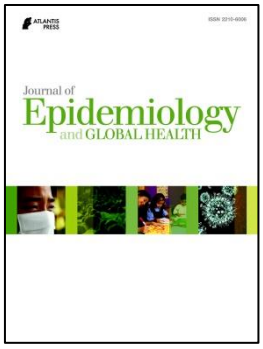

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Patterns of antituberculous drug resistance in Eastern Saudi Arabia: A 7-year surveillance study from 1/2003 to 6/2010

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KEYWORDS
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Abstract *Objective:* To examine the patterns of antituberculous drug resistance of *Mycobacterium tuberculosis* in patients with pulmonary and extra-pulmonary tuberculosis in the Eastern province of the Kingdom of Saudi Arabia.

Methods: This is a retrospective study of antibiotic susceptibility of 1681 non-repetitive *M. tuberculosis* isolates from 1/2003 to 6/2010.

Results: Of the total patients, 41% ($n = 687$) were Saudis and 59% ($n = 994$) were non-Saudis. The pulmonary and extra-pulmonary specimens constituted 68% ($n = 1148$) and 32% ($n = 533$), respectively. The incidence of resistance was 15.5% to one or more of anti-tuberculosis drugs. The resistance rates to first-line drugs were as follows: streptomycin (10.4%), INH (9.8%), rifampicin (1.5%) and ethambutol (1.0%). Multi-drug resistant tuberculosis was present in 1.4% ($n = 24$) of the sample.

Conclusion: INH resistance in this study was relatively high, whereas the rate of MDR-TB was low. A rate of MDR-TB observed in this study was 1.4%. Thus, an empiric four-drug therapy is required to treat patients with tuberculosis in this area of Saudi Arabia.

Abbreviations: MDR-TB,; multi-drug resistance tuberculosis,; SDR-TB; single drug resistance tuberculosis,; NTBCP,; national tuberculosis control program,; DST,; drug sensitivity test.

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1. Introduction

Tuberculosis (TB) is one of the oldest diseases known to man and remains a major health problem throughout the world; it is a major cause of morbidity and mortality. According to the Centers for Disease Control and prevention (CDC), TB incidence in the United States reached 13,767 cases in 2006 with a 3.2% decline from 2005 [1]. The incidence of TB in 2006 was the lowest recorded rate since 1953; however, the rate of decline has slowed since 2000 [1]. An initial reversal of downward trend was attributed to the AIDS epidemic, the emergence of drug resistance, and the involvement of foreign-born persons and racial/ethnic minority populations [2–4]. In India – the largest populated country of the world – HIV epidemic has also contributed to increased incidence of drug resistance [5]. Drug resistance of *Mycobacterium tuberculosis* showed marked geographic variation from one country to the other. The latest reported global rates of single-drug resistance tuberculosis (SDR-TB) ranged from 1.6% to 33.3% [6]. In Saudi Arabia the pattern of *M. tuberculosis* resistance is also dependent on the region of reporting. The range of drug resistance rates against isoniazid reported from various regions of Saudi Arabia has been 3.4–19.4% in Riyadh (central region), 10.3–28% in Jeddah (western pilgrims hub), 41% in Jizan (near Yemen border), 6.5% in Taif and 6–12.5% in Dammam eastern area; resistance rates against rifampicin has been 9% in Riyadh, 5.1–23.4% in Jeddah; 15.3% in Taif; 20% in Jizan and 0.2–7.5% in Dammam area. Rates of MDR-TB ranged between 3.7% and 11.85% in Riyadh; 44% in Jizan and 0.7–6% in Dammam area [7–10]. There has been no recent large-scale sequential study on this topic in Saudi Arabia. Thus, this retrospective study was undertaken in the Eastern province of Saudi Arabia for a period of seven sequential years from 2003 to 2010.

2. Materials and methods

The regional laboratory and blood bank of Dammam medical complex received various specimens for TB culture from different centers in the Eastern province. These specimens included sputum, pleural fluid, pericardial fluid, ascitic fluid, cerebrospinal fluid, urine, and fine needle aspiration and tissue biopsies. Specimens were processed for acid-fast bacilli smear (AFB) using Ziehl–Neelsen stain, and were processed for *M. tuberculosis* cultures and susceptibility to first-line anti-TB drugs. All specimens were processed according to the specimen type. Sputum and other respiratory specimens were decontaminated and concentrated by NALC–NAOH method. Sterile body fluids were centrifuged and deposit was used for the culture. Culture and susceptibility testing was done using MGIT medium and BACTEC MGIT 960 instrument (Becton, Dickinson and Company, 7 Loveton Circle, Sparks, Maryland 21152, USA) [11]. MGIT media consisted of Middle Brooke medium with PANTA (antibiotic mixture) and growth supplement. After inoculation tubes were introduced into the BACTEC MGIT 960 instrument and were kept as recommended for 42 days protocol, identification of *M. tuberculosis* complex (*M. tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microoti*) was done by probetec instrument using probetec ET CTB kit (Becton, Dickinson and Company, 7 Loveton Circle, Sparks, Maryland 21152, USA) [11].

Antibiotic susceptibility testing for rifampicin, streptomycin, INH, and ethambutol was done by BACTEC MGIT 960 AST system. A modified Middle-Brook 7H9 Broth, which supports the growth and detection of mycobacterium, was used for susceptibility testing. The critical concentrations of these drugs were as follows: streptomycin 1.0 μg/ml, INH 0.1 μg/ml, rifampicin 1 μg/ml, and ethambutol 5 μg/ml. A strain which showed growth of 1% or more at critical concentration was identified as resistant (BACTEC MGIT 960 AST system User's Manual) [12]. *M. tuberculosis* strain resistant in vitro to both INH and rifampicin was considered multi-drug resistant (Becton, Dickinson, Sparks, MD, USA, BD diagnostics-DST Liquid Media Product and Procedure Manual) [13].

3. Results

During the study period, a total of 1681 non-repetitive *M. tuberculosis* isolates were included. Saudis constituted 41% ($n = 687$), while 59% ($n = 994$) were non-Saudis. Male to female ratio in Saudi patients was 43% ($n = 296$) to 57% ($n = 391$). In non-Saudis there was a male predominance with 71% ($n = 703$) being males and 29% ($n = 291$) females. *M. tuberculosis* isolates were obtained from pulmonary specimens 68.3% ($n = 1148$) and 31.7% ($n = 533$) were of extra-pulmonary origin (Table 1).

The incidence of resistance to any one antituberculous drug was 15.5%. However, resistance rates to individual drugs were as follows: streptomycin (10.4%), INH (9.8%), rifampicin (1.5%) and ethambutol (1.0%), respectively (Table 1). Comparing Saudis and non-Saudi patients, there was no statistically significant difference in the resistance rate to single-line agents (Table 1). Drug resistance

Table 1 Single drug resistance (non-Saudis vs. Saudis).

	Non-Saudi	Saudi	*p*-Value	All
No. %	994 (59.1%)	687 (40.9%)		1681
Streptomycin	98 (9.9%)	77 (11.2%)	0.47	175 (10.4%)
INH	97 (9.8%)	67 (9.8%)	1.0	164 (9.8%)
Rifampicin	14 (1.4%)	12 (1.7%)	0.58	26 (1.5%)
Ethambutol	13 (1.3%)	4 (0.6%)	0.171	17 (1.0%)
Pulm.:extra pulmonary	727:267	421:266	<0.001	1148:533
	73.1:26.9%	61.3:38.7%		68.3:31.7%

Table 2 Extra-pulmonary vs. pulmonary tuberculosis.

	Extra-pulmonary	Pulmonary	*p*-Value
Streptomycin	41 (7.7%)	134 (11.7%)	0.036
INH	58 (10.9%)	106 (9.2%)	0.165
Rifampicin	7 (1.3%)	19 (1.7%)	0.67
Ethambutol	2 (0.4%)	15 (1.3%)	0.178
Saudi:non-Saudi	266:267	421:727	<0.001
	49.9:50.1%	36.7:63.3%	

rates in pulmonary and extra-pulmonary tuberculosis were similar with no significant difference (Table 2). Multi-drug resistance tuberculosis (defined as resistance to INH and rifampicin) was 1.4% (n = 24).

4. Discussion

TB continues to be a major concern as a public health problem throughout the world. On one hand, TB has adverse economic and social bearings on the individual and the society. On the other hand, TB causes increased demand on health care systems for the provision of expertise and constant supply of treatment. The emergence of HIV in 1981 had contributed to the increase in the incidence of pulmonary tuberculosis worldwide and the emergence of MDR-tuberculosis [14]. Worldwide there are approximately 8 million new cases and 3 million deaths from tuberculosis each year [15].

NTBCP in Saudi Arabia was launched in phases in 1997 in collaboration with WHO's Eastern Mediterranean regional office for Middle East. The goal was to lower the incidence rate of smear positive pulmonary tuberculosis to 1/100,000 population among nationals by the year 2010 [16]. In Saudi Arabia the incidence of pulmonary tuberculosis declined from 30.5/100,000 in1987 to −10.2/100,000 in 2002, while the incidence of extra-pulmonary tuberculosis declined from 6.5/100,000 in 1987 to 4.3/100,000 in 2002 [16]. According to a recent study from the Eastern province, the incidence of culture positive tuberculosis per 100,000 populations was 5.2 in 1989, 3.5 in 1993 and 7.6 in 2003, showing an increasing linear trend over the study period [8]. In the same study, the rate of resistance to any first-line agent was 28% [8]. There is a large variation in antituberculous drug resistance between different countries, regions and cities both worldwide and within countries. In this context, knowledge of the susceptibility patterns and prevalence of drug resistance in a given area become essential to tailor initial intensive phase therapy.

In the Kingdom of Saudi Arabia the resistance rates to isoniazid alone vary from one region of the country to another. This has been 3.4—19.4% in Riyadh (central region) [7], 10.3—28.7% in Jeddah (western region) [17], 41% in Jizan (southern region), 6.5% in Taif (southwest region) [7], and 6—12.5% in Dammam area [8,18]. In the current study, isoniazid (1 μg/ml) resistance rate was 9.8% and is in line with the findings in previous studies from the same region. Thus, empiric initial intensive phase anti TB therapy should include four drugs.

The second most common resistance pattern noted in the study was streptomycin (10.4%). Streptomycin resistance in Saudi Arabia has been variable and reported figures are: 15.9% in Taif, 22.7% in Jeddah [7], 1—7% in Dammam area [8,18], and 8.8% in Riyadh [19].

Resistance rate to rifampicin in the study was 1.5%, while previously reported rates in Dammam area were 0.2—7.5% [8,18]. Thus, rifampicin resistance rate falls within the previously reported range. This range is lower than the rates of

rifampicin resistance in Riyadh of 9%, Jeddah 5.1—23.4%, Taif 15.3% and Jizan 20% [6].

According to the WHO report, the rate of MDR-TB in Saudi Arabia is 3.4% [20]. However the rate of MDR-TB in Saudi Arabia is variable depending on the date of the study and region of the country, as well as the proportion of non-Saudi population in each study [7—10]. In Riyadh, MDR-TB ranged between 3.7% in 1979—1982 and 11.85% in 1986—1988 [6]; on the other hand, a very high rate of MDR-TB (44%) was reported from Jizan (southern region) adjacent to Yemen [7]. In Dammam (Eastern region) where this study took place, MDR-TB rates previously reported were between 0.7% and 6% [8,18]; the rate of this range is consistent with the rate of 1.4% in this study.

The variability in the resistance rates of tuberculosis in Saudi Arabia is dependent on multiple factors as mentioned above [7—10]. However, no significant difference in resistance rates were found between Saudis and non-Saudi patients. Many studies [6,16] from Saudi Arabia did not address whether the site of isolation (pulmonary or extra-pulmonary) of *M. tuberculosis* has any impact on the resistance pattern. In a small but recent study in the Eastern region, no difference was shown in the resistance rates between pulmonary and extra-pulmonary isolates [8]. Similarly in the current study, there was no significant difference in drug resistance rates between those having pulmonary or extra-pulmonary tuberculosis.

In conclusion, the pattern of anti-TB drug resistance to first-line agents was examined in this study over a period of 7 years. The resistance rates to isoniazid, rifampicin and MDR-TB were low in this area compared with other areas, but consistent with the findings reported from the same area of the Kingdom. Having a central reference Mycobacteriology laboratory would be ideal to monitor the quality as well as uniformity of materials and methods used in the culture and susceptibility testing. Based on this study, the use of four anti-TB therapies are required empirically to treat affected patients.

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