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DOT associated with reduced all-cause mortality among tuberculosis patients in Taipei, Taiwan, 2006–2008

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Abstract

OBJECTIVE—To determine whether patients receiving directly observed treatment (DOT) had lower all-cause mortality than those treated with self-administered treatment (SAT) and to identify factors associated with mortality among tuberculosis (TB) patients.

DESIGN—All TB patients in Taipei, Taiwan, diagnosed between 2006 and 2008 were included in a retrospective cohort study.

RESULTS—Among 3624 TB patients, 45.5% received DOT, which was disproportionately offered to older patients and those with more underlying illness and severe TB disease. After controlling for patient sociodemographic factors, clinical findings and underlying comorbidities, the odds of death was 40% lower (aOR 0.60, 95% CI 0.5–0.8) among patients treated with DOT than those on SAT. After adjusting for DOT, independent predictors of death included non-Taiwan birth, increasing age, male, unemployment, end-stage renal disease requiring dialysis, malignancy, acid-fast bacilli smear positivity and pleural effusion.

CONCLUSION—DOT was associated with lower all-cause mortality after controlling for confounding factors. DOT should be expanded in Taiwan to improve critical treatment outcomes among TB patients.

Keywords

tuberculosis; mortality; directly observed therapy; treatment

Tuberculosis (TB) remains a common and deadly disease globally. Approximately two billion people are latently infected with TB, and there are almost two million deaths annually due to active disease. In 2009, there were 9.4 million new TB cases, of which 3.3 million (35%) occurred in the South-East Asia region.¹

Of all reportable infectious diseases in Taiwan, TB has for decades been the most prevalent and significant.² From 1990 to 2005, TB incidence in Taiwan almost doubled, from 40 cases per 100 000 population to 72/100 000,² and over 60% of TB treatment ‘failures’ were shown

to be caused by death during treatment rather than defaulting on treatment.² After the World Health Organization (WHO) introduced the 'Plan to Stop TB' in 2006,³ with proposals to halve TB incidence by 2015, the Taiwan Centers for Disease Control (CDC) adopted an aggressive strategy for TB control centred firmly on the implementation of directly observed treatment short course (DOTS) in the hope that increased monitoring would reduce both transmission of new cases and TB mortality.² Directly observed treatment (DOT) was not previously a component of TB control policy in Taiwan, and when the DOTS strategy was implemented by the Taiwan CDC, TB patients at greatest risk for transmitting TB and with the most severe disease (e.g., those with positive acid-fast bacilli [AFB] smear or TB culture) were initially preferentially assigned to DOT.²

While the WHO endorses DOT, which stipulates that every dose of TB medication be observed by a health professional or designee to increase adherence, it has had variable effectiveness on TB treatment outcomes when put into practice.^{4–12} A Cochrane review of DOT in 2009 concluded that there were no statistically significant differences in treatment outcomes between TB patients on DOT and those using self-administered therapy (SAT).¹³ While the studies reviewed controlled for potential confounders, some null findings could have resulted from selection bias and residual confounding.

To determine whether patients receiving DOT had lower all-cause mortality than those treated with SAT, we compared all-cause mortality rates among TB patients receiving TB treatment via DOT vs. SAT between 2006 and 2008 in Taipei City, the second largest city in Taiwan. We hypothesised that after accounting for confounding variables, patients on DOT would have lower all-cause mortality than those on SAT.

METHODS

Study settings and population

The study utilised TB surveillance data from Taipei, Taiwan. The study population included all Taipei City citizens diagnosed with TB and reported to the TB Control Department in Taipei between 2006 and 2008. TB was defined by clinical and/or laboratory findings.¹⁴

This analysis was approved by the Institutional Review Board of Taipei City Hospitals and was determined to be exempt from human subjects research by an ethics committee at the University of California, San Diego.

Data collection and DOT

TB is a notifiable disease in Taiwan. All new patients from 2006 to 2008 were interviewed using a standardised questionnaire that included patients' sociodemographic characteristics, comorbidities and prior TB treatment history. Clinical examination, including chest radiography (CXR), and laboratory findings (excluding human immunodeficiency virus [HIV] testing results) were provided by reporting hospitals. CXR findings, including pleural effusions and other lesions, were recorded directly from radiologists' reports. HIV status was determined by self-report during the intake interview.

Since 2006, DOT has been recommended as the optimal treatment strategy by the Taiwan CDC for patients who were at greatest risk for transmitting TB and those with the severest disease (e.g., patients with positive AFB smear or TB culture) or at highest risk for TB treatment non-adherence and failure (e.g., homeless and relapse cases).² If a patient agreed to DOT, a trained supervisor observed the patient taking medications 5 days/week, while weekend doses were self-administered. Patients on DOT in Taiwan were also given adherence-promoting incentives, including social service support and food coupons equal to US\$2/day.² Those not assigned to DOT or who refused DOT were assigned to SAT.

Outcome variables

The outcome variable for this study was death from any cause during TB treatment vs. survival at the completion of TB treatment. To monitor the treatment outcomes of all TB patients in Taipei, case managers contacted TB patients every other week by phone or in person, regardless of treatment modality. Complete and reliable cause of death data were not available for this analysis.

Main explanatory variable

The main explanatory variable was mode of TB treatment (DOT vs. SAT). DOT took place at either the patients' residence or workplace. If patients who chose SAT after being notified of their TB diagnosis had poor adherence to treatment, they were informed about DOT a second time by their case managers. For patients on DOT, routine practice consisted of starting DOT at the onset of TB treatment and continuing it until treatment completion; however, some patients changed from DOT to SAT and from SAT to DOT during the course of treatment. Consistent with prior studies,^{8,15} DOT patients were defined as patients receiving any DOT during the study period.

Control variables

Control variables included patient sociodemographic factors (age, sex, ethnicity, marital status, educational level, tobacco use, alcohol use, occupation and TB history) and clinical findings (CXR, AFB smear status, TB culture results and drug resistance). Data on significant comorbidities (cardiovascular disease, lung disease, etc.) were also collected. Ages were grouped as follows: 0–29, 30–49, 50–69 and ≥70 years.

Statistical analysis

Descriptive statistics were used to characterise patients by treatment modality. The χ^2 test or Wilcoxon rank sum tests were used for univariate analysis of categorical and continuous variables, respectively. Multivariate analyses were conducted using death vs. survival as the outcome, with treatment modality as the main explanatory variable. Factors found to be associated with mortality on univariate analysis at an alpha level of <0.1 were considered for inclusion in the multivariate analysis. Backward stepwise multiple logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) after controlling for potential confounders. Variables with $P < 0.05$ were included in the final model. Analyses were conducted using SPSS version 15.0 statistical software package (Statistical Package for the Social Sciences Inc, Chicago, IL, USA).

RESULTS

In the 3-year study period, 4952 TB suspects were reported to the Taipei TB Prevention Department. Of these, 458 were excluded as they were found to have non-tuberculosis mycobacteria, 648 were determined by clinical examination not to have TB, 128 died before starting TB treatment, 93 were lost to follow-up during anti-tuberculosis treatment and 1 was still on treatment at the time of this study (Figure 1). The remaining 3624 patients were included in the analysis, including 517 extra-pulmonary TB (EPTB) patients. Among all EPTB patients, 31.7% ($n = 181$) were diagnosed with TB pleurisy and 17.0% ($n = 88$) with TB lymphadenitis. Overall, 43.6% ($n = 1582$) were ≥70 years of age, 64.5% ($n = 2336$) were male, 1.9% ($n = 68$) were foreign-born, 0.6% ($n = 23$) were homeless and 80.1% ($n = 2902$) had education; 45.5% ($n = 1650$) received DOT. The majority (90.1%) of the patients assigned to DOT remained on DOT throughout treatment. Among those who changed from DOT to SAT, the median time on DOT was 61 days (data not shown).

The proportion of patients receiving DOT increased from 32.9% in 2006, to 47.6% in 2007 and 57.5% in 2008 (Figure 2), while all-cause mortality among TB patients decreased from 18.0% in 2006 to 17.1% in 2007 and 16.2% in 2008.

Table 1 shows that compared with patients receiving SAT, patients on DOT were more likely to have positive sputum smears and TB cultures. Moreover, patients on DOT were significantly more likely to have cavitory lesions on CXR.

Variables found to be significantly associated with death on univariate analysis included DOT, age ≥ 30 years, male sex, married and widowed (reference = unmarried), unemployment, end-stage renal disease (ESRD) requiring dialysis, malignancy, cardiovascular disease, AFB smear positivity, TB culture positivity and pleural effusion (Table 2). Variables significantly associated with lower mortality included education, cavity on CXR and smear-negative pulmonary TB and EPTB. While DOT was associated with increased mortality on univariate analysis, after adjusting for sociodemographic factors, clinical findings and underlying diseases, patients receiving DOT had a 40% lower odds of death (OR 0.60, 95%CI 0.5–0.8; Table 3).

As DOT appeared to be associated with increased risk of mortality in univariate analysis, but was protective against mortality in the final multivariate analysis, we repeated the multivariate analysis multiple times, removing a single covariate from the final model to identify which factor(s) contributed to the paradoxical effect of DOT. The only covariate that had a significant effect on the adjusted ORs (aORs) between DOT and mortality when it was removed from the model was 'AFB status' (data not shown). Furthermore, we observed that when AFB status was removed from the final model, the aORs for the other covariates did not change substantially, demonstrating that the other variables in the final model were independently associated with mortality and did not interact with AFB status. The interaction term between DOT and AFB smear status was assessed in the final model, and showed marginal significance ($P = 0.071$).

DISCUSSION

This study found that all-cause mortality in TB patients declined from 2006 to 2008, corresponding with an increase in DOT use over time. After controlling for confounding factors, the odds of death among patients receiving DOT was significantly lower than among patients on SAT. These findings suggest that DOT reduced all-cause mortality among TB patients in treatment.

The paradoxical effect of DOT on TB mortality that was found between the univariate and multivariate analyses in this study appeared to be the consequence of a higher proportion of AFB-positive patients in the DOT group than in the SAT group. When the DOTS strategy was implemented by the Taiwan CDC in 2006, DOT was strongly recommended as the optimal treatment strategy for patients at highest risk for transmitting infection.² Patients on DOT were therefore significantly more likely than patients on SAT to have a positive sputum smear in this study. Previous studies also demonstrated that positive AFB smear was a risk factor for death among TB patients.^{16–18} Hence, after controlling for AFB smear status and other covariates, the odds of death among patients receiving DOT was 40% lower than among those on SAT in this study.

The DOTS strategy was introduced globally in the mid-1990s, and later became the cornerstone of the Stop TB Strategy.¹⁹ This strategy had five key elements, the most prominent being DOT, which has proven to be a key component. However, not all studies have shown DOT to be effective. A 2009 Cochrane review of nine DOT trials^{4–12} concluded that the effects of DOT on cure or treatment completion among TB patients was similar to

that of SAT.¹³ However, some limitations of these studies were discussed. First, although the WHO guidelines mention that treatment observers should be trained by the health care system and patients' family members should not be suggested as designees,²⁰ six trials assigned patients' family members as treatment observers.^{4-8,11} Previous studies have reported that family observation yields lower cure rates and much higher default rates than observation by non-family members.^{21,22} Second, the study populations in some trials may not be representative: for example, the study population in four trials excluded relapses,^{7,8} multidrug-resistant TB cases,^{8,12} patients with HIV infection,⁸ or patients with severe illness.^{6,7,12} Furthermore, some trials did not specify how patients were assigned to treatment arms.^{6,8,9} Although DOT was not assigned at random to TB patients in our sample, factors that resulted in selection bias were collected and controlled for on statistical analysis. Moreover, the treatment observers in Taipei were trained supervisors employed by the health department instead of family members.² These differences could account for the positive effect of DOT in the Taipei sample.

This study also found the odds of death was 3.8 times higher among foreign-born patients than Taiwanese patients. Poorer access to health care could account for this difference. A prior study in Taiwan revealed that foreign-born TB patients were more likely to delay treatment compared with Taiwanese patients.²³ Delay in treatment of TB increases the risk not only of TB transmission, but also of morbidity and mortality. Although Taiwan established a national health insurance system in 1995,²⁴ foreign-born individuals must pay for all medical expenses personally unless they join the national single-payer system. Non-nationals may typically only enter the system if they are hired by Taiwanese employers; health care utilisation among the foreign-born is thus low. Consistent with previous studies, this study also found advanced age,^{25,26} male sex,²⁶ unemployment,^{17,27} ESRD receiving dialysis,²⁷ malignancy^{25,27} and positive AFB smear¹⁶⁻¹⁸ to be risk factors for mortality.

Some limitations should be considered when interpreting these findings. First, this study involved secondary analysis of surveillance data limiting us to variables collected by the surveillance system. Second, the diagnosis of 29.7% of TB cases was based on clinical findings and was not confirmed by AFB smear or culture. While this may have led to misdiagnosis of TB in some cases, it is unlikely, as the Taiwan CDC expert committee met monthly to clarify the diagnosis of discrepant TB cases.² Furthermore, given that DOT was offered preferentially to patients with positive AFB smears or cultures, patients misdiagnosed with TB were more likely to be assigned to SAT. This misclassification could bias the results toward DOT appearing harmful; thus, our finding of a protective effect is conservative. Third, DOT was defined as having ever been on DOT, regardless of whether the patient later switched to SAT (9.9% of patients receiving DOT switched to SAT). If DOT truly reduced mortality, then those who had DOT interruptions could cause the protective effect of DOT to be underestimated, adding further confidence in our findings. Finally, since Taiwan passed legislation in 2007 requiring providers to obtain informed consent from patients before testing them for HIV, TB patients are not routinely tested for HIV. HIV prevalence among TB patients was therefore collected by self-report in this study, and was 0.4%. This is lower than the 8% prevalence reported among TB patients in the United States²⁸ and the United Kingdom.²⁹ While HIV prevalence in our sample might have been underestimated due to the fact that it was self-reported, our results would only be biased if misclassification was differential across treatment groups. We have no data to suggest there was differential misclassification that would have significantly affected our results.

Strengths of this study include the fact that all eligible TB patients in Taipei were included in this analysis; sample size was therefore not based on considerations of statistical power. Another strength was the tight regulation of the TB reporting system in Taiwan—active

pulmonary TB cases were required to report to local TB control departments within 24 hours and other TB cases no later than 7 days from diagnosis; therefore, data were collected uniformly from patients proximal to the time of diagnosis and prior to death.

CONCLUSIONS

DOT was associated with 40% lower all-cause mortality compared to patients on SAT, after controlling for confounders. By 2008, 57.5% of TB patients in Taipei were receiving DOT, indicating substantial progress toward achieving Taiwan's goal of successfully treating 85% of all TB by 2015. However, DOT in Taiwan has not been implemented to the extent recommended by the WHO for controlling TB. Expanding DOT coverage to all TB patients could yield significant decreases in TB mortality in Taipei and across Taiwan.

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Figure 1.
Study population. TB = tuberculosis; NTM = non-tuberculosis mycobacteria.

Figure 2. All-cause mortality among TB patients and the proportion of TB patients on directly-observed therapy or self-administered treatment in Taipei, Taiwan, 2006–2008. TB = tuberculosis.

Table 1

Demographic and clinical characteristics of TB patients treated by DOT compared with SAT, Taipei, Taiwan, 2006–2008

Characteristic	DOT (<i>n</i> = 1650) <i>n</i> (%)	SAT (<i>n</i> = 1974) <i>n</i> (%)	<i>P</i> value
Positive AFB smear	1117 (67.7)	246 (12.5)	<0.001
Positive TB culture	1486 (90.1)	885 (44.8)	<0.001
Cavity on chest X-ray	355 (21.5)	263 (13.3)	<0.001
Pleural effusion on chest X-ray	41 (2.5)	179 (9.1)	<0.001
Mean age at diagnosis, years $\pm$ SD	63.8 $\pm$ 20.9	58.2 $\pm$ 21.4	<0.001
Male	1152 (69.8)	1184 (60.0)	<0.001
Foreign-born	26 (1.6)	42 (2.1)	0.22
Homeless	16 (1.0)	7 (0.4)	0.02
Unmarried status	337 (20.4)	468 (23.7)	0.02
Ever educated	1282 (77.7)	1620 (82.1)	0.001
Smoker	328 (19.9)	301 (15.2)	0.001
Any alcohol use	146 (8.8)	139 (7.0)	0.12
Unemployment	1204 (73.0)	1287 (65.2)	<0.001
Comorbid conditions			
ESRD receiving dialysis	21 (1.3)	67 (3.4)	<0.001
Malignancy	92 (5.6)	95 (4.8)	0.3
Cardiovascular disease	403 (24.4)	418 (21.2)	0.02
Chronic lung diseases	48 (2.9)	32 (1.6)	0.009
HIV infection (self-report)	7 (0.4)	9 (0.5)	0.89
Prior treatment of TB	71 (4.3)	48 (2.4)	0.002
MDR-TB	16 (1.0)	15 (0.8)	0.5
Extra-pulmonary TB	32 (1.9)	485 (24.6)	<0.001
Duration between initiating treatment and death, days, median [IQR]	67 [26–149]	38 [10–98]	<0.001

TB = tuberculosis; DOT = directly observed treatment; SAT = self-administered treatment; AFB = acid-fast bacilli; SD = standard deviation; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; IQR = interquartile range.

Table 2

Univariate analysis of factors associated with mortality among TB patients in Taipei, Taiwan, 2006–2008

Factor	Total patients <i>n</i>	All-cause mortality		
		<i>n</i> (%)	OR (95%CI)	<i>P</i> value
Mode of treatment				
SAT	1974	300 (15.2)	1	
DOT	1650	320 (19.4)	1.3 (1.1–1.5)	0.001
Place of birth				
Taiwan	3556	613 (17.2)	1	
Foreign-born	68	7 (10.3)	0.6 (0.3–1.2)	0.14
Age, years				
0–29	442	4 (0.9)	1	
30–49	659	32 (4.9)	5.4 (1.9–15.4)	0.001
50–69	941	97 (10.3)	11.7 (4.3–31.8)	<0.001
≥70	1582	487 (30.8)	40.1 (15.0–107.3)	<0.001
Sex				
Female	1288	464 (36.0)	1	
Male	2336	156 (6.7)	1.7 (1.4–2.0)	<0.001
Year of diagnosis				
2006	1257	225 (17.9)	1	
2007	1282	219 (17.1)	0.9 (0.8–1.2)	0.59
2008	1085	176 (16.2)	0.9 (0.8–1.1)	0.28
Marital status				
Unmarried	805	83 (10.3)	1	
Married	2061	353 (17.2)	1.7 (1.3–2.2)	<0.001
Divorced	170	23 (13.5)	1.3 (0.8–2.1)	0.22
Widow	547	148 (27.1)	2.9 (2.2–3.8)	<0.001
Unknown	41	13 (31.7)	3.0 (1.7–5.4)	<0.001
Education				
None	563	134 (23.8)	1	
Any schooling*	2902	443 (15.3)	0.6 (0.5–0.8)	<0.001
Unknown	159	43 (27.0)	1.1 (0.8–1.6)	0.4
Homeless				
No	3601	615 (17.1)	1	
Yes	23	5 (21.7)	1.3 (0.5–3.0)	0.56
Smoker				
No	2969	517 (17.4)	1	
Yes	629	94 (14.9)	0.8 (0.7–1.1)	0.14
Unknown	26	9 (34.6)	1.9 (0.9–3.7)	0.03
Any alcohol use				
No	3317	576 (17.4)	1	
Yes	285	36 (12.6)	0.7 (0.5–0.99)	0.04

Factor	Total patients <i>n</i>	All-cause mortality		
		<i>n</i> (%)	OR (95%CI)	<i>P</i> value
Unknown	22	8 (36.4)	2.1 (1.03–4.2)	0.03
Unemployment				
No	1131	104 (9.2)	1	
Yes	2491	516 (20.7)	2.4 (1.9–3.0)	<0.001
ESRD receiving dialysis				
No	3536	590 (16.7)	1	
Yes	88	30 (34.1)	2.3 (1.6–3.3)	<0.001
Malignancy				
No	3437	536 (15.6)	1	
Yes	187	84 (44.9)	3.4 (2.7–4.3)	<0.001
Cardiovascular disease				
No	2803	416 (14.8)	1	
Yes	821	204 (24.8)	1.8 (1.5–2.1)	<0.001
Chronic lung disease				
No	3544	601 (17.0)	1	
Yes	80	19 (23.8)	1.4 (0.9–2.3)	0.11
HIV infection (self-report)				
No	3608	617 (17.1)	1	
Yes	16	3 (18.8)	0.9 (0.3–3.1)	0.86
TB history				
New case	3505	600 (17.1)	1	
Relapse	119	20 (16.8)	0.9 (0.6–1.4)	0.93
Acid-fast bacilli smear				
Negative	2261	291 (12.9)	1	
Positive	1363	329 (24.1)	2.0 (1.7–2.3)	<0.001
TB culture				
Negative	1253	180 (14.4)	1	
Positive	2371	440 (18.6)	1.3 (1.1–1.5)	0.001
Cavity on chest X-ray				
No	3006	539 (17.9)	1	
Yes	618	81 (13.1)	0.7 (0.6–0.9)	0.004
Pleural effusion on chest X-ray				
No	3404	559 (16.4)	1	
Yes	220	61 (27.7)	1.8 (1.4–2.3)	<0.001
MDR-TB				
No	3593	615 (17.1)	1	
Yes	31	5 (16.1)	0.5 (0.2–1.2)	0.88
Infection site				
Smear-positive PTB	1546	360 (23.3)	1	
Smear-negative PTB	1517	181 (11.9)	0.5 (0.4–0.6)	<0.001
EPTB	517	73 (14.1)	0.6 (0.4–0.7)	<0.001

Factor	Total patients <i>n</i>	All-cause mortality		
		<i>n</i> (%)	OR (95%CI)	<i>P</i> value
PTB and EPTB	44	6 (13.6)	0.5 (0.2–1.1)	0.14

TB = tuberculosis; OR = odds ratio; CI = confidence interval; SAT = self-administered treatment; DOT = directly observed therapy; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB; PTB = pulmonary TB; EPTB = extra-pulmonary TB.

*
≥primary education

Table 3

Unadjusted and adjusted odds ratios for factors associated with mortality among TB subjects in Taipei, Taiwan, 2006–2008

Variable	Crude OR (95%CI)	Adjusted OR (95%CI)
DOT	1.3 (1.1–1.5)*	0.6 (0.5–0.8)*
Foreign-born	0.6 (0.3–1.2)	3.8 (1.7–8.3)*
Age, years		
0–29	1	1
30–49	5.4 (1.9–15.4)*	5.7 (2.0–16.3)*
50–69	11.7 (4.3–31.8)*	11.2 (4.1–30.9)*
≥70	40.1 (15.0–107.3)*	36.4 (13.4–99.0)*
Male	1.7 (1.4–2.0)*	1.2 (1.0–1.5) [‡]
Unemployment	2.4 (1.9–3.0)*	1.5 (1.2–1.8)*
ESRD receiving dialysis	2.3 (1.6–3.3)*	1.9 (1.3–2.8)*
Malignancy	3.4 (2.7–4.3)*	2.4 (1.9–3.0)*
Positive AFB smear	2.0 (1.7–2.3)*	2.5 (2.1–3.1)*
Pleural effusion	1.8 (1.4–2.3)*	1.8 (1.3–2.3)*

* $P \leq 0.001$.

[‡] $P \leq 0.05$.

TB = tuberculosis; OR = odds ratio; CI = confidence interval; DOT = directly observed therapy; ESRD = end-stage renal disease; AFB = acid-fast bacilli.