

Treatment interruption and directly observed treatment of multidrug-resistant tuberculosis patients in China

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SUMMARY

BACKGROUND: China has nearly one fifth of global multidrug-resistant tuberculosis (MDR-TB) cases, and follows the 24-month World Health Organization (WHO) standardised regimens.

OBJECTIVE: To assess treatment interruption among MDR-TB patients and its association with the provision of directly observed treatment (DOT).

METHODS: We reviewed clinical charts and conducted a questionnaire survey among all confirmed MDR-TB patients who had been treated for at least 6 months from 1 January 2009 to 30 April 2012 in Shandong Province. Treatment interruption was defined as missing a dose for at least 1 day but for <8 consecutive weeks; the subset 'severe interruption' was defined as missing doses for 2–8 consecutive weeks.

RESULTS: Of 110 patients, 75 (68%) interrupted treatment; 19 (17%) reported severe interruption, with a median duration of 30 days. Of the 110 patients, 26 (24%) received injections from family members and 55 (50%) received DOT, 7 (13%) from village doctors and 48 (87%) from family members. Patients who underwent DOT with a family member had less severe interruptions (OR 0.25, 95%CI 0.05–0.98) than those who were given DOT by a village doctor or who did not undergo DOT.

CONCLUSIONS: Family members may act as treatment supporters for MDR-TB patients to reduce treatment interruptions, but require orientation on their role.

KEY WORDS: MDR-TB; treatment interruption; DOT; community management; family members

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) has become a significant public health threat worldwide. The World Health Organization (WHO) estimated that 3.6% of new cases are MDR-TB, and there were 450 000 new MDR-TB cases in 2012.¹ Although the proportions of MDR-TB among all TB cases are highest in the former Soviet countries, the largest burden of cases is to be found in China and India. China has nearly one fifth of all MDR-TB cases, with a higher proportion (8.3%) of MDR-TB cases than the world average.²

The Chinese government started the programmatic management of MDR-TB in 2008, supported by the Global Fund to Fight AIDS, TB and Malaria (The Global Fund, Geneva, Switzerland). Laboratory and clinical capacity was strengthened in designated TB hospitals at the prefectural level to turn them into MDR-TB diagnosis and treatment centres. By the end of June 2010, a total of 13 281 MDR-TB suspects had been screened, 1756 MDR-TB patients had been

confirmed and 994 cases had been recruited for treatment in China.³

MDR-TB treatment is lengthy, and involves less potent, more toxic drugs. Overall, 48% of patients in 2012 completed treatment, while 28% defaulted.¹ Many studies have reported high default rates among MDR-TB cases, ranging from 13% to 29%.^{4–6} Treatment interruption is more relevant in measuring directly observed treatment (DOT) outcomes, as interruption is more common than default. However, in the only study that has reported treatment interruption rates, conducted in the Philippines, 93% of MDR-TB patients interrupted treatment.⁷ To reduce drug resistance among drug-susceptible cases, the WHO DOTS strategy requires that a health worker or volunteer monitor each dose being taken.⁸ DOT, especially health staff-provided DOT, is recommended by the WHO for drug-resistant TB. However, 11 related trials failed to show evidence of the effectiveness of DOT or the superiority of health staff-provided DOT compared with commu-

nity health worker-provided DOT.⁹ There has thus been much debate on DOT and on the best DOT providers for MDR-TB patients, particularly due to the prolonged treatment period, with higher concerns about infection control and occupational health risks. However, apart from two case studies in Peru and South Africa,^{10,11} few studies have reported treatment outcomes among MDR-TB patients according to type of DOT provider.¹²

Given this research gap on DOT among MDR-TB patients, we conducted the present study to assess treatment interruptions among a cohort of MDR-TB patients in China with the aim of determining the associations between treatment interruption and DOT delivery method.

METHODS

Study setting

The present study was conducted in Shandong Province (population 94 million in 2010). Compared with the national average, the province has a relatively low prevalence rate of culture-positive TB cases (34 vs. 119 per 100 000 population).¹³ The proportion of MDR-TB cases among new and previously treated TB cases in the province was respectively 2.9% and 20% in 2008, also lower than the national average.^{2,14} Shandong province launched a treatment programme for MDR-TB cases under the Global Fund Project in January 2009. All recruited patients were treated in designated prefectural hospitals, where the average staff to MDR-TB patient ratio was 1:25. MDR-TB patients normally came by appointment and waited <5 min before an out-patient consultation. Regular measures were taken under the Global Fund Project to improve patient retention, such as pre-treatment education and tracing of defaulting patients.

Participants

We included all MDR-TB patients who were laboratory-confirmed using solid culture based on Löwenstein-Jensen medium and standard drug susceptibility testing (DST) performed in the provincial reference laboratory between 1 January 2009 and 31 October 2011. Of these, we included those who had been treated for at least 6 months by 30 April 2012. All patients received the WHO-standardised MDR-TB regimens, consisting of a 6-month intensive phase of one injectable drug (kanamycin [KM]) and four oral drugs (pyrazinamide [PZA]), levofloxacin [LFX]/ofloxacin [OFX], para-aminosalicylic acid [PAS] and prothionamide [PTH]), followed by an 18-month continuation phase with four oral drugs (PZA, LFX/OFX, PAS, PTH). Capreomycin (CPM) was used to replace KM if KM had been used previously. In the case of intolerable side effects or drug unavailability, ethambutol (EMB) was used to replace PAS. All anti-

tuberculosis drugs were provided by the Global Fund Project and made free to patients. Patients needed to visit the designated hospital once a month to receive their drugs.

Data collection

Staff from the county TB dispensaries contacted eligible MDR-TB patients to explain the purpose of the study and obtain written informed consent. Trained postgraduate students from Shandong University conducted the structured questionnaire survey in May 2012 to collect patient demographic, socio-economic and clinical information. Clinicians from the provincial reference laboratory reviewed patient charts in August 2012 to ensure that culture results were complete. Information on the length of time any injectable or oral drug administration was missing was recorded in the patient charts as part of national standard MDR-TB care. We also collected information on interruptions in the survey. According to national policy, a designated DOT venue, often the village clinic close to the patient's home, was allocated to each MDR-TB patient. We asked patients the location of the DOT venue, the place where their drugs were stored, who gave them injections, who observed their treatment and who visited them at home. We collected information on medical costs based on patient charts, and other costing information such as food and accommodation in the survey.

Data analysis

χ^2 tests, Fisher's exact test and Mann-Whitney *U*-tests were used to examine differences between males and females where appropriate. The median was reported for variables with skewed distribution. Treatment interruption was defined as any time that a patient missed a prescribed dose of a MDR-TB regimen for at least 1 day but for <8 consecutive weeks. As a subset, severe treatment interruption was defined as the duration of missed doses for 2–8 continuous weeks.¹⁵ The 6-month conversion refers to those who had a negative culture at the end of 6 months of MDR-TB treatment, with negative cultures for 2 subsequent months. We employed separate logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of factors associated with interruption and severe interruption. Covariates were made binominal or categorical, and were selected based on $P < 0.2$ in the univariate analysis or with a strong theoretical association. A backward-stepwise procedure was used to select independent variables using $P < 0.05$ as inclusion criterion.

Ethics issues

Ethics approval was obtained from the Ethics Committees of the University of Leeds, Leeds, UK, and Shandong Provincial Chest Hospital, Jinan, China.

Table 1 Clinical, demographic and socio-economic characteristics of a cohort of 110 MDR-TB patients treated for more than 6 months

	Male (<i>n</i> = 81) <i>n</i> (%)	Female (<i>n</i> = 29) <i>n</i> (%)	Total (<i>n</i> = 110) <i>n</i> (%)	<i>P</i> value
Type of patient				0.327
New patients	28 (34.6)	13 (44.8)	41 (37.3)	
Retreatment patients	53 (65.4)	16 (55.2)	69 (62.7)	
Duration of treatment				0.469
>6 months but <12 months	25 (30.9)	6 (20.7)	31 (28.2)	
>12 months but <18 months	20 (24.7)	9 (31.0)	29 (26.4)	
>18 months but <24 months	19 (23.5)	10 (34.5)	29 (26.4)	
Completed 24 months	17 (21.0)	4 (13.8)	21 (19.1)	
Month 6 culture conversion	54 (66.7)	20 (69.0)	74 (67.3)	0.821
Treatment regimen				0.896
6PzaKmLfx(Ofx)PasPth/18PzaLfx(Ofx)PasPth	55 (67.1)	18 (64.3)	73 (66.4)	
6PzaCpmLfx(Ofx)PasPth/18PzaLfx(Ofx)PasPth	17 (20.7)	7 (25.0)	24 (21.8)	
6PzaKmLfx(Ofx)EmbPth/18PzaLfx(Ofx)EmbPth	10 (12.2)	3 (10.7)	13 (11.8)	
Age, years, median [IQR]	47 [30–58]	39 [27–52]	45 [29–57]	0.060
Married	57 (70.4)	22 (75.9)	79 (71.8)	0.970
Level of education				0.281
Primary school and below	30 (37.0)	14 (48.3)	44 (40.0)	
Junior high school	36 (44.4)	8 (27.6)	44 (40.0)	
Senior high school and above	15 (18.5)	7 (24.1)	22 (20.0)	
Having medical insurance	78 (96.3)	29 (100.0)	107 (97.3)	0.565
Rural health insurance scheme	71 (91.0)	26 (89.7)	97 (90.7)	0.699
Number of family members, median [IQR]	3.0 [2.0–4.0]	4.0 [3.0–4.0]	3.0 [2.0–4.0]	0.026
Annual household income, RMB, median [IQR]*	12 000 [6 000–25 000]	16 000 [10 000–25 000]	15 000 [7 750–25 000]	0.199
In debt	47 (58.0)	16 (55.2)	63 (57.3)	0.790
Amount of debt, RMB, median [IQR]*	7 000 [3 500–30 000]	11 000 [5 000–28 500]	10 000 [4 500–30 000]	0.568
Did not work during MDR-TB treatment	51 (63.0)	17 (58.6)	68 (61.8)	0.680

* RMB1 = USD 0.16.

MDR-TB = multidrug-resistant tuberculosis; PZA = pyrazinamide; KM = kanamycin; LFX = levofloxacin; OFX = ofloxacin; PAS = para-aminosalicylic acid; PTH = prothionamide; CPM = capreomycin; EMB = ethambutol; IQR = interquartile range.

RESULTS

A total of 213 patients initiated MDR-TB treatment between 1 January 2009 and 31 October 2011. By 30 April 2012, 56 (26%) patients had been treated for <6 months, 28 (13%) had defaulted and 12 (6%) had died. Of the remaining 117 patients, 7 (6%) refused to participate in the study after three invitations at different times. A total of 110 MDR-TB cases were included in the final study. Of these, 42 (38%) were found to have MDR-TB during their first course of treatment, while 68 (62%) were retreatment cases. By 30 April 2012, 21 (19%) had completed the 24 months of treatment, 58 (53%) had been treated for between 12 and 24 months and 31 (28%) had been treated for between 6 and 12 months. The overall 6-month conversation rate was 67%. At the time of the study, a total of 73 (66%) patients had received or were meant to receive 6 months of PZA, KM, LFX/OFX, PAS and PTH followed by 18 months of PZA, LFX/OFX, PAS and PTH; for 24 (22%) patients KM was replaced by CPM during the intensive phase and for 13 (12%) patients PAS was replaced by EMB. All patients were non-human immunodeficiency virus (HIV) infected.

The median age of the patients was 45 years: 81 (74%) were male, and 79 (72%) were married; 44

(40%) had primary school level education or below. Of the 107 patients with health insurance, 97 (91%) were covered by rural health insurance schemes. The annual median household income was renminbi (RMB) 15 000 (US\$2459); 63 (57%) patients were in debt due to TB, ranging between RMB4500 and RMB30 000 (US\$738–4918; Table 1).

Treatment interruption

A total of 75 (68%) patients interrupted treatment, 59 (73%) males and 16 (55%) females, with a median of three interruptions each; 58 (53%) patients interrupted oral drugs and 50 (46%) interrupted injectable drugs. No one reported stopping injectable drugs for >2 weeks (severe interruption), but 19 (17%) patients reported stopping oral drugs for >2 weeks. The median duration of severe interruption was 30 days. When asked the main reason for interruption, 28 (37%) mentioned side effects, 20 (27%) said they had forgotten and 18 (24%) reported feeling better. Only 26 (35%) reported having received any kind of reminder to take their drugs during the interruptions (Table 2).

Provision of DOT and community management

On initiating treatment, each patient was assigned an

Table 2 Treatment interruptions of a cohort of 110 multidrug-resistant tuberculosis patients during treatment

	Male (<i>n</i> = 81) <i>n</i> (%)	Female (<i>n</i> = 29) <i>n</i> (%)	Total (<i>n</i> = 110) <i>n</i> (%)	<i>P</i> value
Interruptions	59 (72.8)	16 (55.2)	75 (68.2)	0.080
Number of interruptions, median [IQR]	3 [1–4]	2 [1–4]	3 [1–4]	0.583
Interruptions of				
Injectable drugs	40 (49.4)	10 (34.5)	50 (45.5)	0.167
Oral drugs	47 (58.0)	11 (37.9)	58 (52.7)	0.063
Severe interruption	16 (19.8)	3 (10.3)	19 (17.3)	0.250
Duration of severe interruption, days, median [IQR]	30.0 [14.3–55.0]	30.0 [15.0–50.0]	30.0 [15.0–50.0]	0.737
The most important reason for interruption (<i>n</i> = 59)				0.369
Side effects	21 (35.6)	7 (43.8)	28 (37.3)	
Forgetfulness	18 (30.5)	2 (12.5)	20 (26.7)	
Feeling better	14 (23.7)	4 (25)	18 (24)	
Economic burden	4 (6.8)	1 (6.3)	5 (6.7)	
Others	2 (3.4)	2 (12.5)	4 (5.3)	
Having received any reminders during interruptions	21 (35.6)	5 (31.3)	26 (34.7)	0.746

IQR = interquartile range.

official DOT venue, usually the village clinic. Patients reported that most of the DOT venues were within a 5-min walk, but that they lacked private rooms during their visits. Respectively 81 (74%) and 103 (94%) patients stored their injectable and oral TB drugs at home. Eighty-two (76%) patients received injections from village doctors, and 26 (24%) from family members. Only 55 (50%) patients received their treatment with DOT: 7 (13%) from village doctors and 48 (87%) from family members. Of the 48 family DOT observers, 25 (52%) did not receive any relevant training.

Of the 110 patients included in the study, 78 (72%) reported being afraid to reveal their TB status to others. More females reported facing serious difficulties in treatment than males ($P < 0.006$); 87 (80%) reported being unwilling to visit the village clinic to take their drugs and 15 (14%) reported being unwilling to visit the designated hospital to collect their drugs. A total of 94 (86%) reported having serious difficulties in treatment: 46 (49%) claimed financial reasons, 19 (20%) complained of the long treatment duration, 13 (14%) referred to side effects and 10 (9%) reported long travel times to the designated hospital (Table 3).

We categorised patient costs into in-patient and out-patient costs (Table 4). A total of 38 (35%) patients received in-patient care for a median of 56 days. The average in-patient costs were RMB12 040 (US\$1974), of which the majority were medical costs. The Global Fund Project paid RMB7560 (US\$1239), and health insurance schemes covered the remaining medical costs. Patients paid for meals and accommodation during their hospitalisation (RMB825/US\$135). During the out-patient treatment period, patients paid a median of RMB30 (US\$4.9) per month in the intensive phase (mainly for injection fees), but almost zero during the continuous phase

when injections were not needed. The median travel cost was RMB29 (US\$4.8) per month, for which patients received a travel allowance of RMB5 (US\$0.8).

Factors associated with treatment interruption

Males were identified to be 3.1 times more likely to interrupt treatment than females (Table 5). Patients who stored their injectable drugs at the DOT venue (usually the village clinic) were 8.4 times more likely to experience severe interruptions than those who stored their TB drugs at home. Patients who received DOT from family members were less likely to have severe interruptions than patients who did not, including those observed by a village doctor and those who did not receive treatment under DOT (OR 0.247).

DISCUSSION

Our study shows that the long duration of MDR-TB treatment and high frequency of drug toxicity posed a significant challenge for drug adherence in an early cohort of MDR-TB patients in China. A serious concern is that 24% of patients received injections from family members, which raises the question as to whether the drugs were given in the appropriate dosage or with the appropriate sterilisation and infection control measures.

Missing $\geq 10\%$ of doses in any 6-month period has been shown to result in poor treatment outcomes and further transmission of MDR-TB strains.¹⁶ In our study, 68% of patients reported treatment interruptions, which, although a matter of concern, was lower than reported in the Philippines (93%).⁷ Patients interrupted treatment on average three times during their treatment, which was less than that reported in Latvia (5 times).⁹ Of greater concern is the fact that 17% of patients reported severe interruptions of at

Table 3 Community management of multidrug-resistant tuberculosis treatment among a cohort of 110 patients treated for more than 6 months

	Male (<i>n</i> = 81) <i>n</i> (%)	Female (<i>n</i> = 29) <i>n</i> (%)	Total (<i>n</i> = 110) <i>n</i> (%)	<i>P</i> value
Provision of DOT				
Distance to the designated DOT venue, minutes on foot, median [IQR]	5.0 (2.0–15.0)	5.0 (2.0–10.0)	5.0 (2.0–10.0)	0.557
DOT venue with private rooms	21 (25.9)	11 (37.9)	32 (29.1)	0.222
Storage place of injectable drugs				0.785
Home	60 (75.0)	21 (72.4)	81 (74.3)	
DOT venue	20 (25.0)	8 (27.6)	28 (25.7)	
Person providing injection				0.314
Family member	21 (26.6)	5 (17.2)	26 (24.1)	
Village doctor	58 (73.4)	24 (82.8)	82 (75.9)	
Storage place of oral drugs				1.000
Home	76 (93.8)	27 (93.1)	103 (93.6)	
DOT venue	5 (6.2)	2 (6.9)	7 (6.4)	
Received DOT	40 (49.4)	15 (51.7)	55 (50.0)	0.829
Observed by village doctor	6 (15.0)	1 (6.7)	7 (12.7)	0.660
Observed by family member	34 (85.0)	14 (93.3)	48 (87.3)	
Family member received DOT training	16 (47.1)	7 (50.0)	23 (47.9)	0.611
Frequency of DOT				0.236
Always	35 (87.5)	11 (73.3)	46 (83.6)	
Occasionally	5 (12.5)	4 (26.7)	9 (16.4)	
Follow-up visits by health staff				
Received follow-up visits	69 (85.2)	26 (89.7)	95 (86.4)	0.755
By staff in the specialist hospital	67 (97.1)	26 (100.0)	93 (97.9)	1.000
By staff in the county TB dispensary	15 (21.7)	3 (11.5)	18 (18.9)	0.381
By village doctors	2 (2.9)	0	2 (2.1)	1.000
Reported patient attitudes towards treatment				
Afraid to reveal TB status to others	54 (68.4)	24 (82.8)	78 (72.2)	0.139
Unwilling to visit the village clinic to take drugs	64 (80.0)	23 (79.3)	87 (79.8)	0.937
Unwilling to visit the designated hospital to renew drugs	10 (12.7)	5 (17.2)	15 (13.9)	0.541
Unwilling to be seen by health staff at home	17 (21.5)	6 (20.7)	23 (21.3)	0.926
Having serious difficulties in treatment	65 (80.2)	29 (100.0)	94 (85.5)	0.006
Economic burden	32 (49.2)	14 (48.3)	46 (48.9)	
Long treatment duration	14 (21.5)	5 (17.2)	19 (20.2)	
Side effects	9 (13.8)	4 (13.8)	13 (13.8)	
Long travel to the TB specialist hospital	7 (10.8)	3 (10.3)	10 (10.6)	
Others	3 (4.6)	3 (10.3)	6 (6.4)	

DOT = directly observed treatment; IQR = interquartile range; TB = tuberculosis.

least 2 weeks. In our cohort, only half of the patients received treatment under DOT.

A pressing question is who should provide treatment support to MDR-TB patients. Studies have

shown the need for strong patient support and treatment supervision, and that DOT may reduce default and improve treatment success among MDR-TB patients.^{6,10} The WHO recommends that treat-

Table 4 Costs of multidrug-resistant tuberculosis treatment among the cohort of 110 patients treated for more than 6 months (RMB)

	Male (<i>n</i> = 81) Median [IQR]	Female (<i>n</i> = 29) Median [IQR]	Total (<i>n</i> = 110) Median [IQR]	<i>P</i> value
In-patients				
In-patient rate, <i>n</i> (%)	27 (33.3)	11 (37.9)	38 (34.5)	0.655
In-patient days	51 [28–64]	57 [35–87]	56 [34–76]	0.215
Total in-patient cost, RMB	11 456 [6 459–17 124]	13 542 [8 871–21 172]	12 040 [7 424–17 503]	0.204
Medical costs, RMB	10 706 [5 097–16 449]	12 942 [8 153–15 472]	11 132 [6 182–16 006]	0.342
Health insurance reimbursement, RMB	2 480 [1 000–6 938]	4 093 [1 974–5 715]	2 480 [1 083–6 928]	0.606
Global Fund reimbursement	7 560 [3 720–9 860]	7 463 [5 701–9 896]	7 560 [4 139–9 869]	0.551
Out-of-pocket cost, RMB	0 [0–100]	1 [0–2 115]	0 [0–144]	0.289
Meals and accommodation costs	660 [400–1 200]	900 [700–2 200]	825 [560–1 200]	0.181
Out-patients				
Monthly intensive phase medical costs, RMB	30 [0–150]	60 [1–193]	30 [0–180]	0.432
Monthly continuous phase medical costs, RMB	0 [0–30]	0 [0–38]	0 [0–35]	0.288
Monthly travel costs, RMB	34 [20–50]	40 [30–52]	29 [24–50]	0.630
Monthly financial aid for travel, RMB	0 [0–60]	30 [0–60]	5 [0–60]	0.470

* RMB1 = USD0.16.

IQR = interquartile range.

Table 5 Multivariate analysis of risk factors associated with treatment interruptions among a cohort of 110 multidrug-resistant tuberculosis patients

Dependent variables	Independent variable*	Coefficient	P value	OR (95%CI)
Interruption	Male sex [†]	1.135	0.046	3.112 (1.020–9.493)
	Constant	–2.278	0.173	0.103
Severe interruption	More education [‡]	1.814	0.024	6.134 (1.269–29.643)
	DOT venue storage of injectables [§]	2.125	0.017	8.371 (1.470–47.659)
	Observed by family members	–1.400	0.046	0.247 (0.051–0.979)
	Willingness to visit the designated hospital [#]	2.167	0.026	8.736 (1.304–58.533)
	Constant	–3.339	0.068	0.035

* Selected independent variables were in four categories: 1) demo-socio-economic (sex, age group, marriage, education, occupation and annual household income), 2) clinical (new or retreated patients, and in-patient care), 3) psychological (willingness to renew drugs, willingness to visit the DOT venue, willingness to receive follow-up visits and having confidence to complete treatment) and 4) community management (storage place of injectable and oral drugs, paying for injections, DOT by family member, having significant side effects and reporting serious challenges during treatment).

[†] 0 = female, 1 = male.

[‡] 0 = primary school and below, 1 = junior high school and above.

[§] 0 = stored injectable drugs at home, 1 = stored injectable drugs at the DOT venue.

^{||} 0 = those who were not observed by family members, including those observed by village doctors and those without DOT, 1 = observed by family member.

[#] 0 = unwilling to visit TB specialist hospitals, 1 = willing to visit TB specialist hospitals.

OR = odds ratio; CI = confidence interval; DOT = directly observed treatment.

ment be provided under DOT throughout the duration of MDR-TB treatment, and the practice of DOT needs to be acceptable to patients.¹⁷ Health staff are often the suggested option, while trained community workers or family members may act as alternatives.⁸ However, the beneficial effects of DOT are unlikely to be related to DOT alone; they are also associated with the patient support and supervision activities that come with DOT.^{8,18} In practice, busy health staff may be reluctant to observe patients taking drugs and may not be able to provide adequate counselling and support during DOT provision. Studies have found that rates of health staff DOT were low (between 5% and 20%) among drug-susceptible TB cases in China and elsewhere.^{19–22} International trials have shown no additional benefits from DOT provided by health staff compared with that provided by family members or community health workers among drug-susceptible TB patients;^{23–25} however, DOT by health staff costs patients much more than DOT by other means.²⁶ A review of MDR-TB cohorts also found that family member or community health worker DOT was associated with the lowest default rate.¹⁰ Our results are compatible with this finding.

In China, village doctors are recommended to provide DOT to MDR-TB patients throughout treatment. National guidelines recommend that if village doctors are not available, another trained person should be selected.¹⁵ However, the choice of ‘others’ is always unclear. China’s village doctors, formerly known as barefoot doctors, are mostly private medical practitioners. The Global Fund Project gives village doctors a fee of RMB100 (US\$16) per month for providing DOT to a MDR-TB patient, which may not be a sufficient incentive. Having TB patients in the village clinic may deter other visitors from attending due to the fear of infection.²⁷ In addition, the stigma of having TB may also prevent patients from visiting village clinics.²⁸ In our study, patients who received DOT from family

members were less likely to have severe interruptions; this is in line with research findings from other developing countries suggesting that home-based DOT was feasible among MDR-TB patients^{10,11} and more cost-effective than in-patient care.²⁹ Future studies need to pilot family member DOT, with extra training and support for adverse event monitoring and management. Results of such a pilot will be useful for amending MDR-TB treatment guidelines.

Patient’s financial status was not found to be associated with treatment interruption, as the Global Fund Project and patient health insurance schemes covered almost all medical costs. The total out-of-pocket costs for MDR-TB treatment were far less than the amount spent on treating a drug-susceptible case in China (around US\$500–1000).^{30,31} However, the economic burden was still heavy for MDR-TB patients, as most had been treated for TB previously.

The study is subject to a number of limitations. First, we collected information on MDR-TB patients from only one province in China, and these results cannot be extrapolated to the whole country due to regional variations. Second, we did not include defaulters and those who refused to participate in the study; the characteristics of these patients may be different from those who answered the questionnaire. Third, as information regarding patient interruptions was collected retrospectively, some record data may be missing and responses may be subject to recall bias. We believe the missing information is random, however. To minimise missing data, we triangulated information on patient interruption from both patient records and their responses. In addition, we did not collect other factors that may potentially influence interruptions, such as alcohol or drug abuse, depression and housing conditions. Due to the small number of patients, we did not collect DST results for those whose sputum culture did not convert after 6 months of treatment; we cannot therefore explore associations between interruptions and acquired drug resistance.

CONCLUSION

The study found that DOT by family members was linked to fewer severe treatment interruptions, which indicates that family members should be properly trained to provide DOT to MDR-TB patients and that more structured involvement of family members should be prospectively studied as a potentially effective service delivery approach for MDR-TB.

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RESUME

CONTEXTE : La Chine comprend presque un cinquième des cas mondiaux de tuberculose multirésistante (TB-MDR). La Chine suit les protocoles standardisés de 24 mois de l'Organisation Mondiale de la Santé.

OBJECTIF : Evaluer les interruptions de traitement parmi les patients TB-MDR et leur association avec la fourniture de traitement sous observation directe (DOT).

MÉTHODES : Nous avons revu les dossiers cliniques de tous les patients TB-MDR confirmés qui avaient été traités pendant au moins 6 mois du 1^{er} janvier 2009 au 30 avril 2012 dans la province de Shandong. Une interruption de traitement a été définie comme des doses manquées au moins 1 jour mais pas plus de 8 semaines consécutives et une interruption grave comme des doses omises pendant 2 à 8 semaines consécutives.

RÉSULTATS : Parmi 110 patients, 75 (68%) ont interrompu leur traitement et 19 (17%) ont admis une interruption grave de durée médiane égale à 30 jours. Sur tous ces patients, 26 (24%) ont reçu des injections de membres de leur famille et 55 (50%) ont reçu DOT : 7 (13%) par des médecins dans leurs villages et 48 (87%) par des membres de leurs familles. Les patients recevant le DOT avec des membres de leurs familles ont connu des interruptions moins graves (OR 0,25 ; IC95% 0,05–0,98) que ceux qui ont reçu leur traitement, DOT ou non, de médecins villageois.

CONCLUSION : Les membres de la famille des patients peuvent servir de soutien au traitement de la TB-MDR afin de réduire les interruptions, mais il est nécessaire de bien leur expliquer leur rôle.

RESUMEN

MARCO DE REFERENCIA: Cerca de un quinto de los casos mundiales de tuberculosis multidrogorresistente (TB-MDR) ocurre en la China, donde se aplican los regímenes normalizados de 24 meses de la Organización Mundial de la Salud.

OBJETIVOS: Evaluar las interrupciones del tratamiento de los pacientes con diagnóstico de TB-MDR y su asociación con el suministro de un tratamiento directamente observado (DOT).

MÉTODOS: Se analizaron las historias clínicas y se llevó a cabo una encuesta mediante cuestionarios a todos los pacientes con diagnóstico confirmado de TB-MDR que recibieron como mínimo 6 meses de tratamiento del 1^o de enero del 2009 al 30 de abril del 2012, en la provincia de Shandong. Se definió la interrupción del tratamiento como la omisión de una dosis por lo menos 1 día pero durante <8 semanas consecutivas y se calificó la interrupción como grave cuando se omitieron dosis entre 2 y 8 semanas consecutivas.

RESULTADOS: De 110 pacientes, 75 presentaron interrupción del tratamiento (68%) y 19 refirieron interrupciones graves con una duración mediana de 30 días (17%). En 26 casos, los miembros de la familia aplicaban los medicamentos inyectables (24%) y 55 pacientes recibían el DOT (50%): 7 por parte de médicos del pueblo (13%) y 48 por parte de familiares (87%). Los pacientes que recibían el DOT de un miembro de la familia presentaron interrupciones menos graves (OR 0,25; IC95% 0,05–0,98) que los pacientes que recibían el DOT de un médico del pueblo o cuyo tratamiento no era DOT.

CONCLUSION: Los miembros de la familia pueden actuar como facilitadores del tratamiento de la TB-MDR a fin de disminuir las interrupciones del tratamiento, pero es necesario orientarlos con respecto a su función.
