MAJOR ARTICLE

Extensively Drug-Resistant *Mycobacterium tuberculosis* during a Trend of Decreasing Drug Resistance from 2000 through 2006 at a Medical Center in Taiwan

Chih-Cheng Lai,[1] Che-Kim Tan,[4] Yu-Tsung Huang,[2,3] Chien-Hong Chou,[5] Chien-Ching Hung,[2] Pan-Chyr Yang,[2] Kwen-Tay Luh,[2,3] and Po-Ren Hsueh[2,3]

[1]Department of Internal Medicine, Yi-Min Hospital, and Departments of [2]Internal Medicine and [3]Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, [4]Department of Intensive Care Medicine, Chi-Mei Medical Center, Tainan, and [5]Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin, Taiwan

Background. Drug resistance rates are one of the most important aspects in the national tuberculosis (TB) control program, and drug-resistant TB, especially extensively drug-resistant (XDR) TB, is not well understood in Taiwan. The objectives of this study were to investigate the prevalence of drug resistance from 2000 through 2006 and to identify XDR TB isolates to elucidate the clinical characteristics of patients with XDR TB at National Taiwan University Hospital.

Methods. The prevalence of drug resistance among clinical, nonduplicate *Mycobacterium tuberculosis* isolates was analyzed. Testing of susceptibility to antituberculosis agents, including isoniazid, rifampicin, ethambutol, streptomycin, rifabutin, ofloxacin, ethinamide, and para-aminosalicylic acid, was performed using the proportional method. Minimum inhibitory concentrations of amikacin, capreomycin, isepamycin, linezolid, cycloserine, ciprofloxacin, levofloxacin, moxifloxacin, and gemifloxacin were determined for 40 available multidrug-resistant *M. tuberculosis* isolates.

Results. Significant decreasing trends in rates of resistance to isoniazid, ethambutol, and at least 1 of the 3 first-line agents were observed among 2625 *M. tuberculosis* isolates from 2000 through 2006. Among these 2625 isolates, 150 (5.7%) were multidrug resistant, and 10 *M. tuberculosis* isolates (0.4%) fulfilled the definition of XDR *M. tuberculosis*. Nine (90%) of 10 patients with XDR TB had a previous history of TB and received anti-TB treatment before acquisition of XDR TB.

Conclusions. The remaining high prevalence of multidrug-resistant TB and the presence of XDR TB during a trend of decreasing drug resistance are alarming. Continuous surveillance of clinical isolates of *M. tuberculosis* is needed to identify XDR TB, especially in patients who have a history of TB and have received prior anti-TB treatment.

The World Health Organization estimates for 2005 indicated that the Southeast Asian Region had the largest number of new tuberculosis (TB) cases, which accounted for 35% of the global burden of new and relapse cases. There were 1.6 million deaths resulting from TB in 2005 [1]. In 2005, the Center for Disease Control of Taiwan recorded 15,378 newly diagnosed TB cases. A TB incidence of 72.7 cases per 100,000 population and a TB mortality rate of 4.2 deaths per 100,000 population were reported [2]. Despite being one of the oldest known diseases, TB is still a growing problem worldwide. Drug-resistant TB mainly arises from inconsistent or partial treatment because of poor drug compliance, incorrect treatment regimens, or an unreliable drug supply. Isoniazid was introduced for the treatment of TB in 1952. The prevalence of isoniazid resistance ranged from 8.4% of isolates in the early 1960s to 22.6% in the 1970s but decreased to 6.8% in the 1980s [3]. Rifampin-based chemotherapy has been widely used in Taiwan since 1978. Although there was

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Reprints or correspondence: Dr. Po-Ren Hsueh, Depts. of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Rd., Taipei, 100, Taiwan (hsporen@ha.mc.ntu.edu.tw).

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no rifampin resistance in the early 1980s in Taiwan [4], resistance to rifampin gradually increased thereafter. Multidrug-resistant (MDR) TB is defined as TB with resistance to both isoniazid and rifampin, the 2 most effective anti-TB drugs. It is a particularly dangerous form of drug-resistant TB that has resulted from inappropriate treatment in Taiwan and represents a growing threat. Inappropriate treatment for drug-resistant TB not only results in treatment failure but is also responsible for further dissemination of drug-resistant strains, rendering the control of TB a more difficult public health issue. Furthermore, extensively drug-resistant (XDR) TB, defined as TB that is resistant to at least isoniazid and rifampin (MDR-TB), in addition to any fluoroquinolone, and ⩾1 of the 3 injectable drugs (capreomycin, kanamycin, and amikacin), has recently emerged as a global health problem, threatening the success of TB-control programs worldwide [5, 6].

In Taiwan, there are only 8 hospitals and 1 official TB-control institute that have routinely performed antimycobacterial susceptibility testing for clinical isolates obtained from individuals with TB in recent decades. However, the use of different methods for susceptibility testing and different definitions of resistance to isoniazid have contributed to variations in reported resistance rates [7]. Moreover, rates of resistance to second-line agents have rarely been reported in Taiwan. The objective of this study was to investigate the prevalence of drug resistance in clinical and nonduplicate isolates of *M. tuberculosis* from 2000 through 2006 at National Taiwan University Hospital (NTUH; Taipei, Taiwan). We also try to identify XDR *M. tuberculosis* isolates to elucidate the clinical characteristics of patients with XDR TB.

PATIENTS AND METHODS

Setting and bacterial isolates. This study was conducted at NTUH, a 2000-bed tertiary care center in northern Taiwan. Isolates obtained from patients who had a culture positive for *M. tuberculosis* at NTUH from January 2000 through December 2006 were included in this retrospective analysis. A total of 2625 nonduplicate isolates from 2625 patients were collected during the 7-year period. These isolates were recovered from various clinical specimens, including 2253 (85.8%) from respiratory secretions (sputum and bronchial washing), 190 (7.2%) from pleural effusion specimens, 73 (2.8%) from surgical wounds samples, 31 (1.2%) from lymph node specimens, 10 (0.4%) from pericardial effusion specimens, and the rest from other specimens. Nonduplicate isolates were defined as a single isolate collected for evaluation from a single patient who visited the hospital. If a patient had multiple isolates, only the first isolate was analyzed. All specimens were processed and pretreated as described elsewhere [8, 9]. A fluorometric BACTEC technique (BACTEC MGIT 960 system; Becton-Dickinson Diagnostic Instrument Systems) was used for routine culture.

Drug susceptibility testing. Testing of susceptibility to first-line anti-TB drugs, including isoniazid (0.2 μg/mL and 1.0 μg/mL), rifampin (1 μg/mL), and ethambutol (5 μg/mL), was performed in the mycobacteriology laboratory of NTUH. Since 1 January 2005, testing of susceptibility to second-line anti-TB drugs, including streptomycin (2 μg/mL and 10 μg/mL), rifabutin (0.5 μg/mL), ofloxacin (1 μg/mL), ethionamide (5 μg/mL), and para-aminosalicyclic acid (2 μg/mL), was also performed. Drug susceptibility testing for these anti-TB drugs was performed in the mycobacteriology laboratory of NTUH using the agar proportion method [10]. *M. tuberculosis* suspension was inoculated onto Middlebrook 7H10 agar (BBL Microbiology Systems) that contained anti-TB drugs at respective concentrations. The number of colony-forming units growing on the drug-containing medium was compared with the number of colony-forming units growing on a drug-free medium. Isolates for which growth on the drug-containing media presented <1% of the number of colonies that developed on the drug-free media were considered to be resistant to that agent. For quality control, the standard sensitive strain, H37Rv, and the resistant strain, Vertulo, were also tested for drug susceptibility with the same procedures.

Drug resistance was defined as resistance to isoniazid (0.2 μg/mL), rifampin (1 μg/mL), ethambutol (5 μg/mL), or streptomycin (2 μg/mL). An MDR isolate was defined as being resistant to at least isoniazid (0.2 μg/mL) and rifampin (1 μg/mL). XDR *M. tuberculosis* was defined as resistant to at least isoniazid and rifampin, as well as resistant to any fluoroquinolone and ⩾1 of the 3 injectable drugs (capreomycin, kanamycin, and amikacin) [5].

HIV-infection status and drug resistance. Among the 2625 patients, 504 patients had received antibody screening and/or Western blot confirmation tests for HIV. For detecting HIV-1 and/or HIV-2 antibody, a passive particle agglutination method (Bio-Rad) was used through 2006 and an ELISA method (Axsym; Abbott) was used in 2007 and after. For confirmation testing, an immunoblotting method (Bio-Rad) was used during the study period. Patients who had both positive antibody screening results and immunoblotting test results positive for HIV were considered to be HIV infected. Patients with results negative for HIV antibody were not considered to be infected with HIV. Resistance profiles of isolates collected from these patients were analyzed on the basis of HIV status of the patient.

Determination of MICs. MICs of 9 second-line anti-TB agents for 40 preserved MDR *M. tuberculosis* isolates recovered during the period 2000–2006 were determined using the agar dilution method. Concentrations of 0.03–32 μg/mL were tested for amikacin, capreomycin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, linezolid, cycloserine, and isepamicin. The MICs were determined by serial dilution on agar plates as described elsewhere [10]. The MIC for each isolate-drug pair

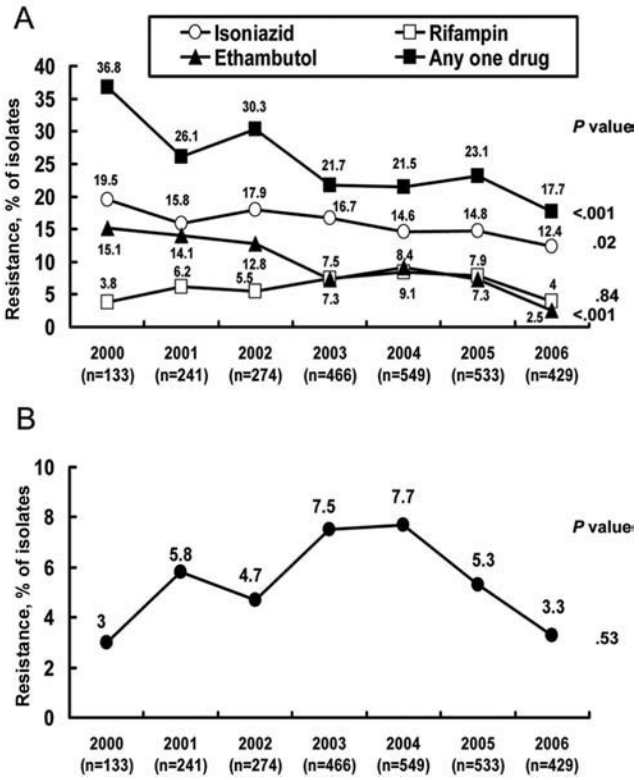

Figure 1. Trends of rates of resistance to isoniazid, ethambutol, rifampin, and any 1 of these 3 drugs *(A)* and multidrug resistance *(B)* among *Mycobacterium tuberculosis* isolates recovered from patients treated at the National Taiwan University Hospital (Taipei, Taiwan) from 2000 through 2006, determined using the modified proportional method. *P* values <.05 were considered to be statistically significant.

was defined as the lowest concentration of the agent that inhibited >99% of the growth of colonies on the drug-free control culture. Resistance was presumptively defined as follows: MICs of >2.5 μg/mL for capreomycin; >2 μg/mL for ciprofloxacin; >1 μg/mL for levofloxacin, linezolid, amikacin, and isepamicin; and >0.5 μg/mL for moxifloxacin [11–14].

Statistical analysis. Differences in drug susceptibility between MDR *M. tuberculosis* and non-MDR *M. tuberculosis* isolates and between isolates obtained from HIV-infected and from non–HIV-infected patients were analyzed using the χ^2 test. Drug resistance trends over time were evaluated by Cochran-Armitage trend test. A *P* value of <.05 was considered to be statistically significant.

RESULTS

A total of 2625 nonduplicate *M. tuberculosis* isolates were collected during the study period. Of these isolates, 403 (15.4%) were resistant to isoniazid, 175 (6.7%) were resistant to rifampin, 224 (8.5%) were resistant to ethambutol, and 613 (23.4%) were resistant to any 1 of these 3 drugs. A total of 150 isolates (5.7%) met the criteria for classification as MDR *M. tuberculosis*. Trend analysis showed that the resistance rate to isoniazid, to ethambutol, and to any 1 of isoniazid, ethambutol, and rifampin increased significantly during the 7-year study period (figure 1).

Additional tests for susceptibility to 5 second-line anti-TB agents, including streptomycin, rifabutin, ofloxacin, ethionamide, and para-aminosalicyclic acid, were performed for 962 isolates in 2005 and 2006. Of these isolates, 42 were MDR *M. tuberculosis*. The rate of resistance to each of the 5 agents was significantly higher for MDR isolates than it was for non-MDR isolates (table 1).

The MICs at which 50% of the isolates were inhibited (MIC_{50}) and at which 90% of the isolates were inhibited (MIC_{90}) and the MIC ranges for the 40 MDR *M. tuberculosis* isolates are shown in table 2. Among the 4 fluoroquinolones tested, moxifloxacin showed the greatest activity against the MDR *M. tuberculosis* isolates, followed by levofloxacin, and ciprofloxacin. Gemifloxacin was the most inactive fluoroquinolone against the isolates tested. Of the other 5 agents, linezolid and isepamicin were most active against MDR *M. tuberculosis* isolates, followed by cycloserine, capreomycin, and amikacin.

Demographic characteristics and clinical manifestations of the 10 patients with XDR TB are shown in table 3. Of the 10 XDR *M. tuberculosis* isolates, all were resistant to ofloxacin and levofloxacin, 1 (10%) was susceptible to ciprofloxacin, and 1 (10%) was susceptible to moxifloxain. Most of the patients were male, and the mean age (±SD) of the patients infected with XDR *M. tuberculosis* was 56.8 ± 16.6 years. Diabetes mellitus was the most frequent underlying disease (found in 60% of patients), followed by chronic pulmonary disease (20%), lung cancer (10%), and end-stage renal disease (10%). A total of 90% of patients had a history of TB, and 50% of patients had received fluoroquinolones >1 month before acquisition of XDR

Table 1. Drug resistance patterns of second-line agents for multidrug-resistant (MDR) and non-MDR *Mycobacterium tuberculosis* isolates obtained from 2005 through 2006, determined using the modified proportional method.

Agent, concentration	No. (%) of resistant isolates: Non-MDR isolates (*n* = 920)	MDR isolates (*n* = 42)	*P*
Streptomycin			
2 μg/mL	61 (6.6)	22 (52.4)	<.001
10 μg/mL	24 (2.6)	27 (64.3)	<.001
Rifabutin, 0.5 μg/mL	2 (0.2)	20 (47.6)	<.001
Ofloxacin, 2 μg/mL	1 (0.1)	7 (16.7)	<.001
Ethionamide, 5 μg/mL	4 (0.4)	10 (23.8)	<.001
Para-aminosalicylic acid, 2 μg/mL	10 (1.1)	7 (16.7)	<.001

Table 2. In vitro activity of 8 agents against 40 multidrug-resistant *Mycobacterium tuberculosis* isolates.

Agent	MIC, μg/mL		
	Range	MIC_{50}	MIC_{90}
Amikacin	0.25 to >32	1	>32
Isepamicin	<0.03 to 1	0.5	1
Capreomycin	2 to >32	4	32
Gemifloxacin	0.5 to >32	16	>32
Ciprofloxacin	0.25 to >32	1	16
Levofloxacin	0.25 to 16	0.5	8
Moxifloxacin	0.25 to 8	0.25	8
Linezolid	<0.03 to 4	0.5	0.5
Cycloserine	<0.03 to 32	1	16

TB. In 7 patients, radiological findings showed cavitary lesions, but only 1 patient had pleural effusion.

Of the 504 patients with TB for whom data regarding HIV infection status were available, 75 were HIV infected, and 429 were not HIV infected. There were no significant differences between the 2 groups with respect to most of the drug resistance patterns, except for a significantly higher prevalence of high-level isoniazid resistance ($P = .03$) among the HIV-infected patients (table 4).

DISCUSSION

In 2005, there were an estimated 8.8 million new cases of TB and 1.6 million TB-related deaths worldwide [1]. Control of TB remains one of the most challenging issues in global health [1]. A new and potentially devastating threat to TB control is the emergence of strains that cannot be cured by standard anti-TB drug regimens. Drug resistance rates are regarded as one of the most important aspects of surveillance in the national TB control program in Taiwan.

In this study, the overall rate of resistance to any 1 of the 3 drugs isoniazid, rifampin, or ethambutol was 23.4%. These rates are lower than those from other regions, including southern Taiwan (29%) [15], Guatemala (30%) [16], and New York (31%) [17]. Liaw et al. [18] reported that, during the period 1998–2002, 19.0% of TB isolates analyzed at NTUH were resistant to isoniazid, 6.1% were resistant to rifampin, and 15.7% were resistant to ethambutol. Our study revealed a decrease in the rates of resistance to isoniazid (from 16.7% to 12.4%) and ethambutol (from 9.1% to 2.5%) in the 2003–2006 period. In fact, this study found decreasing rates of resistance to isoniazid, ethambutol, and any 1 of the 3 drugs isoniazid, rifampin, and ethambutol during the 2000–2006 period. Similar decreasing rates of resistance have been reported by recent studies from Taiwan [19, 20], Hong Kong [21], and Saudi Arabia [22].

In Taiwan, the implementation of 2 effective interventions might explain the decreasing rates of resistance to anti-TB drugs. In 1997, stricter regulation mandated that each treated TB case be reported to the Center for Disease Control of Taiwan. Since then, the percentage of patients with TB who receive a complete course of treatment has increased, and the percentage of those lost to follow-up has decreased. Second, directly observed short-course therapy, which is a proven and effective measure, was also started in Taiwan during this period. Our findings suggest that these measures have increased the rate of treatment completion and might have played a role in decreasing the emergence and spread of drug-resistant TB.

In spite of the encouraging findings of decreasing rates of resistance to anti-TB agents, MDR TB still poses a challenge to TB control. In this study, 3.0%–7.7% of the isolates were MDR *M. tuberculosis,* and this percentage remained fairly stable during the study period. This prevalence is considerably higher than the median rate of MDR *M. tuberculosis* (1.0%; range,

Table 3. Demographic and clinical features of 10 patients with extensively drug-resistant (XDR) tuberculosis (TB) infection.

Patient	Year	Age, years	Sex	Underlying disease	Acid-fast stain result	Previous history of TB	Radiographic findings of cavitary lesions	Treatment with anti-TB drugs ⩾1 month before acquisition of XDR TB
1	2000	25	F	…	Negative	Yes	Yes	H, E, R, Z, levofloxacin, streptomycin
2	2004	73	M	DM	Negative	Yes	Yes	H, E, R, Z, levofloxacin
3	2004	82	M	COPD	Negative	Yes	No	NA
4	2004	53	M	DM	Positive	No	Yes	H, E, R, Z
5	2005	59	M	DM	Positive	Yes	No	H, E, R, Z, streptomycin
6	2005	49	M	DM, ESRD, HCC s/p transplant	Negative	Yes	Yes	No
7	2005	59	F	DM	Positive	Yes	Yes	H, E, R, Z, moxifloxacin
8	2006	65	F	Lung cancer	Negative	Yes	No	H, E, R, Z
9	2006	65	M	DM, pneumoconiosis	Positive	Yes	Yes	H, E, R, Z, moxifloxacin, streptomycin, levofloxacin, PAS, ethionamide
10	2007	38	M	No	Positive	Yes	Yes	H, E, R, Z, streptomycin, levofloxacin, amikacin, PAS

NOTE. COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; E, ethambutol; ESRD, end stage renal disease; H, isoniazid; HCC, hepatocellular carcinoma; NA, not applicable; PAS, para-aminosalycilic acid; R. rifampin; s/p, status post; Z, pyrazinamide.

Table 4. Comparison of drug resistance for *Mycobacterium tuberculosis* isolates recovered from 504 patients for whom HIV infection status data were available from 2000 through 2006, determined using the modified proportional method.

Agent, concentration	No. (%) of isolates		
	From HIV-infected patients (n = 75)	From non–HIV-infected patients (n = 429)	P
Isoniazid			
0.2 μg/mL	13 (17.3)	53 (12.4)	.24
1.0 μg/mL	9 (12)	23 (5.4)	.03[a]
Rifampin, 1 μg/mL	5 (6.7)	17 (4.0)	.29
Ethambutol, 5 μg/mL	3 (4.0)	11 (2.6)	.49
Streptomycin			
2 μg/mL	5 (6.7)	39 (9.1)	.49
10 μg/mL	2 (2.7)	24 (5.6)	.29
Resistant to any drug	19 (25.3)	76 (17.7)	.12
Multidrug resistant	2 (2.7)	14 (3.3)	.79

[a] Statistically significant.

0.0%– 14.2%) in the 76 countries or geographical settings included in the World Health Organization/International Union Against Tuberculosis and Lung Disease surveillance report for 1999–2002 [23]. However, comparison of MDR TB prevalence in an individual country with prevalence in a referral hospital is inappropriate, because the referral hospital receives the most complicated cases.

Previous studies from Taiwan have reported a prevalence of MDR TB of 5.1%–17.3% [15, 18, 19, 24, 25]. Moreover, a high percentage of resistance to the second-line anti-TB agents usually used to treat MDR TB was also noted [15, 18, 19, 24, 25]. The present study clearly demonstrated that there is higher rate of resistance to streptomycin, rifabutin, ofloxacin, ethionamide, and para-aminosalicyclic acid among MDR isolates than among non-MDR isolates, with overall rates of resistance to these 5 agents ranging from 16.7% to 52.4%. The high prevalence of MDR TB and the high rate of resistance to both first-line and second-line agents is still a growing threat in Taiwan, and more-effective TB-control interventions and more-potent anti-TB agents are urgently needed.

The recent emergence of XDR TB has become another global health problem that constitutes a deadly threat to patients and hampers TB-control programs [6]. In Taiwan, XDR TB has rarely been reported, and only 22 (10.2%) of 215 MDR isolates have fulfilled the criteria for XDR TB [26]. Although only 10 isolates of XDR TB were identified in our study, this low number was attributed to a failure to perform drug susceptibility testing for injectable drugs and fluoroquinolone for all MDR *M. tuberculosis* isolates. Our study revealed that patients with XDR TB had a high prevalence of previous TB and that many had received prior anti-TB treatment.

These findings are consistent with those of a previous study from Korea [27]. Fluoroquinolones and aminoglycosides were prescribed to 5 and 4 patients, respectively. The rate of treatment with second-line anti-TB drugs, such as fluoroquinolones and aminoglycosides, was lower in our study than in the study by Kim et al. [27], who reported that 35 (81.4%) of 43 and 38 (88.4%) of 43 patients with XDR TB had received fluoroquinolones and aminoglycosides, respectively. Although the number of cases in our study is limited, our findings suggest the need for continuous surveillance of clinical isolates of *M. tuberculosis* to identify cases of XDR TB, especially among patients with a previous history of TB and those who have received prior anti-TB treatment, including fluoroquinolones and aminoglycosides.

Kim et al. [28] reported that 37 (86%) of 43 patients with XDR TB had chest radiograph findings showing a cavitary lesion, but only 2 (4.7%) had diabetes mellitus. Our study revealed that patients with XDR TB had a high prevalence of diabetes mellitus and cavitary lesions in the lungs; in addition, men were more likely than women to have XDR TB. These findings may imply that individuals with XDR TB were more likely than others to have pulmonary cavities, but more epidemiological data is required to clarify the relationship between diabetes mellitus, sex, and XDR TB.

Fluoroquinolones have broad-spectrum antimicrobial activity and may play useful roles in prophylactic treatment for patients exposed to MDR TB, treatment of proven MDR TB, and empirical treatment of TB disease in settings with high rates of MDR TB [29–31]. In this study, we compared the activity of the different fluoroquinolones against 40 clinical isolates of MDR *M. tuberculosis*. Levofloxacin and moxifloxacin showed better in vitro activity against MDR *M. tuberculosis* than did other drugs, suggesting their increasingly important role in the treatment of MDR TB. Gemifloxacin had the poorest in vitro activity, not only against MDR *M. tuberculosis* isolates, but also against non-MDR *M. tuberculosis* isolates (data not shown). The naphthyridone structure of gemifloxacin was identified as a negative factor in a quantitative structure-activity relationship study of antimycobacterial activity [31], which might explain its poor anti-TB activity.

The activities of other classes of antimicrobials in addition to fluoroquinolones, such as aminoglycosides and oxazolidinonoes, were also tested against MDR *M. tuberculosis* in this study. Our results showed that linezolid displayed potent activity against MDR TB. These results are consistent with the findings of Tato et al. [32]. Because clinical experience with and in vitro study of linezolid has been limited, its potential role as a treatment for MDR TB deserves additionalevaluation.

Our results showed that, among the aminoglycosides tested, isepamicin was the most active antimycobacterial agent against MDR *M. tuberculosis*. However, an in vivo study in mice found that amikacin was more active than isepamicin against TB [11].

The reason for these different results remains to be determined, but this difference could be attributable to differences in study design, including the use of an in vitro versus an animal model and the use of different strains of *M. tuberculosis* versus MDR *M. tuberculosis.* Considerable additional study is needed to evaluate the potential role of aminoglycosides in the treatment of TB.

Infection with HIV is an important risk factor for the development of TB. Taiwan has a low prevalence of HIV infection. HIV-positive patients with TB comprise only a small portion of all TB patients in Taiwan. In this study, the rates of drug resistance among isolates from HIV-infected patients were not significantly different from those among isolates from HIV-negative patients. These findings are consistent with a previous study from this institution [14] and the study of Espinal et al. [33], which supported a lack of association between HIV infection and the development of MDR TB, per se.

This retrospective and laboratory-based surveillance study had 2 noteworthy limitations. First, we were unable to precisely distinguish between newly diagnosed and previously treated cases and, therefore, were only able to report the combined resistance rate. Second, this study was conducted in a tertiary care center and, as such, its findings might not reflect the overall situation in Taiwan.

In conclusion, although there was a decreasing overall trend of anti-TB drug resistance in recent years, the prevalence of MDR TB remains high, and the presence of XDR TB will impose a new challenge in the control of TB. Continuous surveillance of clinical isolates of *M. tuberculosis* is needed to identify MDR TB or XDR TB, especially in patients with a history of TB and those who have received prior anti-TB treatment.

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