authorized laboratories should be accredited. Taiwan CDC also encourages authorized laboratories to upload their laboratory results to the web-based National Notifiable Communicable Diseases Reporting System to facilitate the real-time monitoring of laboratory services. To improve the quality of mycobacteriology laboratory examinations, additional efforts should be made on enhancing delivery efficiency, conducting proficiency testing, certifying laboratories and medical technologists, standardizing operating procedures and quality control indices. By re-enforcement of competency and capacity of laboratory as well as establishment of internal and external quality control can promote overall tuberculosis diagnosis services.

Acknowledgments

We deeply appreciated the staff of the National Reference Laboratory of Mycobacteriology of Taiwan CDC, for conducting blinded rechecking of AFB smear, and for providing proficiency tests on both drug susceptibility testing and molecular assays. We also would like to thank all clinical mycobacteriology laboratories for participating in the external quality program.

References

1. Taiwan CDC.Taiwan tuberculosis control report (2010). Available at: http://www2.cdc.gov.tw/public/data/1117169971.pdf.（in Chinese）
2. Taiwan CDC. The manual of the tubercle germ examines 2004. Available at: http://www.cdc.gov.tw/uploads/files/3ecca975-d3e9-4049-be77-3686059714ca.pdf.（in Chinese）

3. Yu MC, Chen HY, Wu MH, et al. Evaluation of the rapid MGIT™ TBc identification test for culture confirmation of *Mycobacterium tuberculosis* complex. J Clin Microbiol. 2011;49(3):802-7.
4. External Quality Assessment for AFB Smear Microscopy. Washington, DC: Association of Public Health Laboratories; 2002.
5. Jou R, Chiang CY, Yu CY, et al. Proficiency of Drug Susceptibility Testing for *Mycobacterium tuberculosis* in Taiwan, Int J Tuberc Lung Dis 2009;13(9):1142-7.
6. Clinical and Laboratory Standards Institute. Laboratory Detection and Identification of Mycobacterium; Approved Guideline. CLSI M48-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

The Taiwan Epidemiology Bulletin series of publications is published by Centers for Disease Control, Department of Health, Taiwan (R.O.C.) since Dec 15, 1984.
Publisher : Feng-Yee Chang
Editor-in-Chief : Yi-Chun Wu **Telephone No :** (02) 2395-9825
Executive Editor : Li-Gin Wu, Hsiu-Lan Liu **Website :** http://teb.cdc.gov.tw/
Address : No.6, Linshen S. Road, Taipei, Taiwan 100 (R.O.C.)
Suggested Citation :
[Author].[Article title].Taiwan Epidemiol Bull 2012;28:[inclusive page numbers].