

Drug resistance among tuberculosis patients who sought care at private sector before taking treatment at public health service

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As drug resistant tuberculosis (TB) is an emerging problem, delay in achieving correct diagnosis and effective treatment may lead to occurrence of drug resistant cases. This study aimed to explore the bacteriological factor of TB patients who had considerable delay while seeking treatment at private sector (general practitioners, traditional healers, self proclaimed healers) before taking treatment at public health service (TB Clinic under National TB Programme). New sputum smear positive pulmonary TB patients attending TB Centre, Yangon Division were divided into two groups as direct patients (patients attending TB Centre directly and those taking treatment at private sector for <3 weeks before reaching TB Centre) and indirect patients (patients taking treatment at private sector for >3 weeks before TB Centre). Drug susceptibility testing of *Mycobacterium tuberculosis* strains isolated from 140 direct patients and 140 indirect patients was carried out to determine bacteriological contributing factor. Resistance to at least one of anti-TB drugs was documented in 15(10.71%) direct patients and 31(22.14%) indirect patients. Mono-resistance (resistance to one drug) was noted in 6(4.29%) direct patients and 16(11.43%) indirect patients. Poly-resistance (resistance to two or more drugs) was noted in 9(6.49%) direct patients including 3(2.14%) multi-drug resistant cases (resistance to at least isoniazid and rifampicin) and 15(10.71%) indirect patients including 12(8.57%) multi-drug resistant cases. Any anti-TB drug and multi drug resistant rates were significantly higher in indirect than in direct patients ($P<0.05$). This study highlighted that patients who had considerable delay while seeking treatment in private sectors before reaching public health service have greater opportunity for occurrence of drug resistance.

INTRODUCTION

Tuberculosis (TB) is a major health problem and the world's foremost cause of death from a single infectious agent, *Mycobacterium tuberculosis*. TB causes about 8 million new cases and 2 million deaths every year. Myanmar is one of the 22 countries with highest prevalence of TB [1].

The World Health Organization (WHO) has promoted Directly Observed Therapy, Short Course (DOTS) as the policy for delivering

treatment [2]. This strategy has largely been communicated to the public health sector and implemented with various degrees of success. In Myanmar, National Tuberculosis Programme (NTP) has introduced DOTS since 1997 and all TB patients in NTP clinics are routinely treated with rifampicin, ethambutol, isoniazid, pyrazinamide and streptomycin. The DOTS detection rate of new sputum smear positive TB cases and DOTS treatment success rate were 73% and 81% respectively in 2002 [1].

Information on health expenditure suggests that poor countries have a large and growing private medical sector. Private practitioners are widely used to treat people with diseases such as TB, malaria, sexually transmitted infections, diarrhoeal diseases and acute respiratory infection [3].

The previous studies suggested that many low-income TB endemic countries with large private health sectors play a significant role in the initial stages of health seeking by symptomatic TB individuals. The large share of first contact has important implication for TB control if private practitioners follow poor diagnostic practices leading to delay in diagnosis. The delay in diagnosis is due to a delay in seeking care (patient's delay) or due to the inability of the provider to diagnose promptly (provider's delay) [4]. Lonnroth *et al.* [5] pointed that patients who had turned first to private sector were more likely to have a long provider delay than those who turned first to NTP [5].

Private health expenditure in Myanmar is 87.4% of total health expenditure [4]. A recent study which was carried out in a township in Yangon, the capital of Myanmar, pointed that 73.3% of patients at public TB centre first sought treatment at general practitioners' clinics [6].

Poor management practices in the private health sector such as delay in diagnosis and ineffective treatment dilute the epidemiological impact of DOTS programme. Such practices could also contribute to a growing incidence of drug resistant tuberculosis, which is a serious threat to TB control programme. The consequences include high morbidity and mortality, a heavy socio-economic burden and serious rate of multi-drug resistance. Thus, this study was conducted to explore the bacteriological impact in terms of occurrence of drug resistance on patients who had considerable delay while seeking treatment at private sector before taking care at public health service.

MATERIALS AND METHODS

A cross - sectional comparative study was carried out in TB Centre, Yangon Division from October 2003 to July 2005. New sputum smear positive pulmonary TB patients irrespective of age and sex were included in the study. New smear positive cases were divided into two groups: direct and indirect patients.

Direct patients included

Patients attending TB Centre without seeking treatment at private sectors and those taking treatment at private sectors for less than three weeks before reaching to the TB Centre.

Indirect patients included

Patients taking treatment at private sectors for more than three weeks before reaching to the TB Centre.

Private sector in this study means for general practitioners, traditional medical practitioners and self proclaimed healers.

Public health service means for government health care service. In this study, the study area is TB Centre, Yangon Division which is a main centre of NTP.

This study was approved by the Ethical Committee of Department of Medical Research (Lower Myanmar).

Field Survey Procedure

Patients who gave informed consent were included in the study and divided into direct and indirect groups according to case definition. They were interviewed using a pre-tested questionnaires designed to elicit the socio-demographic data and other contributory factors of drug resistance by trained interviewers at TB Centre. The data included age, sex, occupation, education, income, history of TB contact, how they reached TB Centre, history of taking treatment at private clinic, history of self medication, length of time between the appearance of symptoms and receiving anti-TB treatment and history of investigations done at private sector.

Laboratory Procedure

The sputum specimens of the patients were collected and transported to Bacteriology Research Division, Department of Medical Research (LM) for isolation of *M. tuberculosis*.

The sputum specimens were decontaminated with 4% sodium hydroxide and inoculated onto egg-based Lowenstein-Jensen (LJ) medium and incubated at 37°C for 6-8 weeks. *M. tuberculosis* isolates were identified by growth rate and pigmentation.

Drug susceptibility testing of culture isolates were carried out at Reference TB Laboratory, NTP by proportion method as described in Bacteriological Methods in Laboratory Diagnosis of Tuberculosis by Tuberculosis Research Centre (ICMR) Chetput, Chennai [7].

The tested anti-TB drugs and their minimum inhibitory concentration were isoniazid (0.2 mg/L, rifapicin 40 mg/L, dihydrostreptomycin 4 mg/L and ethambutol 2 mg/L). The results were interpreted at 42 days of incubation at 37°C and the proportion of bacilli resistant to a given drug is determined by expressing the resistant portion as a percentage of total proportion tested. The result of 1% or more proportion to a above drug concentration is interpreted as resistant.

Analysis of Results

The data were analyzed by using SPSS software. Descriptive statistics were used to describe socio-demographic data. The drug susceptibility pattern was compared between the direct and indirect groups.

RESULTS

1. Demographic data of direct patients and indirect patients

The demographic data of 152 direct and 142 indirect patients is shown in Table 1. The mean age of direct patients was 33.90 (range= 14-70 years) and that of indirect

patients was 36.34 (range= 13-70 years). There were 117 men and 35 women in direct patients and 103 men and 39 women in indirect patients. Among direct patients, 62 (40.8%) were skilled workers and 68 (44.7%) had middle school education level. Among indirect patients, 76 (53.5%) were skilled workers and 55 (38.7%) had middle school education level.

Table 1. Demographic data of direct and indirect patients

Demographic data	Direct patients (n=152)		Indirect patients (n=142)	
	No.	%	No.	%
Age				
mean age in years (range)	33.90 ± 12.42 (14-70 yrs)		36.64 ± 12.31 (13-70 yrs)	
Sex				
Male	117	77	103	72.50
Female	35	23	39	27.50
Occupation				
Unskilled worker	16	10.50	24	16.90
Semi skilled worker	23	15.10	10	7.00
Skilled worker	62	40.80	76	53.50
Dependent	21	13.80	15	10.60
Students	26	17.10	16	11.30
Others	4	2.60	1	0.70
Education				
Illiterate	4	2.60	5	3.50
Read and write	12	7.90	7	4.90
Primary school	27	17.80	23	16.20
Middle school	68	44.70	55	38.70
High school	31	20.40	32	22.50
Under graduate	8	5.30	9	6.30
Graduate	2	1.30	11	7.70

2. Drug susceptibility pattern

A total of 280 *M. tuberculosis* strains isolated from 140 direct patients and 140 indirect patients were tested for susceptibility to first line anti-TB drugs isoniazid (I), rifampicin (R), streptomycin (S) and ethambutol (E). One hundred and twenty five *M. tuberculosis* strains isolated from direct patients and 109 *M. tuberculosis* strains isolated from indirect patients were sensitive to all tested anti-TB drugs. Resistance to at least one of anti-TB drugs was documented in 15 (10.71%) of direct

patients and 31(22.14%) of indirect patients. Mono-resistance (resistance to one drug) was noted in 6(4.29%) of direct patients and 16(11.43%) of indirect patients. Poly-resistance (resistance to 2 or more drugs) was noted in 9(6.43%) of direct patients and 15(10.71%) of indirect patients.

Among the drug resistant strains isolated from direct patients, 3(2.14%) isolates were resistant to I and R, 5(3.57%) were resistant to S and I, 1(0.71%) isolate was resistant to S and R and 6(4.29%) were resistant to I. Of the mono-resistant strains of indirect patients, 13(9.29%) isolates were resistant to I, 2(1.43%) were resistant to R and 1(0.71%) isolate was resistant to E. Of poly-resistant strains of indirect patients 10(7.14%) isolates were resistant to I and R, 2(1.43%) isolates were resistant to S, I and R, 2(1.43%) isolates were resistant to S and R and 1(0.71%) isolate was resistant to S and I.

Multi-drug resistant strains were isolated (resistant to at least isoniazid and rifampicin) in 15(5.36%) of both 140 direct and 140 indirect patients comprising of 3(2.14%) direct patients and 12(8.57%) indirect patients.

Total resistance of individual anti-tuberculosis drug were: I (14, 10%), S (6, 4.29%), R (4, 2.86%) of direct patients and I (26, 18.57%), S (5, 3.57%), R (16, 11.43%), E (0.71%) of indirect patients(Table 2).

3. Comparison of any anti-TB drug resistance between direct and indirect patients

Any anti-TB drug resistant rate in indirect patients is significantly higher than that of direct patients.(P =0.01, chi square = 6.657) (Table 3).

4. Comparison of Multi- drug resistant TB between direct and indirect patients

MDR-TB rate in indirect patients is significantly higher than that of direct patients. (P = 0.02, chi square = 5.71) (Table 4).

Table 2. Drug resistant pattern of direct and indirect patients

Anti-TB drug	Direct Patients (n=140)	Indirect Patients (n=140)
I	6 (4.29%)	13 (9.29%)
R	-	2 (1.43%)
E	-	1 (0.71%)
S	-	-
IR	3 (2.14%)	10 (7.14%)
SI	5 (3.57%)	1 (0.71%)
SR	1 (0.71%)	2 (1.43%)
SIR	-	2 (1.43%)
Any-anti TB Drug resistant	15 (10.71%)	31 (22.14%)
MDR-TB	3 (2.14%)	12 (8.57%)
Mono-resistance	6 (4.29%)	16 (11.43%)
Poly-resistance	9 (6.43%)	15 (10.71%)

I= isoniazid, R= Rifampicin, E= Ethambutol, S= Streptomycin
MDR-TB= Multi-drug resistant TB

Table 3. Any-anti TB drug resistant rate between direct and indirect patients

Drug Susceptibility	Direct Patients	Indirect Patients	Total
Resistant patients	15	31	46
Sensitive patients	125	109	234
Total	140	140	280

P = 0.01, chi square = 6.657

5. Relevant history of indirect patients

One twenty one (85.21%) of indirect patients sought treatment at General Practitioners'(GP) clinics before seeking care at NTP. The mean of duration of treatment at private sector was 40.79 days with the range of 22 days to 2 years. Six (4.2%) patients had anti-TB treatment in private clinics. The commonest investigation done at private clinics was Chest X ray 71(50%). Sputum smear examination was carried out in 30 (21.13%) patients. Twenty four (16.9%) patients had history of tuberculosis in their close contacts. Among them, 13(54.17%) took treatment from private clinics and 7(29.17%) sought treatment from NTP.

Table 4. Multi-drug resistant TB rate between direct and indirect patients

Drug Susceptibility	Direct Patients	Indirect Patients	Total
MDR-TB patients	3	12	15
Non-MDR TB patients	137	128	205
Total	140	140	280

P = 0.02, chi square = 5.71

DISCUSSION

Spread of drug resistant TB and disastrous rate of HIV-TB co-infection pose a serious threat to TB Control Programmes around the world. The prevalence of MDR-TB and any anti-TB drug resistance among new sputum smear positive TB patients at Union Tuberculosis Institute, Yangon were 5% and 32.4% respectively in 2002 [8]. Most disease control programmes are designed to deliver exclusively through government channel. Many of the notified cases have come to NTP after seeking care from one or more private providers. Private health sectors are often more preferred by patients because of convenient hours and more personalized service. They can offer a variety of services and often more accessible to the general population and are frequently the first contact with health system when a person feels ill [9].

A recent study in Yangon, Myanmar showed that 73.3% of patients first sought treatment at two to five general practitioners' clinics before seeking care at township TB Centre and the duration of treatment was ranging from 2 days to one and half year [6]. Delay in achieving correct diagnosis and effective treatment may lead to development of drug resistance [10].

The present study showed that MDR-TB rate of all new smear positive pulmonary TB patients (140 direct and 140 indirect patients) was 5.36 % (15/280) and any anti-TB drug resistance rate was 16.43% (46/280). In spite of a decrease in any anti-

TB drug resistant rate, MDR-TB rate is almost the same when it is compared to 2002 study. These findings pointed that drug resistance still plays as a serious threat to NTP.

The most common resistant drug of direct patients was isoniazid (14, 10%) and the second resistant drug was streptomycin (6, 4.29%). Among indirect patients, the most common resistant drug was isoniazid (26, 18.57%) and the second was rifampicin(16, 11.43%). Rifampicin and isoniazid are the main bactericidal drugs and their resistance accounts for multi drug resistance (Table 2).

Demographic data of direct and indirect patients showed that the mean age of the direct patients and indirect patients were 33.0 years and 36.63 years respectively and most of the patients were within the working age group (20-59 years). Men were found to be more affected than women comprising of a large percentage of skilled workers (Table 1). Therefore, the impact of TB on that population leads to a big socio-economic burden. Moreover, there is a greater risk of transmission of TB to the community and even worse if the disease is hard to treat drug resistant case.

The relevant history of indirect patients documented that general practitioner's clinic was the most common place for first medical consultation before seeking care at NTP. The mean duration of treatment at private sector was 40.79 days ranging from 22 days to two years. Six (4.2%) of these patients have been treated with anti- TB drugs for less than one month by private practitioners. The most common investigation done at private clinics was chest X-ray (50%) and sputum examination was done only on 21.13% cases. Sputum microscopy is the main diagnostic tool for TB and categorization of patients for choice of appropriate treatment regimen is depending upon sputum smear results. Therefore, there are reasons to be delay and inadequacy in anti- TB treatment and diagnosis of private practitioners who have not kept current anti-TB therapy.

Table 3 and 4 showed that both any anti-TB drug resistance and MDR-TB rate were significantly higher in indirect patients than those of direct patients. The mean duration of treatment at private clinics was 40.79 days with the range of 22 days to 2 years. These findings indicated that indirect patients who had more delay in achieving anti-TB treatment than direct patients attending NTP directly or after being treated at private clinics for less than three weeks are more likely to be resistant to anti-TB drugs. In order to shorten the provider's delay, all medical practitioners especially in the private sectors, should be aware of the importance of early diagnosis and proper management of TB. Linking private and public sectors in TB treatment is an important task for TB Control Programmes to improve treatment outcome of TB patients who initially seek care in private sector.

The present study highlighted that drug resistance plays as a bacteriological factor for patients who have considerable delay while seeking treatment at private sector before reaching public health service. As NTP Myanmar is encouraging a private-public partnership in implementation of DOTS with the efforts like continuing medical education program, training of GPs on DOTS management, promoting of proper referral system between NTP and GP, further studies should be carried out in future to access the success of these efforts among the private practitioners..

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