

Mortality among tuberculosis patients in Saudi Arabia (2001-2010)

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BACKGROUND AND OBJECTIVES: Tuberculosis (TB) still contributes to deaths in Saudi Arabia, among both Saudis and non-Saudis. Exploring the trend of deaths caused by TB and determinants associated with high fatality rate among TB patients is considered as a part of monitoring and evaluation of the performance of National Tuberculosis Control Program to help planners improve policies and procedures used to achieve the targets of TB control.

DESIGN AND SETTINGS: The current study is a retrospective one, which used the official notifications of NTP in Saudi Arabia over a period of 10 years (2001-2010).

METHODS: A 10-year retrospective study included all TB cases registered in Saudi Arabia with known outcome of survival or death while under anti-TB therapy covering the period January 1, 2001, to December 31, 2010.

RESULTS: Mortality among TB patients show a declining trend among Saudis starting from the year 2003 (7.2%-6.1%) and a stagnant trend among non-Saudis. Saudi nationality was associated with higher fatality rate compared to non-Saudis (6.4% and 5.4%, respectively). Mortality was positively correlated with advancing age, male sex among Saudis (7.3% compared to 5.3% among females), and female sex among non-Saudis (6% compared to 5% among males), prior history of anti-TB therapy, smear positivity, and human immunodeficiency virus (HIV) seropositivity.

CONCLUSIONS: We recommend WHO to modify the definition of death among TB patients. We recommend NTP in Saudi Arabia to adopt and implement International Classification of Diseases (ICD10) for TB patients' registration, improve health care services provided for elderly, monitor and strengthen NTP performance to decrease defaulter and early detect and treat patients, initiate a collaborative TB/HIV activities, and screen all suspected TB patients for HIV. In addition to these, more extended research has to be initiated concerning delayed diagnosis and comorbidities with TB.

Despite big investments in the field of tuberculosis (TB) control since the declaration of TB as a global health problem in 1993,¹ TB remains one of the greatest public health challenges worldwide. In the year 2010, there were 8.8 million (range, 8.5–9.2 million) incident cases of TB, 1.1 million (range, 0.9–1.2 million) deaths from TB among human immunodeficiency virus (HIV)-negative people, and an additional 0.35 million (range, 0.32–0.39 million) deaths from HIV-associated TB.²

TB is a disease of poverty. In many parts of the globe, the resources are deficient and health systems are overwhelmed, which lead to the sloppy implementation of directly observed treatment (DOTS) programs and ex-

acerbation of the TB problem.³

DOTS is the only available method for reducing TB transmission and deaths worldwide and preventing emergence of multidrug resistant strains.⁴ The implementation of DOTS in Yavatmal, India, resulted in doubling of the success rate and reduction in the death rate with an approximate 18 additional lives saved per 100 patients treated.⁵

According to the WHO definition, any case died while under anti-TB treatment is considered regardless of the cause of death.⁶ Many risk factors have been claimed as determinants of death among TB patients such as old age, prior history of TB, multidrug resistance,⁷ HIV co-infection,⁸ and non-compliance with

treatment,⁹ in addition to delayed therapy.⁴

Although Saudi Arabia has adopted the global strategy for TB control and has implemented directly the observed treatment, i.e., the short course since the year 2000, TB still represents an important public health problem in the country, affecting all age groups and Saudis and non-Saudis alike. As most of non-Saudis are originated from high TB endemic areas of the world, they had nearly twice the TB incidence rate compared to Saudis.¹⁰

In the current article, the official national surveillance data of National Tuberculosis Control Program (NTP) regarding mortality over a period of 10 years was analyzed to determine the mortality trends and explore some determinants associated with deaths among TB patients.

METHODS

A retrospective 10-year study included all TB cases reported in Saudi Arabia during the period January 1, 2001, to December 31, 2010. Saudi Arabia had mandatory reporting of all TB cases, and returns were made monthly and notified by the patient's name to the central unit of the program and then entered into an Epi-info program. Patients were classified according to WHO criteria¹¹ and treated according to the adopted WHO protocols.¹² New patients were treated by 4 drugs for 2 months (intensive phase) followed by 2 drugs for 4 months (continuation phase). New patients who remained smear positive by the end of the second month of treatment had their intensive phase and continuation phase extended for an extra month. Retreatment patients were treated by 5 drugs for 3 months (streptomycin always discontinued after 2 months) followed by 3 drugs for 5 months. All patients under treatment were followed up by the treating physicians and by district coordinator till the end of treatment or death to confirm the outcome of the treatment.

District coordinators in all districts (20 districts) were mandated to notify the results of treatment outcomes for all registered prenotified patients on a monthly basis to the central unit of National Tuberculosis Control Programme, where the data entered into an electronic file, which then joined to one of the prenotified patients using the district name and the unique TB code. Only patients with confirmed death were included. Patients who left the country before completing their treatment period and those who were excluded from the registers because of misdiagnosis in addition to those without confirmed treatment outcomes were excluded. Patients who died while under anti-TB treatment were considered in analysis, regardless of the primary cause of

death. In calculation of the case fatality rate, the numerator used was the number of patients died while under anti-TB therapy, regardless of the cause, and the denominator was the total patients registered for anti-TB therapy and had a confirmed notification of outcome.

Data were then organized, tabulated, and analyzed for case fatality rates (calculated as percentage) by year, nationality, sex, case type, form of TB, HIV status, and age using SPSS statistical package, version 16. Chi-square was used for linear trends; Pearson chi-square technique and Poisson log linear regression were used as appropriate. The significance level was set at .05.

Ethics Statement

Ethical approval or written patient consent were not required for the study, as this was a retrospective review of routine surveillance data collected anonymously by the Saudi Arabia NTP and also because Saudi Arabia Ministry of Health had a mandate to review and evaluate the NTP performance.

RESULTS

The case fatality rate shows an upward trend starting from the year 2001 reaching a peak in the year 2003 (7.2% and 6.2% among both Saudis and non-Saudis, respectively). Starting from the year 2004, the result shows a declining trend to exhibit a total decline of 20.4% among Saudis and 27.3% among non-Saudis, among both Saudi and non-Saudis. Changes in the mortality rate reported among Saudis were statistically significant ($P < .05$) but that among non-Saudis were not significant ($P > .05$), (Table 1).

The case fatality rate was found to be increased with the increase in age, among both Saudis and non-Saudis. The highest rates reported among those aged ≥ 65 years (20.8% among Saudis and 25.2% among non-Saudis). The rate among Saudis increased from 1.2% among those aged ≤ 15 years to 20.1% among those aged ≥ 65 years. While among non-Saudis the rate increased from 3.1% among those aged ≤ 15 years to 25.2% among those aged ≥ 65 years. The total case fatality rate was significantly higher among Saudis (6.4%) compared to non-Saudis (5.4%) (OR=1.2, 95% CI 1.1-1.33), (Table 2). Elderly people (≥ 65 years) represent 46.3% of the total deaths among Saudis compared to only 13.5% among non-Saudis. The productive age groups (15-44 years) still represent the greatest proportion of TB mortality among both Saudis and non-Saudis (36.8% and 71.8%, respectively).

Concerning sex, the case fatality rate was significantly higher among Saudi males (7.3%) compared to Saudi females (5.3%) (OR=1.4, 95% CI=1.24-1.58). However,

Table 1. Registered TB cases and deaths in Saudi Arabia (2001-2101) by year and nationality.

Year	Saudi			Non-Saudi		
	Registered	Died	Fatality rate (%)	Registered	Died	Fatality rate (%)
2001	1833	108	5.3	1075	45	4.2
2002	1840	118	5.8	1164	56	4.8
2003	1833	143	7.2	1115	69	6.2
2004	1839	137	6.7	1174	66	5.6
2005	2003	143	6.7	1285	77	6.0
2006	2115	129	5.8	1345	71	5.3
2007	2179	137	5.7	1506	73	4.9
2008	2228	152	5.9	1490	67	4.5
2009	2237	118	5.6	1436	87	6.1
2010	2321	127	5.7	1650	100	6.1
Total	20428	1312	6.4	13240	711	5.4
χ^2_a		5.2			1.5	
<i>P</i>		<.05			>.05	

TB: Tuberculosis. ^aChi-square test for linear trend. Note: Saudis vs. non-Saudis; OR=1.2195% CI (1.1-1.33).

Table 2. Registered TB cases and deaths in Saudi Arabia (2001-2010) by nationality and age group.

Nationality	Age group	Total	Died	Fatality rate (%)	95% CI ^a	
					Lower	Higher
Saudi	0-14	1330	16	1.2	-3.274	-2.296
	15-24	4796	87	1.8	-2.623	-2.175
	25-34	4235	127	3.0	-2.089	-1.707
	35-44	2652	119	4.5	-1.691	-1.299
	45-54	2358	150	6.4	-1.325	-0.969
	55-64	2029	205	10.1	-0.843	0.527
	65+	3028	608	20.1	0	
	Total	20428	1312	6.4		
Non-Saudi	0-14	615	19	3.1	-2.565	-1.591
	15-24	2884	74	2.6	-2.585	-1.981
	25-34	4470	170	3.8	-2.143	-1.643
	35-44	2579	152	5.9	-1.710	-1.200
	45-54	1602	115	7.2	-1.527	-0.986
	55-64	709	85	11.9	-1.033	-0.451
	65+	381	96	25.2	0	
	Total	13240	711	5.4		

TB: Tuberculosis. ^aPoisson Log linear analysis.

Table 3. Registered TB cases and deaths in Saudi Arabia (2001-2010) by sex, cases type, form of TB, and HIV status.

Characteristics			Registered	Died	Fatality rate (%)	OR	95% CI
Sex	Saudi	F	8675	459	5.3	1.4	1.2-1.58
		M	11752	853	7.3		
	Non-Saudi	F	5254	314	6.0	1.22	1.04-1.42
		M	7986	397	5.0		
Case Type	Saudi	New	19267	1211	6.3	1.42	1.14-1.77
		Retreatment	1161	101	8.7		
	Non-Saudi	New	12610	673	5.3	1.14	0.8-1.6
		Retreatment	630	38	6.0		
Form of TB	Saudi	SS+ ^a	9321	688	7.4	1.34	1.20-1.50
		Other forms ^b	11107	624	5.6		
	Non-Saudi	SS+ ^a	6286	437	7.0	1.47	1.26-1.72
		Other forms ^b	6954	274	4.0		
HIV Status	Saudi	Seronegative	2624	128	4.9	5.25	2.7-10.06
		Seropositive	66	14	21.2		
	Non-Saudi	Seronegative	2028	104	5.1	12.18	6.98-21.22
		Seropositive	68	27	39.7		

TB: Tuberculosis, HIV: human immunodeficiency virus. ^aPulmonary smear positive TB. ^bIncludes pulmonary smear negative and extra-pulmonary forms.

non-Saudi females were more vulnerable to death (6%) than non-Saudi males (5%) (OR=1.22, 95% CI=1.24-1.58). Retreatment TB patients were significantly more vulnerable to death than new TB patients, among both Saudis and non-Saudis.

As regards to the form of TB, the pulmonary smear positive form was found to be more associated to death among both Saudis and non-Saudis (95% CI 1.21-1.53 and 1.24-1.71, respectively). Among TB patients with known HIV status, HIV seropositive patients were significantly more prone to death than HIV seronegative patients, among both Saudis and non-Saudis (95% CI=2.7-10.06 and 6.98-21.22, respectively), (Table 3).

Mortality data were analyzed by province, but there were no statistical significant differences, and all provinces showed figures around the national case fatality rate.

DISCUSSION

According to the WHO and Stop TB Partnership, the targets are to halve the prevalence and death rates by 2015 compared with their levels in 1990 and to reduce the global incidence of active TB to 1 case per 1 mil-

lion population by the year 2050.¹³ Saudi Arabia has achieved the target related to the death rate from TB compared to 1990 (12% in 1990)¹⁴ and case fatality rate showed a declining trend since the year 2003, that could be attributed to the widespread network of health care facilities providing services free of charge for all TB patients. Case fatality rate from TB in the country is also, lower than that reported in other countries of the region, except for Iran and United Arab Emirates.² Actually, WHO should modify the definition of death from TB to include only patients where TB was the primary cause of death according to the International Classification of Diseases (ICD10).¹⁵ Strengthening the laboratory network and provision of recent molecular technology could result in more decline in fatality from TB as a result of early diagnosis and treatment of suspected patients.

Age is an important determinant of death from TB. The case fatality rate was found to be positively correlated with age, among both Saudis and non-Saudis. Patients with age group ≥ 65 years showed the highest case fatality rate followed by those in the age group 55 to 64 years, and this agrees with the findings of Ochoa

et al. in Cuba.¹⁶ The high case fatality rate among this age group was coincident with the high incidence rate of TB among this age group (65.2/100 000 in the year 2000).¹⁰ This could be attributed to other comorbidities prevailed among elderly people such as cardiovascular diseases, cancer,⁷ liver disease, renal diseases, and diabetes,^{17,18} which may be the primary cause of death rather than TB. Also these comorbidities may change the presentation of TB making it difficult to diagnose and treat, in addition to the increased risk of anti-TB drugs toxicity.¹⁹ Moreover, elderly people are exposed to unfavorable living conditions, malnutrition, and less access to health care. Elderly TB patients may also present with atypical nonspecific symptoms that may delay diagnosis and treatment and add to the risk of death.²⁰ Mortality still mostly affects the productive age groups, which means that actions have to be taken to save the work force in the country and worldwide. Elderly patients (≥ 65 years) represent a respective proportion of deaths among Saudis compared to non-Saudis. This reflects only the demographic composition of both communities rather than indicating old age as a determinant for death among Saudis.

The male sex by itself could not be considered as a risk factor for death in TB patients, as there is other confounding. Being more prone to death has been attributed to low compliance with treatment leading to repeated short interruptions or defaulting from treatment²¹ and also the effect of social stigma that affects female access to health care leading to delayed diagnosis and treatment.¹⁰

Saudi males are more prone to death from TB than females, and this agrees with other studies.^{7,16,22} In 2008, the analysis of European surveillance data showed that male TB patients had approximately 50% higher risk of death.²³ In contrast, non-Saudi females were found to be more prone to death, a finding that could be linked to the higher incidence of TB among non-Saudi females who were mostly of low socioeconomic status and originated from countries of high burden of TB.¹⁰

Regarding the case type, the history of prior TB was associated with an increased risk of death among both Saudis and non-Saudis. The result was in agreement with the findings of Shen et al in China 2009,²⁴ who reported that retreatment patients were 50% more prone to death than new cases. This could not be attributed to the previous history of TB but to behavioral causes such as noncompliance with treatment or defaulting that led to the failure of treatment when they were new cases, and which could also be a cause of the second failure of treatment and occurrence of complication and finally death.

Sputum smear positivity was found to be associated with high fatality among both Saudis and non-Saudis, which was in agreement with the findings of Shen et al²⁴ in China. They attributed these findings to high bacillary load, severe form of TB, and difficulty with treatment. In contrast Davis et al in England²⁵ reported that pulmonary smear negative TB was more associated with mortality, a finding that could be attributed to delayed diagnosis and therapy till it presents with a severe form.

HIV is a known risk factor for TB infection and mortality²⁶ because it is associated with atypical presentation leading to diagnostic delay and therapy contributing to mortality, especially in the case of advanced immune suppression.²⁷ Saudi Arabia is not affected by the pandemic of HIV,²⁸ even for non-Saudis who are mandated to check their HIV status at their home countries before having entry visa and on their arrival to the country before issuing the official residential permission (Iqama). In the current study, HIV seropositive patients, among both Saudis and non-Saudis were more prone to death, which was in agreement with other studies.^{27,29}

As the proportion of TB patients with the known HIV status in the country is very low, improving the management of TB suspects by including HIV screening, monitoring the collaboration between NTP and HIV/AIDS program in the country to screen all registered TB patients for HIV, and initiating antiretroviral therapy for those living with HIV will improve this proportion.

In conclusion, the current study revealed that the mortality rate from TB showed a declining trend among Saudis and stagnant trend among non-Saudis. The Saudi nationality was associated with the higher fatality rate, which reflected the demographic composition of the Saudi population where elderly proportion was higher than that among non-Saudis. Mortality was positively correlated with advancing age, male sex among Saudis and female sex among non-Saudis, prior history of anti-TB therapy, smear positivity, and HIV seropositivity. We recommend WHO to modify the definition of death among TB patients to include only deaths where TB is the primary cause. We recommend NTP in Saudi Arabia to adopt and implement ICD10 for the registration of TB patient, improve health care services provided for elderly, monitor and strengthen NTP performance to decrease defaulter and early detect and treat patients, initiate a collaborative TB/HIV activities and screening all suspected TB patients for HIV. In addition, more extended research has to be initiated concerning delayed diagnosis and comorbidities with TB.

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