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An integrated MDR-TB management programme results in favourable outcomes in northern Taiwan

To the Editor:

Multidrug-resistant tuberculosis (MDR-TB) is caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin (RIF). MDR-TB is difficult to treat and has become an obstacle to tuberculosis control programmes worldwide [1]. The global burden of MDR-TB has been increasing and the World Health Organization (WHO) estimated there were 450 000 incident MDR-TB cases in 2012 [2]. Based on drug-resistance surveys, 3.6% of patients newly diagnosed and 20.2% of patients previously treated for tuberculosis had MDR-TB [2]. MDR-TB demands treatment with second-line drugs that have a limited sterilising capacity, and are less effective and more toxic than first-line drugs. Among the estimated 20% of the worldwide MDR-TB cases that were enrolled in treatment in 2010, only 48% were successfully treated [2]. High mortality rates and loss to follow-up are threatening to destabilise global tuberculosis control.

In Taiwan, MDR-TB occurred in 1% of new tuberculosis cases and in 6% of re-treated tuberculosis cases [3]. In addition, laboratory-based analyses revealed that 10% of MDR-TB cases in Taiwan were extensively drug-resistant (XDR-TB) [4]. Faced with the challenge of the low treatment success rate of MDR-TB, a designated, government-organised and hospital-initiated programme led by experienced pulmonary specialists with diligent case managers, and cooperative and integrated medical groups, providing comprehensive and high-quality medical care for MDR-TB cases, was implemented by the Centers for

Disease Control, Taipei, Taiwan, in May 2007. The consortium provides patient-centred care including consultation, financial support and hospital-initiated directly observed therapy (DOT), surgical intervention, and strengthened side-effect and comorbidity management for MDR-TB patients. Patients enrolled in the consortium were under periodic evaluation and review by a designated expert committee. In the conventional MDR-TB programme for non-enrolled patients, treatment and DOT are carried out by hospitals and public health settings, respectively. To evaluate our MDR-TB management programme, we conducted the first retrospective study on outcomes of 151 bacteriologically confirmed MDR-TB cases in northern Taiwan from 2007 to 2009 at 30 months after their commencement of treatment.

Drug susceptibility testing (DST) for INH, RIF, ethambutol (EMB), streptomycin, pyrazinamide (PZA), ofloxacin (OFX), amikacin, kanamycin (KM) and capreomycin, *p*-aminosalicylic acid, ethionamide, and rifabutin was performed by a national reference mycobacteriology laboratory using standardised methods [5]. The treatment regimens were prescribed according to the WHO-recommended guidelines [6]. Individualised regimens consisting of a combination of EMB and PZA, a fluoroquinolone, an injectable drug, and other oral second-line bacteriostatic drugs, resulting in a total of at least four drugs to which resistance has not been demonstrated by DST, were used for treatment in the consortium in northern Taiwan. These MDR-TB patients initially received in-patient treatment that was followed by outpatient DOT in the community. Favourable outcomes were cure or treatment completion. Unfavourable outcomes were defined as death during treatment, failure or default.

Of 151 confirmed MDR-TB patients, the male/female ratio was 2.4. The median age was 49 years, ranging from 15 to 93 years. The most prevalent age group was 45–64 years (39.1%) followed by 25–44 years (28.5%). Based on treatment history, 45.7% (69 out of 151 patients) were re-treated tuberculosis cases and

TABLE 1 Correlation of the characteristics and treatment outcomes of multidrug-resistant tuberculosis (MDR-TB) cases enrolled in the treatment consortium in northern Taiwan: univariate analysis, 2007–2009

Characteristic	Subjects[#] n	Treatment outcome n (%)		p-value
		Favourable[¶]	Unfavourable[+]	
Sex				
Males	89	75 (84.3)	14 (15.7)	0.54
Females	35	31 (88.6)	4 (11.4)	
Age years				
<65	96	93 (96.9)	3 (3.1)	<0.01
⩾65	28	13 (46.4)	15 (53.6)	
BMI[§] kg·m^{-2}				
<18.5	29	22 (75.9)	7 (24.1)	0.01
⩾18.5	86	80 (93.0)	6 (7.0)	
Ethnicity				
Aboriginal	5	5 (100)	0 (0)	1.00
Nonaboriginal	119	101 (84.9)	18 (15.1)	
Category of case				
New	64	56 (87.5)	8 (12.5)	0.51
Re-treated	60	50 (83.3)	10 (16.7)	
Diabetes mellitus				
Yes	37	31 (83.8)	6 (16.2)	0.72
No	87	75 (86.2)	12 (13.8)	
Sputum smear				
Positive	70	59 (84.3)	11 (15.7)	0.66
Negative	54	47 (87.0)	7 (13.0)	
Cavitary lesion on CXR				
Yes	49	46 (93.9)	3 (6.1)	0.03
No	75	60 (80.0)	15 (20)	
Drug resistance				
MDR-TB[f]	101	85 (84.2)	16 (15.8)	0.38
Pre-XDR[##] and XDR[¶¶]	23	21 (91.3)	2 (8.7)	0.76

BMI: body mass index; CXR: chest radiography; XDR-TB: extensively drug-resistant tuberculosis. [#]: n = 124; two MDR-TB cases were transferred out. [¶]: cured or completion (n = 106, 85.5%). [+]: death during treatment, failure or default (n = 18, 14.5%). [§]: BMI of nine cases was unknown. [f]: *Mycobacterium tuberculosis* that is resistant to at least isonazid and rifampicin, and excluding pre-XDR-TB and XDR-TB. [##]: MDR-TB *M. tuberculosis* isolates resistant to either ofloxacin or at least one of three injectable drugs. [¶¶]: MDR-TB *M. tuberculosis* isolates with additional resistance to at least one fluoroquinolone and any one of three injectable drugs.

had previously received at least 1 month of treatment at the time of diagnosis as a MDR-TB case, and 16.6% (25 out of 151) had been treated with any second-line drug. According to the clinical characteristics, 54.3% (82 out of 151) were acid-fast bacillus (AFB) smear-positive, and 33.3% (50 out of 150) had a cavitary disease, which was radiographically confirmed. Additionally, 25.8% (39 out of 151) of the MDR-TB cases had diabetes mellitus. Excluding one multidrug-resistant *M. tuberculosis* isolate lacking a DST result for KM, the baseline DST results showed that 22.0% (33 out of 150) were pre-XDR-TB (multidrug-resistant *M. tuberculosis* isolates resistant to either OFX or at least one of three injectable drugs), and 1.3% (two out of 150) were XDR-TB (MDR *M. tuberculosis* isolates with additional resistance to OFX and at least one of three injectable drugs) and 76.7% (115 out of 150) of the studied cases were MDR-TB excluding pre-XDR and XDR-TB.

Enrolment of MDR-TB cases in a designated MDR-TB treatment consortium is highly recommended but not compulsory. In this study, 126 (83.4%) out of 151 MDR-TB patients were enrolled in a treatment consortium in northern Taiwan (table 1). In the univariate analysis, excluding two transferred out cases, 14.5% (18 out of 124) experienced unfavourable outcomes (16 deaths and two treatment failures). Factors such as sex, ethnicity, case category, comorbidity (mainly diabetes mellitus) and AFB smear were not associated with unfavourable outcomes. However, 15 (83.3%) of the patients who experienced unfavourable treatment outcomes were older than 65 years ($p<0.01$). Seven (24.1%) of the patients with unfavourable treatment outcomes had a body mass index <18.5 $kg \cdot m^{-2}$ ($p=0.01$). Even though in the univariate analysis, the patients without cavitary lesions on chest radiography had a higher proportion of unfavourable outcomes ($p=0.03$), in the multivariate analyses, age ⩾65 years (adjusted OR 27.6, 95% CI 4.8–158.3; $p<0.001$) was the only risk factors associated with unfavourable treatment outcomes. Nevertheless, of the 25 (16.6%) cases treated outside the consortium, excluding one that was transferred out, 10 (40.0%) experienced favourable outcomes (crude OR 8.83, 95% CI 3.44–22.69; $p<0.001$).

In this study, 85.5% of MDR-TB patients experienced favourable treatment outcomes. This rate was significantly higher than the treatment outcomes reported in the 1990s, when the cure rate was only 51.2% and the default rate was 29.1% [7]. Despite patient categories and bacteriological characteristics, our results revealed the effectiveness of adopting the WHO treatment guidelines using individual regimens [6] and a public–private mix strategy of a patient-centred DOT programme.

Nevertheless, 16 deaths were observed. However, only two patient deaths were due to direct causes of tuberculosis; the remaining 14 deaths were due to unrelated causes, including septic shock, pneumonia, cancer and heart failure. Although our team provided comprehensive and delicate patient-centred treatment, the mortality rate was 12.9%. In our study, death was associated with advanced age, while other studies revealed that death was significantly associated with HIV infection [8], diabetes [9] and chronic renal disease [9]. Although diabetes mellitus was the most common comorbidity among our MDR-TB patients, diabetes was not a poor prognostic factor because we included a diabetes mellitus control strategy in our programme.

Two treatment failure cases with severe side-effects were noted in our study. Two potent new drugs, delamanid and bedaquiline, may potentially improve treatment outcomes and reduce mortality in MDR-TB [10, 11]; the European Medicines Agency has recommended a conditional approval for delamanid for the treatment of MDR-TB (November 2013) and WHO also published an interim guidance for the use of bedaquiline for MDR-TB treatment [12]. To further increase the cure rate and shorten the treatment duration, a policy on rapid uptake of new or repurposed drugs requires advocacy for the MDR-TB programme.

In conclusion, we demonstrated the government-organised and hospital-initiated treatment consortium adopting individualised regimens with a patient-centred management programme can result in 85.5% favourable outcomes when facing the challenge of MDR-TB in an ageing population with a high proportion of comorbidities. Nevertheless, the age group older than 65 years was associated with unfavourable treatment outcomes and was an obstacle to MDR-TB control in Taiwan. Furthermore, 54.3% of the cases were new MDR-TB cases, suggesting the need for stringent tuberculosis control measures in general to prevent MDR-TB transmission.

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Ming-Chih Yu[1,2], Huang-Yao Chen[1], Shen-Hsuan Chien[1] and Ruwen Jou[3,4]
[1]Division of Pulmonary Medicine, Dept of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. [2]School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan. [3]Reference Laboratory of Mycobacteriology, Center for Research, Diagnostics and Vaccine Development, Centers for Disease Control, Taipei, Taiwan. [4]Institute of Microbiology and Immunology, National Yang-Ming University, Taipei, Taiwan.

Correspondence: Ruwen Jou, Reference Laboratory of Mycobacteriology, Research and Diagnostic Center, Centers for Disease Control, Ministry of Health and Welfare, 161 Kun-Yang Street, Nan-Kang, Taipei, 115, Taiwan. E-mail: rwj@cdc.gov.tw

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