J Microbiol Immunol Infect 2010;43(4):285–290

Contents lists available at ScienceDirect

Journal of Microbiology, Immunology and Infection

Journal homepage: http://www.e-jmii.com

Original Article

# Drug Resistance Pattern of *Mycobacterium Tuberculosis* Complex at a Medical Center in Central Taiwan, 2003–2007

**Chia-Chuan Yu[a], Chih-Yen Chang[a], Chun-Eng Liu[a,b]*, Li-Fong Shih[b], Ju-Hua Hsiao[b], Chang-Hua Chen[a]**

[a]Division of Infectious Diseases, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan.

[b]Laboratory of Clinical Microbiology, Department of Laboratory Medicine, Changhua Christian Hospital, Changhua, Taiwan.

**BACKGROUND/PURPOSE:** Drug-resistant tuberculosis (TB) is an important issue for public health. This study was conducted to evaluate the prevalence of drug resistance to *Mycobacterium tuberculosis* complex at Changhua Christian Hospital in central Taiwan.

**METHODS:** We retrospectively reviewed 1,961 non-duplicate isolates of *M. tuberculosis* complex from 2003 to 2007. The following data were collected: demographic characteristics, previous anti-TB therapy and drug susceptibility testing. Antimicrobial drug susceptibility testing was performed using the BACTEC MGIT 960 System from January 2003 to February 2005. Starting in March 2005, the agar proportion method was used for antimicrobial drug susceptibility testing.

**RESULTS:** A total of the 1,961 patients were analyzed. The majority (66.5%) of cases were ≥65 years of age. A total of 151 patients had undergone previous anti-TB treatment. Individual drug resistance was as follows: 229 isolates (11.7%) were resistant to isoniazid, 55 (2.8%) to rifampin, 49 (2.5%) to ethambutol, and 218 (11.1%) to streptomycin. The overall resistance to any drug was 19.1%, while 39 isolates (2.0%) were resistant at least to isoniazid and rifampin (multidrug-resistant). A significant decreasing trend in resistance rates to the four first-line anti-TB drugs, and any other drug, was observed during the 5-year period. Drug resistance was associated with a history of previous anti-TB treatment ($p=0.017$).

**CONCLUSION:** The study found a significant decrease in drug resistance from 2003 to 2007. The multidrug resistance also decreased, although this was not statistically significant. This decreasing resistance rate may be due to the effect of the direct observed treatment, short-course strategy which was enhanced in Taiwan after 2006.

**KEYWORDS:** drug resistance, HIV, *Mycobacterium tuberculosis* complex

*Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Changhua Christian Hospital, 135 Nanhsiao Street, Changhua 500, Taiwan.

E-mail: 63557@cch.org.tw

**Article History:**
Received: Apr 30, 2009
Revised: Jun 5, 2009
Accepted: Jul 29, 2009

## Introduction

Tuberculosis (TB) is a major cause of illness and death worldwide, especially in Asia and Africa. The World Health Organization (WHO) estimates that 9.2 million new cases of TB occurred in 2006 (139 per 100,000 population). Asia (South-East Asia and Western Pacific regions) accounts for 55% of global cases, and Africa accounts for 31%. Among the 9.2 million new cases of TB in 2006, 4.1 million were new smear-positive cases (44%) and 0.7 million human immunodeficiency virus (HIV)-positive cases (8%). The global incidence peaked around 2003, but has now stabilized. However, because of population growth in Asia, Africa and Europe, the number of new cases was still increasing between 2005 and 2006—from 9.1 million to 9.2 million.[1] In addition, multidrug resistant (MDR)-TB, which is resistant to isoniazid (INH) and rifampin (RIF), emerged worldwide. The WHO estimated the number of incident MDR-TB cases was 489,139 in 2006. Three countries, China, India, and Russia, accounted approximately 50% of the global burden of MDR-TB.[2]

A notification system for TB cases was established in Taiwan in July 1997; if there were any suspected TB cases reported to the public health administration, the hospital would not receive any reimbursement from the National Health Insurance. Because of this, more TB cases have been identified.[3] In 2006, the Centers for Disease Control (CDC) of Taiwan reported 15,378 newly diagnosed TB cases. An incidence of 67.4 cases per 100,000 population and a mortality rate of 3.6 deaths per 100,000 population were reported.[4] The incidence was higher in aborigines and in people living in mountainous counties or regions.[5]

INH was introduced for TB treatment in 1952 and RIF in 1978. In Taiwan, drug-resistant pulmonary TB has been reported since 1962.[6] Wu et al reported primary drug resistance in Taiwan from October 1970 to September 1972 as follows: INH 22.6%, ethambutol (EMB) 0.2%, streptomycin 15.4% and any drug 30.8%.[6] Primary resistance rates to RIF have increased in the recent decade as a result of RIF-containing mass chemotherapy.[5] In addition, both MDR-TB and extensively-drug-resistant TB have emerged as a challenge. Since drug resistance is a critical indicator of TB control, the laboratory-based Taiwan Surveillance of drug resistance was established in 2003.[7] Continuing the published study discussing the drug resistance rate in central Taiwan from July 2001 through June 2002,[8] this study aimed to further analyze drug resistance trends from 2003 to 2007.

## Methods

### *Patients*

Changhua Christian Hospital is a 1,613-bed teaching hospital in central Taiwan, providing both acute and chronic care services. The study analyzed the records of all patients with positive *Mycobacterium tuberculosis* complex (MTBC) cultures between January 2003 and December 2007. When multiple isolates were obtained from a patient, only the first isolate was analyzed. Information was collected on demographic characteristics of age and sex, HIV tests, history of TB and any previous therapy.

### *Laboratory procedures*

All drug susceptibility tests were performed in the mycobacteriology laboratory of the Changhua Christian Hospital. Prior to the end of 2004, the digested and decontaminated specimens were inoculated into a Mycobacteria Growth Indicator Tube (MGIT) and placed into the BACTEC MGIT 960 system (Becton Dickinson, Sparks, MD, USA) for culture. Since the end of 2004, in addition to the MGIT 960 system, the specimens were cultured on Löwenstein-Jensen media. After the identification of MTBC, a BACTEC MGIT 960 SIRE kit was used for antimicrobial susceptibility testing (AST) prior to March 1, 2005. Critical concentrations of INH (0.1 μg/mL), RIF (1.0 μg/mL), EMB (5.0 μg/mL), and streptomycin (1.0 μg/mL) were tested. After March 1, 2005, this method was replaced by the agar proportion method. Middlebrook 7H10 agar was used for AST, containing the standard sensitive strain, H37Rv, for quality control. The media comprised were 0.2 μg/mL INH, 1.0 μg/mL RIF, 5.0 μg/mL EMB and 2.0 μg/mL streptomycin. Organisms were considered resistant to a given drug if any growth ≥ 1% of the drug free control was observed.

Primary resistance was defined as the presence of drug resistance in new cases, or in patients who had received anti-TB treatment for < 1 month. Drug resistance among previously treated cases was defined as resistance in patients who had already received anti-TB therapy for ≥ 1 month, or were retreated. Combined resistance was defined as any

resistance regardless of previous treatment. MDR-TB was resistant to INH and RIF.

### *Statistical analysis*

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Differences in drug resistance between different age groups, sexes, or previous anti-TB treatment were analyzed using the $\chi^2$ test or Fisher's exact test. Trends in drug resistance were evaluated by logistic regression analysis. A $p$ value of $<0.05$ was considered statistically significant.

## Results

During the 5-year study period, 92,808 specimens submitted for mycobacterial cultures from inpatient and outpatient services and yielded 4,945 isolates of MTBC (positive rate, 5.3%). A total of 1,961 first isolates with AST were collected. Of the 1,961 isolates, 1,712 (87.3%) were from respiratory secretions (sputum and bronchial washing), 101 (5.2%) from pleural effusions, 31 (1.6%) from urine, 18 (0.9%) from gastric juices, 16 (0.8%) from cerebrospinal fluid, 13 (0.7%) from pericardial effusions, 13 (0.7%) from ascites, and the rest 57 (2.9%) from other specimens including synovial fluid, abscess, bone, blood, and tissue. There were 1,353 men and 608 women with a mean age of 67.5 years. Two-third of cases were ≥65 years of age. A total of 151 patients had a previous history of anti-TB therapy for ≥1 month.

Of these first isolates, 229 (11.7%) were resistant to INH, 55 (2.8%) to RIF, 49 (2.5%) to EMB and 218 (11.1%) to streptomycin. Overall, 19.1% of isolates were resistant to one or more drugs. Thirty-nine isolates (2.0%) were resistant to at least INH and RIF. The trend of drug resistance during 2003–2007 is shown in Table 1. A significant decrease in the resistance rates to the first-line drugs, or any drug, was noted ($p<0.05$). The decreasing trend was significant, especially after 2006 ($p=0.009$ and $p=0.034$ for any drug resistance; Table 2). A comparison of drug resistance between patients with and without previous anti-TB therapy is shown in Table 3. Higher resistance rates to INH, RIF, EMB, streptomycin, and higher MDR was seen in those patients that had been previously treated ($p<0.05$).

The drug resistance was reviewed by sex and age (Table 4). The overall drug resistant rate was higher in those aged 45–64 years (25.2%), followed by those aged 25–44 years (19.6%), those aged <25 years (18.8%), and those aged ≥65 years (17.0%). MDR-TB was highest among the group aged 25–44 years (4.5%) compared with the groups aged 45–64 years (3.5%) and ≥65 years (1.2%). The drug resistant rate was similar in male (19.3%) and female (18.8%) patients ($p=0.778$). However, a significant difference was noted ($p=0.003$) between the different age groups.

Of the 1,961 patients, an HIV screening test was available for 222 (11.3%) patients. Of these, seven (3.2%) patients had HIV infection as confirmed by Western blot. Sixty-five patients had been tested for HIV antibody before diagnosis of TB, and four were HIV-positive. The remaining 157

**Table 1.** Resistance to first-line anti-tuberculosis agents, 2001–2002 and 2003–2007

| Drugs | No. of resistant isolates (%) | | | | | | | $p^b$ |
|---|---|---|---|---|---|---|---|---|
| | 2001–2002, from Liu CE et al [8][a] ($n=513$) | 2003 ($n=397$) | 2004 ($n=448$) | 2005 ($n=403$) | 2006 ($n=396$) | 2007 ($n=317$) | Total ($n=1,961$) | |
| INH | 86 (16.8) | 63 (15.9) | 47 (10.5) | 52 (12.9) | 36 (9.1) | 31 (9.8) | 229 (11.7) | 0.010 |
| RIF | 25 (4.9) | 16 (4.0) | 13 (2.9) | 15 (3.7) | 7 (1.8) | 4 (1.3) | 55 (2.8) | 0.010 |
| EMB | 21 (4.1) | 11 (2.8) | 16 (3.6) | 13 (3.2) | 8 (2.0) | 1 (0.3) | 49 (2.5) | 0.016 |
| SM | 63 (12.3) | 51 (12.8) | 60 (13.4) | 39 (9.7) | 40 (10.1) | 28 (8.8) | 218 (11.1) | 0.026 |
| Any drug | 115 (22.4) | 93 (23.4) | 92 (20.5) | 77 (19.1) | 61 (15.4) | 52 (16.4) | 375 (19.1) | 0.002 |
| MDR-TB | 20 (3.9) | 11 (2.8) | 8 (1.8) | 11 (2.7) | 6 (1.5) | 3 (0.9) | 39 (2.0) | 0.104 |

[a]The drug susceptibility test was performed by the BACTEC MGIT 960 system; [b]$\chi^2$ test for trend from 2003 to 2007. INH = Isoniazid; RIF = rifampin; EMB = ethambutol; SM = streptomycin; MDR-TB = multidrug resistant tuberculosis.

**Table 2.** Logistic regression analysis of drug resistance from 2003 to 2007

| Year | Total | Resistance | Multiple analysis | |
|---|---|---|---|---|
| | | *n* (%) | OR (95% CI) | *p* |
| 2003 | 397 | 93 (23.4) | 1.000 | |
| 2004 | 448 | 92 (20.5) | 0.851 (0.613–1.180) | 0.333 |
| 2005 | 403 | 77 (19.1) | 0.793 (0.563–1.116) | 0.183 |
| 2006 | 396 | 61 (15.4) | 0.618 (0.431–0.886) | 0.009 |
| 2007 | 317 | 52 (16.4) | 0.664 (0.454–0.969) | 0.034 |

OR=Odds ratio; CI=confidence interval.

**Table 3.** Drug resistance among patients with or without previous anti-tuberculous therapy

| Drugs | No. of resistant isolates (%) | | *p* |
|---|---|---|---|
| | Without previous TB therapy (*n*=1,810) | With previous TB therapy (*n*=151) | |
| INH | 202 (11.2) | 27 (17.9) | 0.013 |
| RIF | 36 (2.0) | 19 (12.6) | 0.000 |
| EMB | 39 (2.2) | 10 (6.6) | 0.003 |
| SM | 192 (10.6) | 26 (17.2) | 0.013 |
| Any drug | 335 (18.5) | 40 (26.5) | 0.017 |
| MDR-TB | 23 (1.3) | 16 (10.6) | 0.000 |

INH=Isoniazid; RIF=rifampin; EMB=ethambutol; SM=streptomycin; MDR-TB=multidrug resistant tuberculosis.

patients were tested for HIV antibody after TB diagnosis, and three (1.9%) were HIV-seropositive.

## Discussion

The WHO reported that the global incidence of TB peaked around 2003 and appeared to stabilize, or began to decline. However, the number of new cases increased between 2005 and 2006.[1] The estimated TB burden varied in different countries. In 2006, the estimated incidence in Taiwan, calculated from the WHO equation, was 87 per 100,000 per year; and the estimated prevalence was 113 per 100,000 per year.[4] The results were similar to those of Republic of Korea, but higher than those in Hong Kong (incidence of 62 per 100,000 per year; prevalence of 64 per 100,000 per year) and Singapore (incidence of 26 per 100,000 per year; prevalence of 25 per 100,000 per year).

**Table 4.** Drug resistance, by sex and age

| | Total | Any drug resistance[a] *n* (%) | *p* | Multidrug resistance *n* (%) |
|---|---|---|---|---|
| Sex | | | | |
| Male | 1,353 | 261 (19.3) | 0.778 | 31 (2.3) |
| Female | 608 | 114 (18.8) | | 8 (1.3) |
| Age group | | | | |
| <25 | 64 | 12 (18.8) | 0.003 | 0 (0) |
| 25–44 | 179 | 35 (19.6) | | 8 (4.5) |
| 45–64 | 433 | 109 (25.2) | | 15 (3.5) |
| ≥65 | 1,285 | 219 (17.0) | | 16 (1.2) |

[a]Refers to "at least one drug".

In Taiwan, the number of new TB cases declined from 16,784 cases in 2004 to 15,378 in 2006. In this study (from 2003 to 2007), which combines the data of a previous study by Liu[8] from 2001 to 2002, the number of cases also decreased gradually—from 513 to 317 (Table 1). There may be many factors influencing the incidence of TB, e.g. direct observed treatment, short course (DOTS) strategy, HIV prevalence and others. DOTS may have a great impact on decreasing TB transmission. However, DOTS can be augmented by a more integrated approach or other developments, e.g. HIV control, rapid and accurate diagnosis, new drugs or new vaccines.[9]

The Global Project on Anti-Tuberculosis Drug Resistance Surveillance was initiated in 1994.[10,11] In new cases of TB, the median prevalence of resistance to any drug during 2002–2007 was 11.1%, and to MDR was 1.6%.[10] The prevalence of MDR among new cases ranged from 0% in eight countries to 22.3% in Baku and Azerbaijan. In previously treated cases, the median prevalence of resistance to any drug was 25.1% and to MDR was 11.7%. This study revealed that the drug resistance rate at this hospital in central Taiwan was close to the global median rate. Compared with the resistance rate in Hong Kong (11.1% any drug and 0.9% MDR in new cases) and Singapore (6.5% any drug and 0.2% MDR in new cases), this study showed higher drug resistance rates, whereas the resistance rates were lower than that in the Republic of Korea.

The combined resistance reported in Taiwan from 1982 to 2004 was: INH=13.9–35.9%, RIF=4.9–18.2%, EMB=4.1–15.7%, streptomycin=8.3–28.6% and MDR=3.9–17.3%.[7]

From recent reports,[12–15] the combined resistance to any drug was 23.4% in northern Taiwan, 52.4% in southern Taiwan and 28.6% in eastern Taiwan. The combined resistance to any drug in this study was much lower than that in northern, southern and eastern Taiwan. In addition, the overall drug resistance of individual first-line drugs in this study was lower than that in previous studies,[12,13,15] except for the overall drug resistance to streptomycin, which was lower in eastern Taiwan. This finding was the same for MDR-TB. Overall, drug resistance was lower at this hospital than in other regions. This may be due to a smaller number of TB cases in central Taiwan and certain patients with MDR-TB being transferred to referral hospitals.

In this study, the drug resistance trends for first-line drugs or any drug significantly decreased, (also noted in northern and southern Taiwan).[12,13] Compared with the data from 2001–2002 in the report by Liu,[8] the resistance rate during 2003–2007 was lower (although resistance to any drug or streptomycin was higher in 2003, but decreased thereafter). It may, therefore, be concluded that drug resistance was decreasing in western Taiwan. Starting in 2006, DOTS was strengthened in Taiwan and may have contributed to this study result, which found a significant decrease in 2006 and 2007. This result was not due to the different AST, since the agar proportion method was used after March 2005. Although DOTS may be one reason for the decreasing resistance rate, many other factors such as patient characteristics, case number, non-referral center and local TB control program may have influenced drug resistance in this hospital. To observe the full effect of DOTS, long-term follow-up is needed.

As expected, the resistance rate observed in this study was higher in previously treated patients ($p < 0.05$), as reported previously.[14,16,17] The resistance rate to any drug was similar in men and women, but men were more likely to have MDR-TB than women, which is different to results in previous studies.[17–19] We found that age was a significant factor in the development of drug resistance. Younger patients showed higher resistance rates than those ≥65 years. Resistance to any drug was highest in those aged 45–64 years, and those aged 25–44 years had the highest rate of MDR. WHO mentioned that MDR-TB was likely to be associated with male sex and a younger age group (25–44 years).[2] Our data show similar results. There may be many factors contributing to these age and sex differences, e.g. the year in which they received effective anti-TB drug[20] or patient compliance.

The association between TB and HIV/acquired immunodeficiency syndrome (AIDS) has frequently been discussed. The prevalence of HIV infection in new TB cases varies between regions and countries: from 1% in the Western Pacific region to 38% in the African region. Nine percent (7–12%) of all new TB cases in adults aged 15–49 years are attributable to HIV infection.[21] Screening for HIV is recommended for patients with TB, and HIV testing of TB patients has increased from around 20,000 patients in 2002 to almost 700,000 patients in 2006.[22] In 1996 in Taiwan, Chiang et al reported that only 1/378 patients with active pulmonary TB had HIV, but HIV infection was still not significant at that time.[23] However, cases of HIV/AIDS have increased recently in Taiwan. In 2004, drug injection led to a rise in HIV infection in Taiwan; thus the prevalence of HIV in 2004 was 18.09 per 100,000 population. The number of HIV cases had risen to 15,651 by 2007.[3] Clinicians are alert to TB in Taiwan, but the detection of HIV infection may be delayed or neglected. The CDC in Taiwan reported that 0.7% of new TB patients in 2006 were HIV positive.[4] A recent study from a medical center in northern Taiwan reported that the prevalence of HIV infection among TB patients was 5.6%.[24]

As previously mentioned, 222/1,961 TB patients were tested for HIV. Of these, 3.2% were HIV positive, while the HIV prevalence rate among the TB patients reported by the CDC was 0.7%. There were 1,739 (1,961 minus 222) untested patients, which may have resulted in higher rates of HIV diagnosis. The increase in suspected cases may have been 55 (1,739 multiplied by 3.2%) or seven (1,739 multiplied by 0.7%). Thus HIV screening is very important in TB cases.

This study had some limitations. First, the method used for AST was different before March 2005. As a result, the critical concentrations of INH and streptomycin were not the same. Second, as this was a retrospective study, some data may be incomplete.

In conclusion, this study shows a significant decrease in drug resistant TB from 2003 to 2007. As expected, resistance to anti-TB drugs was associated with previous episodes of anti-TB treatment. Although DOTS may have been effective in controlling TB, MDR-TB remains a challenge.

More policies should be established to strengthen MDR-TB control. Also, because of the TB/HIV co-infection, more attention should be paid to HIV screening for TB patients.

## References


1. World Health Organization. *Global tuberculosis control - surveillance, planning, financing, WHO Report 2008*. Geneva, Switzerland: WHO, 2008 Available at: http://www.who.int/tb/publications/global_report/2008/en/index.html [Date accessed: May 4, 2010]
2. World Health Organization. Anti-tuberculosis drug resistance in the world, Fourth global report. Geneva, Switzerland: WHO, 2008. Available at: http://whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.394_eng.pdf [Date accessed: May 4, 2010]
3. Kuo SH-S, Chou J, Lin T, Shih WY, Chen YH, Wu PF, et al. *CDC Annual Report 2008*. Taipei, Taiwan: Centers for Disease Control, R.O.C (Taiwan), 2008. Available at http://www.cdc.gov.tw/public/data/89116495971.pdf [Date accessed: May 4, 2010]
4. Kuo HS-S, Shi WY, Lin T, Chou JH, Chen YH, Yan JJ, et al. *Taiwan Tuberculosis Control Report 2008*. Taipei, Taiwan: Centers for Disease Control, R.O.C (Taiwan), 2008. Available at http://www.cdc.gov.tw/public/data/9411674871.pdf [Date accessed: May 4, 2010]
5. Hsueh PR, Liu YC, So J, Liu CY, Yang PC, Luh KT. *Mycobacterium tuberculosis* in Taiwan. *J Infect* 2006;52:77–85.
6. Wu YT. Primary drug resistance of *Mycobacterium tuberculosis* in Taiwan. *J Formos Med Assoc* 1973;72:135–42.
7. Jou R, Chuang PC, Wu YS, Yan JJ, Luh KT. Drug-resistant *Mycobacterium tuberculosis*, Taiwan. *Emerg Infect Dis* 2006;12:871–2.
8. Liu CE, Chen CH, Hsiao JH, Young TG, Tsay RW, Fung CP. Drug resistance of *Mycobacterium tuberculosis* complex in central Taiwan. *J Microbiol Immunol Infect* 2004;37:295–300.
9. Maartens G, Wilkinson RJ. Tuberculosis. *Lancet* 2007;370:2030–43.
10. Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, et al. Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Epidemiology of antituberculosis drug resistance 2002–07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet* 2009;373:1861–73.
11. Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, et al. WHO/International Union Against Tuberculosis And Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet* 2006;368:2142–54.
12. Lai CC, Tan CK, Huang YT, Chou CH, Hung CC, Yang PC, et al. Extensively drug-resistant *Mycobacterium tuberculosis* during a trend of decreasing drug resistance from 2000 through 2006 at a medical center in Taiwan. *Clin Infect Dis* 2008;47:e57–63.
13. Lu PL, Lee YW, Peng CF, Tsai JJ, Chen YH, Hwang KP, et al. The decline of high drug resistance rate of pulmonary *Mycobacterium tuberculosis* isolates from a southern Taiwan medical centre, 1996–2000. *Int J Antimicrob Agents* 2003;21:239–43.
14. Su WJ, Feng JY, Huang CC, Perng RP. Increasing drug resistance of *Mycobacterium tuberculosis* isolates in a medical center in northern Taiwan. *J Formos Med Assoc* 2008;107:259–64.
15. Lee JJ, Lee CN, Suo J, Chiang IH, Lin CB, Lin TY, et al. Drug resistance of *Mycobacterium tuberculosis* in eastern Taiwan. *Tzu Chi Med J* 2003;15:229–34.
16. Tsao TCY, Chiou W, Lin H, Wu T, Lin M, Yang P, et al. Change in demographic picture and increase of drug resistance in pulmonary tuberculosis in a 10-year interval in Taiwan. *Infection* 2002;30:75–80.
17. Wang PD, Lin RS. Drug-resistant tuberculosis in Taipei, 1996–1999. *Am J Infect Control* 2001;29:41–7.
18. Chiang CY, Hsu CJ, Huang RM, Lin TP, Luh KT. Antituberculosis drug resistance among retreatment tuberculosis patients in a referral center in Taipei. *J Formos Med Assoc* 2004;103:411–5.
19. Liaw YS, Hsueh PR, Yu CJ, Wang SK, Yang PC, Luh KT. Drug resistance pattern of *Mycobacterium tuberculosis* in a university hospital in Taiwan, 1998–2002. *J Formos Med Assoc* 2004;103:671–7.
20. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systemic review. *Thorax* 2005;61:158–63.
21. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MD, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003;163:1009–21.
22. Lonnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. Semin *Respir Crit Care Med* 2008;29:481–91.
23. Chiang CY, Wu IH, Yu MC, Lee CN, Bai KJ, Suo J, et al. Screening of human immunodeficiency virus infection in pulmonary tuberculosis patients in Taiwan. *J Formos Med Assoc* 1998;97:66–8.
24. Kung HC, Sun HY, Chen MY, Hsieh SM, Sheng WH, Chen YC, et al. Human immunodeficiency virus testing among patients with tuberculosis at a university hospital in Taiwan, 2002 to 2006. *J Formos Med Assoc* 2009;108:320–7.