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A retrospective study of tuberculosis prevalence amongst patients attending a tertiary hospital in Riyadh, Saudi Arabia

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ABSTRACT

Tuberculosis (TB) is a public health challenge that affects all genders and age groups and is a single leading infectious disease killer globally. We retrospectively investigated the prevalence of TB and anti-TB drug resistance among patients treated at the Prince Sultan Military Medical City (PSMMC) between the years 2000 and 2017. Patient demographic variables and drug susceptibility test results were obtained from TB notification records located in the TB laboratory at PSMMC. A total of 58,141 records were reviewed of which 1123 (2%) specimens were positive for *Mycobacterium tuberculosis.* Of the positive, 621 (55%) were from pulmonary specimens. Males over the age of 15 years accounted for 60% of the positive specimens. Drug resistance to at least one drug was detected in 90 (8%) of which 60 (5.3%), 24 (2%) 6 (0.5%) patients were mono-drug-resistant, poly-drug resistant and multidrug resistant (MDR-TB) respectively. Resistance to isoniazid and streptomycin were the most frequently found among first-line tuberculosis drugs, accounting for 4.5% and 3.8% of drug resistance cases respectively. Our findings show low prevalence of tuberculosis and multidrug resistant TB among patients treated at PSMMC over a 17-year period. Nationwide assessment is needed to get a clear picture of the TB burden across Saudi Arabia and inform national policies for eradication of TB.

1. Introduction:

Mycobacterium tuberculosis (MTB) is a causative agent of tuberculosis (TB) [26]. It mainly infects the lungs developing into pulmonary TB (PTB), but it can also invade other body sites causing extra pulmonary TB (EPTB) or a disseminated disease [17,26]. Not all people infected by *M. tuberculosis* develop the disease, but up to 10% of infected immunocompetent individuals will develop tuberculosis within two years of infection [22]. However, the probability of an infection progressing is higher among people with human immunodeficiency virus (HIV) infection [21].

The World Health Organization (WHO) has set a target to reduce the TB incidence rate (new cases per 100,000 of population per year) to 4–5% per year, and to lower TB mortality rate to 10% per year by 2020, [13]. This report revealed that in 2017 around 10 million people developed. TB of which 5.8, 3.2, and 1 million were men, women and children respectively, representing a 2% drop in global TB incidence [13]. The number of TB deaths among HIV-negative people fell by 29% from 1.8 million in 2000 to 1.3 million in 2017 and the number of TB deaths among HIV-positive people dropping by 44% from 534,000 in 2000 to 300,000 in 2017 [13].

The Prince Sultan Military Medical City (PSMMC), Riyadh, Kingdom of Saudi Arabia, is a tertiary-centre serving the workers of the Ministry of Defence and associated agencies in different parts of the country. TB is endemic in Saudi Arabia [1] though the incidence rate dropped from 18 cases per 100,000 people in 2002 to 10 cases per 100,000 in 2017 [13]. PSMMC has the vision to become a centre of excellence for the diagnosis and treatment of TB in Saudi Arabia. Therefore, the objectives of this retrospective study were to ascertain the prevalence of pulmonary and extra-pulmonary TB among patients managed at PSMMC. We sought to determine the annual positivity rate of TB, the demographic characteristics of tuberculosis patients, and to estimate the magnitude of drug resistance in our patient community.

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2. Material and methods

2.1. Data collection and procedures

This study was conducted in the TB Laboratory in PSMMC. TB notification records were utilized to identify all recorded patients who were confirmed TB cases in the period from January 2000 to December 2017. The information was carefully retrospectively reviewed paying particular attention to the participant demographic variables (age, sex, year of treatment, sample types, and drug susceptibility test (DST) results). Patients with pulmonary and extra-pulmonary disease were considered, and only those patients with full information recorded in the TB notification register were included for analysis. Five age groups were designated for this investigation, which were 0–14, 15–29, 30–43, 44–60 and over 60 years old. Risk factors for drug resistance could not be evaluated as there was insufficient data in the charts.

2.2. Laboratory methods

Isolation and identification of *Mycobacterium tuberculosis* were performed following the laboratory standard operation procedure. The process included decontamination and digestion of non-sterile samples, culturing of concentrated samples on solid (Lowenstein-Jensen) and liquid (Bactec Mycobacteria Growth Indicator Tube (MGIT)) media. Smears were also prepared and examined for the presence of acid fast bacilli using fluorescent and conventional AFB stains (Auramine and Kinyoun stain). PCR was done using Xpert MTB/RIF assay (Cepheid, USA) to help identify *Mycobacterium tuberculosis* complex and simultaneously detect Rifampicin resistance. Detailed methods were published previously by Al-Ateah et al. [2].

2.3. Statistical analysis

The data was analyzed using Microsoft Office Excel software programs, and IBM SPSS Statistics for Macintosh, Version 23 (IBM Corp., Armonk, N.Y., USA), for descriptive statistics such as mean, sum and percent distribution. The difference between variables such as age groups, and sex of subjects was computed by using a Chi Square statistic. Significance was considered at a *P-value* of less than 0.05. The percentage of resistance was calculated by dividing the number of resistant isolates tested for a drug or a combination of drugs to the total number of patients tested. Temporal trends were evaluated regarding resistance to each drug alone or in combination with other drugs, as well as trends in multi-drug resistance.

3. Results

A total of 58,141 presumptive TB specimen test records were reviewed across a 17-year period (2000–2017) with annual range was 2796 to 4085 specimen tests. 1123 (2%) of the records had positive TB result with annual positivity rate ranging from 1.21% to 4.60%. There was a sharp drop in positive cases (4.6–2.2%) between 2000 and 2001, after which the positivity rate fluctuated between 1% and 2.5% (Fig. 1)

Among positive TB cases, 621 (55%) and 502 (45%) were pulmonary- and extra-pulmonary TB respectively from extra-pulmonary specimens. The positive TB cases were detected in sputum (n = 543), bronchoalveolar lavage (n = 60) and tracheal aspirate (n = 18) specimens. Extra-pulmonary TB was detected in tissues and biopsies (n = 189), fine needle aspiration (n = 92), abscesses (n = 80), abdominal fluids (n = 20) breast fluid (n = 2), cerebrospinal fluid and spinal fluid (n = 20), urine (n = 5), knee fluid and synovial fluid (n = 6), pericardial fluid (n = 3), peritoneal dialysis (n = 12), pleural fluid (n = 26), spleen fluid (n = 1) and various other aspirates (n = 46).

Males accounted for 672 (60%) of the TB positive cases. When stratified by age, the highest number of cases were found among ≥60 years old, 492 cases (44%) and the lowest positive rate was found in the youngest age group < 14 years old, (2%) (Table 1).

Among the 1123 *M. tuberculosis* (MTB) positive cultures, 1033 (92%) isolates were susceptible to all of the first line anti-TB drugs, whilst 90 (8%) were resistant to at least one drug. Of the drug resistant cases, 60 (5.3%), 24 (2%) and 6 (0.5%) were mono-drug-resistant, poly-drug resistant and multidrug resistant (MDR-TB) respectively. The rate of drug resistance to tuberculosis has decreased over the 17- year period with the highest rate recorded was in the year 2000 (Table 2).

Resistance to isoniazid (INH) was the most common (4.5%) followed by streptomycin (STR) (3.8%), pyrazinamide (PZA) (1.60%), rifampicin (RIF) (1.0%), and ethambutol (EMB) (1.0%). Isoniazid resistance was the most common (n = 23) among the mono-resistant isolates, followed by streptomycin. Combination of isoniazid and streptomycin resistance (n = 16) was at the highest proportion among the poly-resistant isolates. Six isolates were MDR-TB cases while 4 isolates were resistant to all first line anti-tuberculosis drugs (Table 3).

4. Discussion

This study presents the findings of the first retrospective study conducted in PSMMC to determine the prevalence of TB and measure the rate of drug-resistant tuberculosis. We show that the prevalence of TB was generally low among the cases managed in this institute over the study period. The highest TB positive rate was recorded in the year 2000, possibly due to the hospital receiving *M. tuberculosis* positive samples from other military clinical departments throughout the Kingdom during this year.

Much as pulmonary TB is the most common globally, our study showed no significant difference in numbers between pulmonary cases and extra-pulmonary TB cases (P > 0.05) recorded at PSMMC. This finding is consistent with [8] study and inconsistent to [5,9], who found that pulmonary tuberculosis was more common (80–90%), than extra-pulmonary TB (10– 20%).

The results showed that most of the pulmonary TB cases were associated with sputum specimens (48%). Lymph node and other tissues specimens were the major site of extra-pulmonary infection (17%). In terms of the gender of TB patients, 60% of isolates were from males, which is consistent with the WHO's global surveillance report [13] as well as with other studies conducted in Saudi Arabia [1,4,5,9]. The TB-associated gender differences were mainly observed in the age groups over 14 years, and the largest difference was detected in the age group over 60 years (P < 0.05). The association between gender and tuberculosis risk has not been explained, but it may be linked to different factors, for example behavioural and physiological conditions. Behavioural conditions are reported to include a person's social role, activities, smoking and alcohol consumption [30]. Physiologically, gender differences are attributed to sex hormones that may be responsible for modulating the immune responses necessary for fighting tuberculosis and other infectious diseases [12,24].

Being over 14 years of age was associated with TB positivity (P < 0.001) and increased proportionately as age increased. It has been suggested that the reactivation of latent MTB infection and an increase in susceptibility to TB disease in the elderly could be due to Immunosenescence and/or, rise co-morbidities as one grows older [11,29].

Various studies have investigated the rates of drug resistance in different parts of Saudi Arabia. In light of these studies and ours, there is significant temporal and spatial variation in the rates of drug resistant TB in Saudi Arabia. For example, isoniazid resistance rate was varied across the Kingdom, 19.4% in Riyadh [6], 6.5% in Taif and Dammam [7,14]. The highest resistance rates were reported in Gizan (80%) [27] followed by Jeddah (10.3% to 28.7%) [15]. Important to note all studies including ours and WHO annual reports concur on the low prevalence of MDR-TB in Saudi Arabia [3,7,8,10,16,32]. Like the other studies, this study has shown that drug resistance rate in the PSMMC

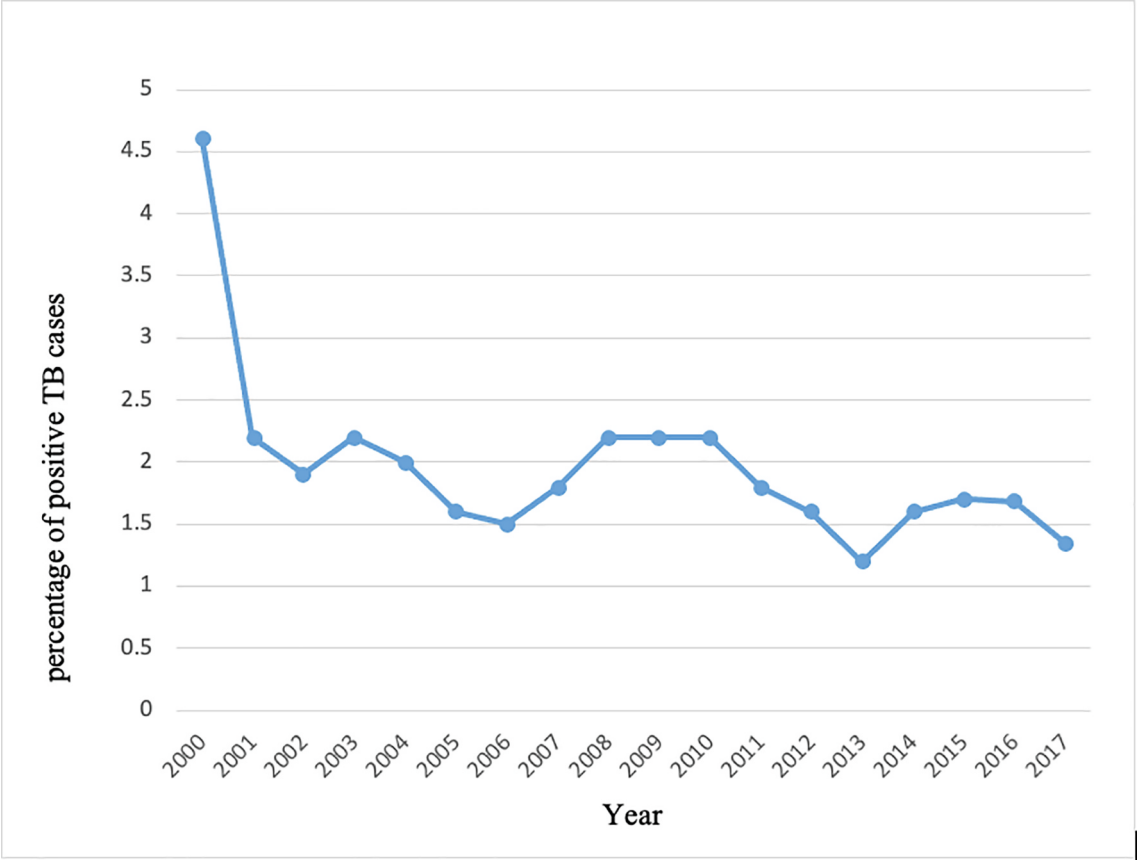

Fig. 1. Annual TB positivity rate at prince sultan Military Medical City from 2000 to 2017. The decline in positivity rates stagnated from 2001 to 2017, fluctuating between 1% and 2.5%.

Table 1
Demographic of tuberculosis patients stratified by age and gender status. Males and people aged 60 and above had the highest TB positivity rates.

	Age group (N) and percent positive cases per age group					
Gender	0–14 (n = 18) (2%)	15–29 (n = 214) (19%)	30–43 (n = 175) (16%)	44–59 (n = 224) (20%)	≥60 n = 492 (44%)	Total (n = 1123)
Male	8 (0.70%)	125 (11%)	03 (9%)	121(10%)	315(28%)	672 (60%)
Female	10 (0.90%)	89 (8%)	72(6%)	103(9%)	177 (16%)	451(40%)
P-value	P > 0.05	P < 0.05	P < 0.05	P > 0.05	P < 0.05	P < 0.05

has significantly decreased over 18 years (P < 0.05) [3,8,10,16]. Reduction in drug resistance could be attributed to improved compliance as a result of direct observed therapy and also due to the improvement in TB diagnosis and detection of resistance.

The results also show that poly-resistance to isoniazid and streptomycin are more common than resistance to other TB drugs, 4.5% and 3.8%, respectively. Isoniazid mono-resistance rate of 2% was found, and could be due the extensive use of INH as the first line drug in the treatment regimen of TB as well as a component of preventative therapy to individuals who are at high risk for developing TB disease [31]. Streptomycin has the second highest mono-resistance of 1.80%, which is understandable as the drug has been used widely for many years for the treatment of many infectious diseases including tuberculosis.

Resistance to other TB drugs and MDR-TB was low, an observation consistent to previous studies [3,8,10,16] and WHO reports [13].

There are several limitations to this study; the data was collected from PSMMC only, the hospital which serves the Ministry of Defence employees and their families who are mostly Saudi nationals, so does not represent the full population structure of the country. The risk factors are for developing drug resistant TB was not evaluated as there was insufficient information in old cases of tuberculosis in the TB notification records. Second-line anti-TB drugs were not included in this study and also patients for whom full information was not available.

5. Conclusion

The prevalence of tuberculosis including MDR-TB remain low among service users of PSMMC, and resistance to isoniazid and streptomycin are more common than resistance to other TB drugs. *Mycobacterium tuberculosis* infects adult male patients than other TB patient groups. Our results suggest male gender and over 60 age group are more susceptible to active TB disease. Further studies are required to investigate nationwide TB prevalence and drug resistance in Saudi Arabia. Furthermore, the need for comprehensive national and international studies of the risk factors for developing active TB diseases and drug resistance cannot be more emphasised.

Table 2
Anti-tuberculosis resistance patterns among patients isolates in PSMMC.

Year	S	I	R	E	P	I + R	I + R + E	I + R + E + P	S + I + R + E + P	S + R + P	R + E	S + I	S + I + P	S + E	S + I + E	I + P	Total
2000	6	4									1	3		1			15
2001	1	5										2					8
2002		1										1					2
2003		1										1					2
2004	1	1	1			1											4
2005	5		1											1			7
2006	1	1		1						1		3					7
2007		1				1			1								3
2008		2		2	2				1			2			1		10
2009	1	2			2							2	1			1	9
2010	2	2		1	1		2					1				1	10
2011		1			1												2
2012		1															1
2013																	0
2014	1	1			3				1								5
2015	1		1														2
2016					1												1
2017	1											1					2
Total	20	23	3	4	10	1	2		1	1	1	16	1	2	1	2	90

S: Streptomycin, I: Isoniazid, R: Rifampicin, E: Ethambutol, P: Pyrazinamide.

Table 3
Prevalence of first line anti-tuberculosis drug resistance in PSMMC, 2000–2017.

Pattern of drug susceptibility testing	Frequency	Percentage %
Susceptible	1033	92
Drug resistance (total)	90	8
Any drug resistance		
STR	43	3.8
INH	49	4.5
RIF	11	1.0
Emb	12	1.0
PZA	18	1.60
Mono-resistance (n = 60)		
STR	20	1.80
INH	23	2.00
RIF	3	0.30
Emb	4	0.40
pza	10	0.90
Poly-resistance, non MDR-TB (n = 24)		
STR + RIF + PZA	1	0.01
RIF + Emb	1	0.01
STR + INH	16	1.40
STR + INH + Pza	1	0.01
STR + Emb	2	0.20
STR + INH + Emb	1	0.01
INH + PZA	2	0.20
MDR-TB (n = 6)		
INH + RIF	1	0.01
INH + RIF + Emb	1	0.01
INH + RIF + Emb + PZA	2	0.20
STR + INH + RIF + PZA	1	0.01
STR + INH + RIF + Emb + PZA	1	0.01%

STR: Streptomycin, INH: Isoniazid, RIF: Rifampicin, EMB: Ethambutol, PZA: Pyrazinamide.

Declarations of interest

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Consent

Not required.

CRediT authorship contribution statement

Souad M. Alateah: Conceptualization, Methodology, Writing - original draft. **Maha W. Othman:** Data curation. **Medina Ahmed:** Writing - review & editing. **Mohammed S. Al Amro:** Supervision. **Nisreen Al Sherbini:** Writing - review & editing. **Hisham H. Ajlan:** Supervision.

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