PREVALENCE AND FACTORS ASSOCIATED WITH MULTIDRUG-RESISTANT TUBERCULOSIS AT SIRIRAJ HOSPITAL, BANGKOK, THAILAND

Anupop Jitmuang[1], Parnwad Munjit[1] and Suporn Foongladda[2]

[1]Department of Medicine, [2]Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract. The objective of this study was to determine the prevalence and factors associated with multidrug-resistant tuberculosis (MDR-TB) at Siriraj Hospital, Bangkok, Thailand. We conducted a retrospective unmatched case-control study of patients clinically diagnosed and microbiologically confirmed to have tuberculosis (TB) at Siriraj Hospital from 2010 to 2012. Patient characteristics, clinical data, microbiological findings, outcomes and drug susceptibilities were recorded. A total of 188 subjects were included in the study; 52.1% (98) were males; the mean age was 48.9 years. Subjects were categorized into one of two groups, as follows: non-MDR-TB (141 patients) and MDR-TB (47 patients). The prevalence of MDR-TB was 2.6%. Co-morbidities of study subjects included diabetes mellitus (16.5%), HIV infection (16%) and cancer (5.9%). One hundred thirty-one patients (69.7%) had pulmonary TB. Factors significantly associated with MDR-TB were age <65 years (OR=6.94; 95% CI: 1.02-45.49; p=0.048), history of TB (OR=51.86; 95%CI: 12.35-217.79; p<0.001), HIV co-infection (OR=3.83; 95% CI: 1.02-14.38; p=0.047) and alcohol consumption (OR=3.90; 95% CI: 1.03-14.72; p=0.045). Of the 146 patients for whom a clinical outcome was available, 51 (34.9%) had an unfavorable outcome. Poor compliance (OR=13.51; 95% CI: 3.97-45.45; p<0.001) and previous history of TB (OR=8.16; 95% CI: 1.76-37.73; p=0.007) were associated with an unfavorable outcome. MDR-TB was significantly associated with: patients aged <65 years, those with a previous history of TB, those with HIV co-infection and those who drank alcohol. These factors should be kept in mind when treating TB patients at Siriraj Hospital, Thailand.

Keywords: tuberculosis, multidrug resistance, associated factors, prevalence, Thailand

INTRODUCTION

Tuberculosis (TB) is a major public health problem. In 2012, the World Health Organization (WHO) estimated the global prevalence of TB to be 8.6 million, with 84,000 cases confirmed to be multidrug-resistant TB (MDR-TB) (WHO, 2013). In Thailand, the rate of MDR-TB in 2010 was estimated to be 1.7% among newly diagnosed TB cases and 34.5% among previously treated cases (WHO, 2010). The Thai Ministry of Public Health funded the development of an extensive laboratory network to perform anti-tuberculosis

Correspondence: Dr Anupop Jitmuang, Division of Infectious Disease and Tropical Medicine, Department of Medicine, Siriraj Hospital, Prannok Road, Bangkok Noi, Bangkok 10700, Thailand.
Tel: +66 (0) 2419 7783; Fax: +66 (0) 2419 7784
E-mail: anupopmix@yahoo.co.th

susceptibility testing (AST) in order to detect MDR-TB earlier. Genotypic detection of rifampicin and isoniazid resistance is now available (WHO, 2008). Conventional AST is normally used to diagnose MDR-TB because the genotypic assay is not widely available. Knowledge of the risk factors associated with MDR-TB can help identify patients who should have AST testing. This study aimed to identify the prevalence of and factors associated with MDR-TB among culture-confirmed TB patients.

MATERIALS AND METHODS

We conducted a retrospective unmatched case-control study to determine the prevalence, risk factors, and the AST patterns of MDR-TB. This study was approved by the Scientific Ethics Committee, Siriraj Institutional Review Board (SIRB). Data regarding cases and controls were obtained from chart reviews of Siriraj Hospital patients aged ≥18 years clinically diagnosed and microbiologically confirmed to have either MDR-TB (case) or non-MDR-TB (control) during the 2010-2012 study period. Data obtained included general demographic characteristics and treatment outcomes. Study subjects were followed until the end of June 2013. All cases and controls had positive cultures for *M. tuberculosis* complex, as identified by conventional Löwenstein-Jensen (LJ) solid agar and/or an automated liquid media system (BACTEC MGIT 960; Becton-Dickinson, Franklin Lakes, NJ). The agar proportion method and/or mycobacterial growth ratio between drug-containing and drug-free broth were performed to identify AST.

Definitions

A MDR-TB was defined as a patient with culture-confirmed *Mycobacterium tuberculosis* resistance to both isoniazid (INH) and rifampicin (RIF), with or without resistance to other drugs. *M. tuberculosis* not resistant to both INH and RIF was classified as non-MDR-TB. Extensively drug-resistant tuberculosis (XDR-TB) was defined as MDR-TB plus resistance to a fluoroquinolone and at least one second-line injectable TB agent, such as amikacin, kanamycin or capreomycin (WHO, 2008). A new TB case was defined as a newly diagnosed case of TB receiving no or less than 1 month of anti-tuberculosis treatment. A previously treated TB case was defined as a patient with a history of TB who had been previously treated with anti-tuberculosis drugs for at least 1 month (WHO, 2008). Pulmonary TB was defined as an infection confined to the lung parenchyma. Extra-pulmonary TB was defined as infection outside the lung parenchyma, such as in the pleura, lymph nodes, meninges, gastrointestinal tract, bone or joints. Disseminated TB was defined as an infection that simultaneously occurred in at least 2 non-contiguous sites, such as miliary TB.

Treatment outcomes were divided into favorable and unfavorable outcomes. Favorable outcomes were defined as follows: 1) *cure*: having received a full course of treatment and having had a clinical response, with microbiological conversion to negative at least 2 times during follow-up and at the end of treatment; 2) *completed treatment*: having received a full course of treatment and having had a clinical response, but having incomplete microbiological evaluation or an indeterminate result. Unfavorable outcomes were defined as: 1) *treatment default*: a patient discontinuing anti-tuberculosis treatment for ≥ 2 consecutive months; 2) *treatment failure*: persistence or reversion of acid-fast bacilli (AFB) smear or positive mycobac-

terial culture after an intensive phase of treatment and/or clinical unresponsiveness to treatment and/or a severe adverse reaction causing the patient to be unable to continue treatment; 3) *death*: death from any cause during treatment. Subjects were classified as having had: 1) *good compliance*: if they had regularly adhered to follow-up schedules and had less than a 20% absence rate or 2) *poor compliance*: if they failed to adhere to the follow-up schedule or had a ≥ 20% absence rate.

Sample size calculation

Casal *et al* (2005) found having a previous history of TB is a risk factor for MDR-TB, with an odds ratio (OR) of 2.6 and control group exposure percentage of 20%. Sample size calculation for our study was based on a control to case ratio of 3:1, 80% power and a 95% confidence level. Due to the large number of patients with non-MDR-TB in our study, the controls (n=141) were chosen randomly from a total of 1,792 patients with non-MDR-TB at our hospital during the study period. Forty-seven cases were included in the study.

Statistical analyses

Statistical analysis was performed using SPSS version 16.0 (IBM, Armonk, NY). Values were expressed as mean ± standard deviation or median (minimum, maximum) for continuous variables and as frequencies for categorical variables. Comparisons of continuous variables between the cases and controls was made using the Student's two-tailed t-test or the Mann-Whitney U test for nonparametric testing. The chi-square and Fisher's exact tests were used to analyze differences among categorical variables. Variables that were significantly associated with multidrug resistance on univariate analysis (p<0.2) were included in a multivariate logistic regression model. All statistical tests were two-sided, with a p<0.05 being considered statistically significant.

RESULTS

The prevalence of MDR-TB at Siriraj Hospital from January 2010 to December 2012 was 2.6%. One hundred eighty-eight culture-confirmed TB patients were included, of whom 47 had MDR-TB. Three had XDR-TB and were included in the MDR-TB group. One hundred fifty-six patients (83%) were new cases and 32 (17%) were previously treated cases. The mean (±SD) age was 49 (±18) years; 52.1% were male. Thirty-eight point five percent (72 of 187) had a positive smear for acid-fast bacilli. The patient characteristics are shown in Table 1. In the MDR-TB group, 25 patients (53.2%) had previously received treatment for TB. AST was conducted in all subjects. One hundred thirty patients (69.1%) had TB susceptible to all drugs and 58 patients (30.9%) had TB resistant to at least one anti-tuberculosis drug. The results of anti-tuberculosis drug sensitivity testing are shown in Table 2.

Risk factors associated with MDR-TB

The results of univariate and multivariate analyses of factors associated with MDR-TB are shown in Table 3. The following factors were found to be significantly associated with MDR-TB: age <65 years (adjusted OR=6.94; 95% CI: 1.02-45.49; p=0.048), previous history of TB (adjusted OR=51.86; 95% CI: 12.35-217.79; p<0.001), HIV co-infection (adjusted OR=3.83; 95% CI: 1.02-14.38; p=0.047), and alcohol consumption (adjusted OR=3.90; 95% CI: 1.03-14.72; p=0.045).

Factors associated with unfavorable outcomes

After excluding those who transferred

Table 1
Comparison of demographic and clinical characteristics between patients with MDR-TB and non-MDR-TB.

Patient characteristics	MDR-TB	Non-MDR-TB	*p*-value
Age (mean ± SD, yrs)	43.87 ± 15.12	50.57 ± 19.16	0.016
Gender			
Male	27/47 (57.4%)	71/141 (50.4%)	0.399
Female	20/47 (42.6%)	70/141 (49.6%)	
BMI (mean ± SD, kg/m²)	19.50 ± 4	19.80 ± 3.47	0.637
TB contact	9/28 (32.1%)	23/135 (17%)	0.067
Prior history of TB	25/47 (53.2%)	7/141 (5.0%)	<0.001
Interval [median (min-max), months between first TB diagnose and recurrence]	24 (4-480)	168 (36-600)	0.013
Favorable outcome (cure or completed treatment)	9/23 (39.1%)	2/3 (66.7%)	0.556
DM	9/47 (19.1%)	22/141 (15.6%)	0.57
HIV infection	11/41 (26.8%)	15/123 (12.2%)	0.026
Cancer	2/47 (4.3%)	9/141 (6.4%)	0.734
CKD	0/47 (0%)	4/141 (2.8%)	0.574
Chronic liver disease	1/47 (2.1%)	4/141 (2.8%)	1
Systemic steroid use	1/46 (2.2%)	8/141 (5.7%)	0.457
Immunosuppressive drug use	0/46 (0%)	8/141 (5.7%)	0.203
Alcohol consumption	12/40 (30%)	23/129 (17.8%)	0.097
Type of infection			
Pulmonary	33/47 (70.2%)	98/141 (69.5%)	0.515
Extra-pulmonary	5/47 (10.6%)	23/141 (16.3%)	
Disseminated	9/47 (19.1%)	20/141 (14.2%)	
Positive AFB smear	26/47 (55.3%)	46/140 (32.9%)	0.006
Follow-up at < 80% of appointments	10/37 (27%)	16/110 (14.5%)	0.085
Outcome			
Favorable (cure or completed treatment)	9/25 (36%)	86/121 (71.1%)	0.001
Unfavorable (default, failure, death)	16/25 (64%)	35/121 (28.9%)	

AFB, acid-fast bacilli; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

out of treatment and those who were still undergoing treatment at the end of June 2013, clinical outcomes were available for 146 patients (77.6%). Of those 146 cases, 15 (10.3%) were cured, 80 (54.8%) had completed treatment, 2 (1.4%) failed treatment, 32 (21.9%) defaulted, 7 (4.8%) died and 10 (6.8%) did not receive treatment. Treatment outcomes were significantly different between non-MDR-TB and MDR-TB subjects (p=0.001) (Table 1). Favorable outcomes were more common among non-MDR-TB cases than MDR-TB cases. Cures occurred in 10 patients (11.6%) and 5 patients (20%) with non-MDR-TB and MDR-TB, respectively. Seventy-six patients (88.4%) and 4 patients (16%) with non-MDR-TB and MDR-TB, respectively, completed treatment. Unfavorable outcomes were more common among MDR-TB cases: failure among 2 patients (12.5%), default among 9 patients (56.3%) and death among 2

Table 2
Anti-tuberculosis resistance rates in patients with MDR-TB and non-MDR-TB[a].

Drugs	MDR-TB	Non-MDR-TB
INH	47/47 (100%)	13/141 (9.2%)
Rifampicin	47/47 (100%)	1/141 (0.7%)
PZA	5/23 (21.7%)	3/60 (5%)
Ethambutol	15/47 (31.9%)	2/139 (1.4%)
Ofloxacin	1/27 (3.7%)	0
Levofloxacin	NA	NA
Moxifloxacin	2/43 (4.7%)	0
PAS	7/44 (15.9%)	0
Cyclosporine	NA	NA
Ethionamide	10/44 (22.7%)	0
Streptomycin	25/45 (55.6%)	5/106 (4.7%)
Kanamycin	2/44 (4.5%)	0
Amikacin	2/44 (4.5%)	0
Ciprofloxacin	5/39 (12.8%)	0

INH, isoniazid; PZA, pyrazinamide; PAS, para-aminosalicylic acid; NA, not available.
[a]By conventional agar proportion method and/or mycobacterial growth ratio between drug-containing and drug-free broth systems.

Table 3
Factors associated with MDR-TB.

Factors	*p*-value (univariate)	*p*-value (multivariate)	Adjusted OR (95% CI)
Age < 65 yrs	0.014	0.048	6.94 (1.02-45.49)
Male	0.400	0.322	1.84 (0.55-6.18)
Previous TB	<0.001	<0.001	51.86 (12.35-217.79)
HIV infection	0.026	0.047	3.83 (1.02-14.38)
Alcohol consumption	0.097	0.045	3.90 (1.03-14.72)
Positive AFB smear	0.006	0.262	1.84 (0.64-5.30)

AFB, acid-fast bacilli; CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug resistant-tuberculosis; OR, odds ratio; TB, tuberculosis.

patients (12.5%). Follow-up at <80% of the appointments (adjusted OR=13.51; 95% CI: 3.97-45.45; $p<0.001$) and previous history of TB (adjusted OR=8.16; 95% CI: 1.76-37.73; $p=0.007$) were significantly related to unfavorable outcomes (Table 4). Twenty-five patients with MDR-TB (excluding those who transferred out or were ongoing treatment) were analyzed to identify factors associated with unfavorable outcomes. We found no significant variables associated with unfavorable outcomes among MDR-TB patients (data not shown).

Table 4
Factors associated with unfavorable outcome[a].

Factors	*p*-value (univariate)	*p*-value (multivariate)	Adjusted OR (95% CI)
MDR-TB	0.002	0.204	2.46 (0.61-9.85)
Age ≥ 65 yrs	0.168	0.641	1.32 (0.41-4.29)
Gender	0.298		
BMI	0.087	0.088	1.15 (0.98-1.35)
HIV status	0.22		
Extrapulmonary or disseminated TB	0.278		
Previous TB	<0.001	0.007	8.16 (1.76-37.73)
Follow-up at < 80% of appointments	0.085	<0.001	13.51 (3.97-45.45)

BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; MDR-TB, multidrug resistant tuberculosis; OR, odds ratio; TB, tuberculosis.
[a]Treatment default, treatment failure, or death.

DISCUSSION

The prevalence of MDR-TB at Siriraj Hospital during the study period was 2.6%, similar to previous studies from hospitals in Thailand (2.4%) (Reechaipichitkul, 2002; Boonsarngsuk *et al*, 2009). The prevalence of MDR-TB in Thailand among HIV patients was found to be 6.2% (Sungkanuparph *et al*, 2007) and among incarcerated persons was found to be 18.8%-19.5% (Pleumpanupat *et al*, 2003; Tansuphasiri *et al*, 2003).

Having a previous history of TB was a risk factor associated with MDR-TB in our study, similar to several other studies (Casal *et al*, 2005; Faustini *et al*, 2006; Boonsarngsuk *et al*, 2009; Bojorquez *et al*, 2013; Liu *et al*, 2013). The median interval for recurrence of MDR-TB infection was 24 months in our study, significantly shorter than the recurrence of non-MDR-TB infection. Patients with a TB relapse within 1-2 years after completing treatment are at increased risk of drug resistance (Luzze *et al*, 2013). Early relapse (within 6 months of completing treatment) and incomplete treatment have both been associated with rifampicin resistance (Boonsarngsuk *et al*, 2009). Among patients with a previous history of TB who have a recurrence of TB infection within 2 years, MDR-TB should be highly suspected.

Another risk factor for MDR-TB in our study was age <65 years; similar to the findings of a review of pooled data from several European countries (Faustini *et al*, 2006).

History of alcohol consumption was also a factor significantly associated with MDR-TB in our study, even after multivariate analysis adjusting for other important factors (age, previous history of TB, and schedule adherence).

HIV co-infection was identified in our study as a risk factor for MDR-TB, similar to several other studies. According to the Thailand TB Active Surveillance Network, 36% of pulmonary MDR-TB co-existed with HIV infection (Akksilp *et al*, 2009). HIV co-infection is a risk factor for single drug resistance TB (Djuretic *et al*, 2002), polydrug-resistance TB (Mac-Arthur

et al, 2001), and multidrug-resistance TB (Schwoebel *et al*, 1998; Irish *et al*, 1999; Demissie *et al*, 2001; Djuretic *et al*, 2002; Faustini *et al*, 2006). A recent meta-analysis showed a 2.28-fold greater risk of primary anti-TB drug resistance with HIV co-infection (Mesfin *et al*, 2014). At Siriraj Hospital, most HIV-infected patients (especially those with low CD4 counts) are impoverished, do not have a caregiver or have frequent hospitalizations due to recurrent medical illnesses. As a result, there is a risk for emergence of primary and/or secondary drug resistance in this group.

Body mass index (BMI), other medical conditions and immunosuppressive therapies were comparable between those with MDR-TB and non-MDR-TB. Although the AFB positive smear rate was significantly higher among patients with MDR-TB, multivariate logistic regression analysis did not show a significant association between a positive AFB smear and drug resistance. Confounding factors, such as collection method, mycobacterial load, burden of disease, and host immune status may have affected these findings.

In some previous studies, male gender (Irish *et al*, 1999; Faustini *et al*, 2006) and number of lobes of the lungs involved (Flament-Saillour *et al*, 1999) were factors associated with MDR-TB. However, in this study, we did not find gender or sites of infection to be risk factors for MDR-TB infection.

In the MDR-TB group, 55.6% of patients exhibited streptomycin resistance, similar to the streptomycin resistance rate (54%) from a previous study (Casal *et al*, 2005). Streptomycin should not be part of an empirical regimen to treat possible MDR-TB. However, resistance to second-line injectable agents, such as amikacin and kanamycin was found in only 4.5%. Resistance to ethambutol and pyrazinamide in the MDR-TB group was found in 31.9% and 21.7%, respectively, which differs from previous studies. Ethambutol resistance rates vary from 8% (Flament-Saillour *et al*, 1999) to 42% (Casal *et al*, 2005). Pyrazinamide resistance was found in 36% in one study (Casal *et al*, 2005). The WHO recommends ethambutol and pyrazinamide be used in the treatment of MDR-TB (WHO, 2011). However, given that pyrazinamide requires an acidic environment to inhibit mycobacterial growth (Hoffner *et al*, 2013), an incorrectly performed AST may lead to a false-positive diagnosis of resistance. Fewer than 5% of MDR-TB cases in our study were resistant to fluoroquinolones, such as ofloxacin and moxifloxacin. However, MDR-TB resistance to ciprofloxin, another fluoroquinolone, was seen in 12.8%. *In vitro* and *in vivo* studies have found fluoroquinolone activity against *M. tuberculosis* in descending order as follows: moxifloxacin > levofloxacin > ofloxacin (JI *et al*, 1995; Alvirez-Freites *et al*, 2002). Ciprofloxacin has not been found to be effective against pulmonary TB in clinical studies (Mohanty and Dhamgaye, 1993; Kennedy *et al*, 1996). Ciprofloxacin should not be used to treat TB. MDR-TB was found to be resistant to para-aminosalicylic acid in 15.9% of cases and ethionamide in 22.7% of cases in our study. Evaluation of *in vitro* activity by these agents is unreliable due to inherent *in vitro* instability, varying drug potencies, and technical errors during drug susceptibility testing (WHO, 2008).

Poor compliance and previous history of TB were the two most important factors related to an unfavorable outcome in our study. Twenty-seven percent of subjects with MDR-TB and 14.5% with non-MDR-TB did not follow-up at least 80% of the appointments. Non-compliance is associated with unsuccessful treatment

outcomes. Patients who receive directly observed therapy (DOT) for the full duration of their treatment had greater treatment success than partial observation or self-administered therapy (Orenstein *et al*, 2009; Anderson *et al*, 2013). DOT has been suggested by WHO as a key factor for successful treatment of tuberculosis (WHO, 2011). DOT has not been implemented at our hospital; a factor that may potentially explain poor patient compliance. Having a previous history of TB was associated with MDR-TB and unfavorable outcomes in our study. Patients with previous history of TB had a significantly greater percentage of positive AFB smears (56.3%) than those who never had TB before (34.8%). A positive AFB smear was usually associated with a high mycobacterial load, which could cause severe disease and a poorer outcome. A previous study found MDR-TB was associated with treatment failure and a greater mortality rate (Lockman *et al*, 2001). We did not find an association between MDR-TB and treatment outcome because most of our MDR-TB patients received care by specialists. HIV was not associated with a poor outcome in our study, contrary to reports from previous studies (Farley *et al*, 2011; Anderson *et al*, 2013). Improved access to anti-retroviral treatment in our study may have resulted in the better outcomes we observed. Subgroup analysis found no factors significantly associated with an unfavorable outcome in MDR-TB. A factor not evaluated in our study was the MDR-TB genotype. We did not identify or evaluate specific strains of MDR-TB. Marais *et al* (2013) found the Haarlem family of *M. tuberculosis* strains to be significantly associated with treatment outcome.

Our study had some limitations. First, the retrospective design of this study prevented us from assessing social factors, TB contacts, history of TB, compliance, and treatment outcomes. Patient data were mostly obtained from medical charts, making information about these variables often unobtainable. HIV status was checked in only 87% of subjects. As such, HIV seropositivity may have been underestimated, preventing an observable association with MDR-TB. The study population was too small to effectively evaluate some factors associated with unfavorable outcomes in MDR-TB. Patients diagnosed with MDR-TB in December 2012 did not have 18-24 months of follow-up due to the June 2013 study cut-off date. Future long-term prospective cohort studies and epidemiological studies should be conducted to more accurately identify and determine risk factors for and prevalence of MDR-TB.

From our study, factors significantly associated with MDR-TB were age <65 years, previous history of TB, HIV co-infection, and alcohol consumption. These risk factors should alert physicians to the possibility of MDR-TB. Prompt identification of high-risk patients and effective treatment could help reverse the increasing trend in drug-resistant TB in Thailand.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Ms Khemajira Karaketklang for assistance with data analysis and the staff of the Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University for their support and collaboration. Funding for this study was generously provided by the Faculty of Medicine Siriraj Hospital, Mahidol University. The authors declare no personal or professional conflicts of interest regarding any aspect of this study.

REFERENCES

Akksilp S, Wattanaamornkiat W, Kittikraisak W, *et al*. Multi-drug resistant TB and HIV in Thailand: overlapping, but not independently associated risk factors. *Southeast Asian J Trop Med Public Health* 2009; 40: 1264-78.

Alvirez-Freites EJ, Carter JL, Cynamon MH. In vitro and in vivo activities of gatifloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2002; 46: 1022-5.

Anderson LF, Tamne S, Watson JP, *et al*. Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007. *Euro Surveill* 2013; 18:pii=20601.

Boonsarngsuk V, Tansirichaiya K, Kiatboonsri S. Thai drug-resistant tuberculosis predictive scores. *Singapore Med J* 2009; 50: 378-84.

Bojorquez I, Barnes RF, Flood J, *et al*. Multidrug-resistant tuberculosis among patients in Baja California, Mexico, and Hispanic patients in California. *Am J Public Health* 2013; 103: 1301-5.

Casal M, Vaquero M, Rinder H, *et al*. Risk factors for multi-drug resistance tuberculosis in four European countries. *Microbial Drug Resistance* 2005; 11: 62-7e.

Demissie M, Lemma E, Gebeyehu M, Lindtjorn B. Sensitivity to anti-tuberculosis drugs in HIV-positive and -negative patients in Addis Ababa. *Scand J Infect Dis* 2001; 33: 914-9.

Djuretic T, Herbert J, Drobniewski F, *et al*. Antibiotic resistant tuberculosis in the United Kingdom: 1993-1999. *Thorax* 2002; 57: 477-82.

Farley JE, Ram M, Pan W, *et al*. Outcomes of multi-drug resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. *PLoS ONE* 2011; 6: e20436.

Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax* 2006; 61: 158-63.

Flament-Saillour M, Robert J, Jarlier V, Grosset J. Outcome of multi-drug-resistant tuberculosis in France: a nationwide case-control study. *Am J Respir Crit Care Med* 1999; 160: 587-93.

Hoffner S, Angeby K, Sturegård E, *et al*. Proficiency of drug susceptibility testing of *Mycobacterium tuberculosis* against pyrazinamide: the Swedish experience. *Int J Tuberc Lung Dis* 2013; 17: 1486-90.

Irish C, Herbert J, Bennett D, *et al*. Database study of antibiotic resistant tuberculosis in the United Kingdom, 1994-6. *BMJ* 1999; 318: 497-8.

JI B, Lounis N, Truffot-Pernot C, Grosset J. In vitro and in vivo activities of levofloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 1995; 39: 1341-4.

Kennedy N, Berger L, Curram J, *et al*. Randomized controlled trial of a drug regimen that includes ciprofloxacin for the treatment of pulmonary tuberculosis. *Clin Infect Dis* 1996; 22: 827-33.

Liu Q, Zhu L, Shao Y, *et al*. Rates and risk factors for drug resistance tuberculosis in Northeastern China. *BMC Public Health* 2013; 13: 1171.

Lockman S, Kruuner A, Binkin N, *et al*. Clinical outcomes of Estonian patients with primary multidrug-resistant versus drug-susceptible tuberculosis. *Clin Infect Dis* 2001; 32: 373-80.

Luzze H, Johnson DF, Dickman K, *et al*; Tuberculosis Research Unit. Relapse more common than reinfection in recurrent tuberculosis 1-2 years post treatment in urban Uganda. *Int J Tuberc Lung Dis* 2013; 17: 361-7.

Mac-Arthur A, Gloyd S, Perdigão P, Noya A, Sacarlal J, Kreiss J. Characteristics of drug resistance and HIV among tuberculosis patients in Mozambique. *Int J Tuberc Lung Dis* 2001; 5: 894-902.

Marais E, Mlambo CK, Lewis JJ, *et al*. Treatment outcomes of multidrug-resistant tuberculosis patients in Gauteng, South

Africa. *Infection* 2013: doi 10.1007/s15010-013-0572-2.

Mesfin YM, Hailemariam D, Biadglign S, Kibret KT. Association between HIV/AIDS and multi-drug resistance tuberculosis: a systematic review and meta-analysis. *PLoS One* 2014; 9: e82235.

Mohanty KC, Dhamgaye TM. Controlled trial of ciprofloxacin in short-term chemotherapy for pulmonary tuberculosis. *Chest* 1993; 104: 1194-8.

Orenstein EW, Basu S, Shah NS, *et al*. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009; 9: 153-61.

Pleumpanupat W, Jittimanee S, Akarasewi P, *et al*. Resistance to anti-tuberculosis drugs among smear-positive cases in Thai prisons 2 years after the implementation of the DOTS strategy. *Int J Tuberc Lung Dis* 2003; 7: 472-7.

Reechaipichitkul W. Multidrug-resistant tuberculosis at Srinagarind Hospital, Khon Kaen, Thailand. *Southeast Asian J Trop Med Public Health* 2002; 33: 570-4.

Schwoebel V, Decludt B, de Benoist AC, *et al*. Multidrug resistant tuberculosis in France 1992-4: two case-control studies. *BMJ* 1998; 317: 630-1.

Sungkanuparph S, Eampokalap B, Chottanapund S, Thongyen S, Manosuthi W. Impact of drug-resistant tuberculosis on the survival of HIV-infected patients. *Int J Tuberc Lung Dis* 2007; 11: 325-30.

Tansuphasiri U, Pleumpanupat W, Pandii W, Rienthong S. Drug-resistant tuberculosis among prisoners of three prisons in Bangkok and the vicinity. *J Med Assoc Thai* 2003; 86: 953-63.

World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. *WHO/HTM/TB/2008.402*, 2008.

World Health Organization (WHO). Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. *WHO/HTM/TB/2010.3*, 2010.

World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update. *WHO/HTM/TB/2011.6*, 2011.

World Health Organization (WHO). Global tuberculosis control WHO report 2013. *WHO/HTM/TB/ 2013.11*, 2013.