

# The rates of sputum conversion among new smear positive open pulmonary tuberculosis patients treated under directly observed treatment, short course strategy

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## ABSTRACT

**الأهداف:** تقييم فعالية دورة العلاج القصيرة المراقبة المباشرة لمعدل تحول البلغم الشهري في الشهر الأول، والثاني، والثالث لدى المرضى الذين شخضوا بالسل الرئوي ودراسة سلوك الآفات على صور أشعة الصدر وعلاقتهم بمسحة البلغم الإيجابية وتسجيل ردة فعل اختبار السلين مانتو للجلد على مرضى السل الرئوي.

**الطريقة:** أجريت دراسة أتراب استباقية على 100 مريض سل رئوي مفتوح تم علاجهم طبقاً لدورة العلاج القصيرة المراقبة المباشرة في مركز السل، مجمع الدمام الطبي، الدمام، المملكة العربية السعودية خلال الفترة من يوليو حتى ديسمبر 2010م. تم دراسة صور الصدر، والآفات وعلاقتها مع الدرجات الإيجابية للبلغم. كما تم اختيار عينات البلغم (حالة الصوم) على 3 أيام بواسطة مسحة المجهر في الشهر الأول، والثاني، والثالث. وبالنظر إلى دورة العلاج القصيرة المراقبة المباشرة امتدت فترة العلاج لأربعة أسابيع للمرضى الإيجابيين وذلك بعد شهرين من استخدام تقنية السلين بروتين المشتق.

**النتائج:** كان معدل تحول البلغم الكلي في الشهر الأول (56%)، الثاني (76%)، الثالث (94%). تم تسجيل تفاعل اختبار الجلد أكثر من 10 ملمتر في مرضى الدراسة 97%.

**خاتمة:** أن دورة العلاج القصيرة المراقبة المباشرة تعد طريقة مناسبة للتحويل الأولي والمتطور للمرضى الإيجابيين لكسر سلسلة التفاعل والتي تعد مهمة وبأثباتها للسيطرة والتخلص والقضاء على السل الرئوي.

**Objectives:** To evaluate effectiveness of directly observed treatment short course (DOTS) by monthly sputum conversion rates at first, second, and third month in newly diagnosed patients of pulmonary tuberculosis (TB) (category-1), and to study patterns of lesions on chest radiographs and their correlation to smear sputum positivity, also to record reaction to Mantoux tuberculin skin test (TST) in active TB patients.

**Methods:** This prospective cohort study was conducted among 100 newly diagnosed patients of open pulmonary tuberculosis CAT-1, admitted and treated under DOTS, at the Tuberculosis Center, Dammam Medical Complex, Dammam, Kingdom of Saudi Arabia between July to December 2010. Chest radiographs were studied for the patterns of lesions and their correlation to the grades of sputum positivity. Three fasting state sputum specimens were tested on 3 consecutive days by direct smear microscopy at first, second, and third month. As per DOTS, intensive phase treatment was extended for another 4 weeks in those still positive at the end of 2 months. Mantoux TST was performed on all patients with tuberculin purified protein derivative-RT-23 2 tuberculin units.

**Results:** The overall sputum conversion rate observed at the first month was 56%, 76% on the second month, and 94% on the third month. Reaction to TST of more than 10 mm was recorded in most of the studied patients (97%).

**Conclusion:** The DOTS is an appropriate strategy for early and progressive conversion of smear positive patients to break the chain of infection, which is epidemiologically important for the control, elimination, and eradication of TB.

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Tuberculosis (TB) continues to be a major health problem, and ranges among the leading causes of morbidity and mortality worldwide.<sup>1,2</sup> In 2011, there were 8.7 million new cases and 1.4 million deaths from the disease, with >95% of these deaths taking place in low- and middle-income countries.<sup>3</sup> Early and accurate diagnosis and prompt effective treatment are fundamental in reducing morbidity, mortality, and curtailing spread of infection.<sup>1</sup> The World Health Organization (WHO) in April 1993, declared global emergency, and directly observed treatment short course (DOTS) was launched with clear goals. According to the WHO global TB control report 2009, the main targets for global TB control are: the rates of new cases of TB, which should be seen falling by 2015; prevalence of TB and death rates should be halved by year 2015 when compared with 1990; at least 70% of new smear positive cases should be detected and treated under DOTS; and at least 85% of new smear-positive TB cases should be successfully treated.<sup>4,6</sup> Infection from *Mycobacterium tuberculosis* results in the death of 3 million people worldwide per annum, of which an estimated one thousand are in the Kingdom of Saudi Arabia (KSA). The WHO has set a target for successful treatment of 85%, however, Saudi Arabia is currently not meeting that target.<sup>7</sup> A recent study reported that the annual incidence rate of TB in KSA ranged between 14 and 17/100,000. For Saudis, the rate ranged between 8.6 and 12.2/100,000. Non-Saudis had 2-3 times higher incidence.<sup>8</sup> In 1992, the Ministry of Health established a National Tuberculosis Control Committee to implement a control program throughout KSA.<sup>7</sup> The National Tuberculosis Control Program (NTBCP) has been implemented in phases since 1970 and the DOTS strategy was adopted since early 1990's. It includes initial intensive phase of 2 months with 4 drug combination (2H [isoniazid]+2R [rifampicin] +2PZA [pyrazinamide] + 2E [ethambutol]), and 4 months with 2 drugs (4H [isoniazid] + 4R [rifampicin]) as continuation phase.<sup>7,9</sup> The main objectives of the NTBCP in KSA was to decrease the incidence of sputum smear positive TB in KSA to 1/100,000 by the year 2010, and increase the case detection of smear positive to more than 85-90% by year 2005, and increase a cure rate of 90% by 2005.<sup>10</sup> The objectives of the present study were: to evaluate effectiveness of DOTS by monthly sputum conversion rates at the first, second, and third month in newly diagnosed patients of pulmonary TB (category [CAT]-1); to study patterns of lesions on chest radiographs and their correlation to smear sputum positivity; and to record reaction to Mantoux tuberculin skin test (TST).

**Methods. Study setting and study population.** This prospective cohort study was started among 104 (age between 14-70 years) newly diagnosed smear positive cases of pulmonary TB admitted at the Tuberculosis Centre of Dammam Medical Complex between July to December 2010. This is a government referral center for the whole of Eastern region of KSA, where all patients of open TB are received from all government and non-government health facilities. Only newly diagnosed smear positive pulmonary TB CAT-1 were included, and those very ill, or CAT-II and CAT III were excluded. The Mantoux TST was performed and read by a single technician at 72 hours. Out of the 104 patients, only 100 patients completed the study as 4 patients were excluded due to compelling reasons mentioned. Among these first patient was a 40-year-old Saudi male who developed severe drug induced hepatic dysfunction, the second patient was a 34-year-old Nepali male patient who underwent emergency lung surgery for having life threatening hemoptysis, the third patient was 30-year-old Indonesian female who developed unusual paradoxical reaction at 3 weeks of treatment and was given adjuvant steroids, and the fourth patient was a 52-year-old Thai male who developed pneumothorax with respiratory failure and was shifted to the intensive care unit (ICU). No ethical approval was required because it was within our recommended routine work.

**Drug combination and dosage.** Selected patients were treated under DOTS strategy with 4 drugs for 2 months (2H+2R+2PZA+2E) as initial intensive phase. The intensive phase of treatment consisting of H3R3Z3E3 is continued for another 4 weeks if the patients are positive at the end of the second month as per DOTS strategy. Weight wise dose given is H5 mg/kg, R10 mg/kg, Z30 mg/kg, and E25 mg/kg. During follow-up, 3 early morning fasting state sputum specimens are collected over 3 consecutive days for Ziehl Neelsen staining, and direct smear microscopy at the first, second, and third month.

**Calculation for sputum conversion.** For calculating sputum conversion rate for new sputum smear positive patients only, all those who converted at the end of IP (intensive phase) at the end of 2 months (n=76), and at the end of EP (extended intensive phase) at the end of 3 months (n=18) should be added to obtain the numerator. In the present study, 94% (n=94) patients at the end of the third month were smear negative.

$$\text{Sputum conversion rate} = \frac{94 \text{ (Number of sputum smear-positive converted to sputum smear negative at the end of intensive phase)}}{100 \text{ (Total number of sputum smear positive patients initiated on DOTS treatment)}}$$

Data analysis was carried out using Microsoft Excel 2002 (Microsoft Corporation, Seattle, WA, USA) and Statistical Package for Social Sciences version 16 (SPSS Inc, Chicago, IL, USA). Results were expressed as absolute frequencies (n) and percentages (%). Pearson chi-squared test was used to compare sputum conversion rate at baseline versus second and third month. A  $p < 0.05$  was considered statistically significant.

**Results.** Most patients (n=89 [89%]) belonged to the non-Saudi expatriate working force (63 males and 26 females), and most of the non-Saudi females were housemaids. There were 11 Saudis (9 males and 2 females). The age of studied patients ranged between 14 and 70 years. The rates of sputum conversion observed in this study at month one, 2, and 3 are illustrated in Table 1. Progressive rates of sputum conversion found in our study at the first month was 56%, 20% on the second month, and 18% on the third month. The overall conversion rate at the end of the third month was 94%. Compared to month 2, the conversion rate was significantly higher at month one ( $p < 0.001$ ) especially in those with low sputum positivity grades at the baseline; a similar trend was observed when compared with month 3 ( $p < 0.001$ ). All 100 patients studied had abnormal chest x-rays, evidence of unilateral lung involvement was observed in 42% (n=42) patients, and bilateral in 58% (n=58) cases. Most (n=63 [63%]) had lesions with cavitation. The grades of sputum

positivity were relatively higher in those with cavitation on chest x-rays. Chest radiographic findings showed variable degrees of cavitation. All patients with 3+ (n=44) sputum had extensive cavitation in one or both lungs. Also, 19 out of 28 patients with grade 2+ and 5 out of 23 patients with grade 1+ had cavitory lesions. This trend towards higher positivity of Mantoux test with pulmonary cavitation was statistically significant ( $p < 0.001$ ). Mantoux TST was performed on all 100 patients with active TB with tuberculin purified protein derivative (PPD) RT-23 2TU, and a reaction of more than 10 mm induration was recorded in most (97%) of the patients (Figure 1).

**Discussion.** There have been many studies on this subject throughout the world, but none in Saudi Arabia since the launching of the DOTS strategy in the early 1990's in KSA. Therefore, we contemplated this prospective cohort study to assess the role and effectiveness of the DOTS strategy at our DOTS center. The overall rates of sputum conversion observed in our study were 56% in the first month, 76% in the second month, and 94% on the third month. Our results are comparable with some of the previous studies carried out on the same category of patients.<sup>11-13</sup> Many previous studies used 2 early morning sputum samples to find out the true negativity.<sup>14</sup> However, in the present study, we took 3 samples to find out the true negativity, which is more convincing evidence of true negativity as per guidelines of the Saudi NTBCP.

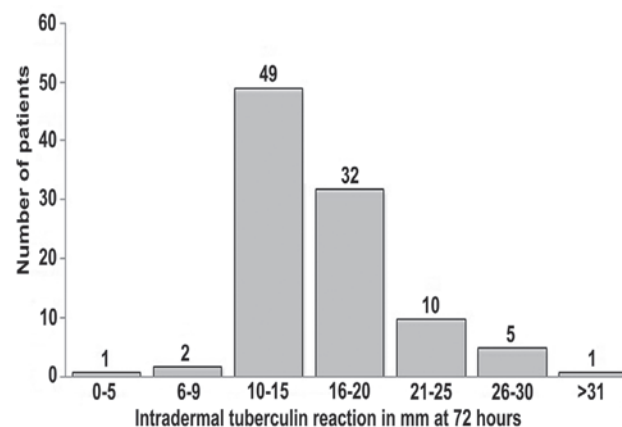
A direct relationship was observed between the grades of sputum positivity and presence of cavitation on the chest radiographs. Therefore, having high bacillary load on direct smear microscopy, they are

**Table 1** - Sputum positivity of the selected patient's at the beginning and end of months one, 2, and 3.

Sputum grades	Baseline	End of month				
		3+	2+	1+	Scanty	Negative n (%)
<b>Month 1 (n=100)</b>						
3+	44	0	16	12	2	14
2+	28	0	0	4	6	18
1+	23	0	0	0	4	19
Scanty	5	0	0	0	0	5
Negative						(56.0)
<b>Month 2 (n=44)</b>						
3+	0	0	0	0	0	0
2+	16	0	0	8	5	3
1+	16	0	0	0	11	5
Scanty	12	0	0	0	0	12
Negative						(20.0)*
<b>Month 3 (n=24)</b>						
3+	0	0	0	0	0	0
2+	0	0	0	0	0	0
1+	8	0	0	0	4	4
Scanty	16	0	0	0	2	14
Negative						(18.0)†

\* $p < 0.001$ , month one versus month 2, Pearson chi-squared test,

† $p < 0.005$ , month one versus month 3, Pearson chi-squared test



**Figure 1** - Size of induration of Mantoux test 2 tuberculin units of purified protein derivative.

more infectious. Response to DOTS was gauged by clinical, radiological, and bacteriological improvement. The goal of anti TB treatment is bacteriological cure, therefore, the best way to monitor treatment outcome in smear positive cases (CAT-1) is by checking sputum conversion from positive to negative on Ziehl Neelsen staining direct smear microscopy at monthly intervals. A slow conversion rate was observed at the first month (56%), especially in those with high grade smear positivity, which is in line with previous studies.<sup>7-9</sup> The highest conversion rate was observed at the completion of 2 months and onwards, in epidemiological terms, it means decreased infectivity. Those with initial high grade sputum positivity required extension of IP anti TB treatment beyond 2 months, as compared to those with low grade positivity at baseline. This observation is shared by almost all the studies carried out so far with little variation on the percentage requiring extended IP.<sup>11-13,15,16</sup> A direct relationship was observed in our patients between grades of sputum positivity and cavitation on chest x-rays were reported previously as well,<sup>17</sup> and therefore more stringent infection control measures are to be taken in the management of such cases with high bacillary load.

Reaction to Mantoux TST with PPD RT-23 2 tuberculin units (TU) in the large majority (n=97, 97%) of these patients with active TB recorded more than 10 mm induration. This observation validates the continued utility of TST in clinical practice as a cheap and reliable diagnostic tool in patients of active TB in this region, until a new quick, reliable, and cheap test is recommended by the WHO and the International Union Against Tuberculosis (IUAT).

In the present study, 6 (6%) patients remained positive at the end of the third month, among these, 4 (4%) patients whose sputum smear examination was positive of 3+ grading at baseline, remained positive (scanty) at the end of the third month, and 2 (2%) remained positive (scanty) from those who had 2+ sputum grade at baseline. This means that patients with high grade sputum positivity (3+ and 2+) require more often extension in the IP, and thus are more prone to treatment failure. Among the 6 patients who were still positive at the end of the third month, 2 had diabetes mellitus. Patients with an undesirable combination of tuberculosis and diabetes mellitus are known to have slow response and delayed sputum conversion, high drug resistance rates, and thus more chances of treatment failure. Therefore, with regard to undesirable relationship of diabetes and tuberculosis when one is present, clinicians should look for the other.<sup>18-20</sup>

The major limitation of this study was the limited number of selected patients, and smear positivity at the third month was not validated with *Mycobacterial* culture as bugs could be dead bacilli.

In conclusion, whereas a permanent patient oriented NTBCP is required in every region of the world for this chronic disease, the DOTS strategy must remain its integral part. Our study has shown DOTS being very affective for early and progressive conversion of smear positive patients to break the chain of infection, which is epidemiologically very important for control, elimination, and finally eradication of TB. More stringent infection control measures are required in those with cavitatory lesions being more infectious with heavy bacillary load. Tuberculin skin test still remains one of the cheap and reliable tool for the diagnosis of active TB in clinical practice, especially in resource poor countries until it is replaced with a new, cheaper, and more reliable test. There is a need for more such studies in large numbers of patients at other DOTS centers in the Kingdom to gather a local pool of experience.

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