

REVIEW OF THE CURRENT STATUS OF DRUG-RESISTANT TUBERCULOSIS IN SAUDI ARABIA

Khaled K. Abu-Amero, PhD, FRSH

After years of decline, tuberculosis has re-emerged as a serious public health problem worldwide. In 1993, the World Health Organization (WHO) declared tuberculosis to be a global emergency, and according to a recent WHO report, there were 7.96 million new cases in 1997 with 2 million deaths.¹ Factors contributing to the resurgence of tuberculosis include the HIV epidemic, immigration of persons from countries with high incidence rates, and political turmoil in some developing countries, which hinder efforts to control the disease. The spread of the disease poses a public health concern, especially with increased drug resistance among *M. tuberculosis* strains, which have acquired varying degrees of resistance to first-line anti-tuberculous drugs. The underlying causes of single drug-resistant *M. tuberculosis* (SDR-TB) and/or multi-drug-resistant *M. tuberculosis* (MDR-TB) have been suggested to be the result of incorrect treatment, poor compliance, shortage of anti-tuberculous drugs due to financial constraints in some developing countries, and deficient or deteriorating TB control programs, resulting in inadequate administration of effective chemotherapy.²⁻³ Previous reports indicate that single-drug resistance and multi-drug resistance to *M. tuberculosis* are on the increase in both developed and developing countries.^{4,5}

The prevalence of SDR-TB or MDR-TB in the Kingdom of Saudi Arabia is largely unknown, except for a few studies confined to large centers. The objective of this article is to review published materials from different regions of the Kingdom on the prevalence of SDR-TB and MDR-TB, and to draw a conclusion of the actual status of drug-resistant tuberculosis in Saudi Arabia, with a discussion of the findings.

Methods

A Medline search was conducted on the worldwide literature on tuberculosis in Saudi Arabia dating from 1966

to March 2002. Surveys of anti-mycobacterial susceptibility testing on isolates from this country were sought, and a search conducted through the Internet and WHO publications for any reported information regarding TB drug resistance in Saudi Arabia. Information was also sought from the Ministry of Health in Riyadh, which is responsible for collecting data regarding tuberculosis incidence, drug resistance status, etc. For single drugs, the percentage of isolates that were resistant to that drug were recorded. Multi-drug resistance reported were for those isolates that were resistant to at least isoniazid and rifampicin combined, or to isoniazid and rifampicin, plus other drug(s) according to the WHO guidelines.⁶

Results

For single drug resistance, reports available from different areas in Saudi Arabia indicate that the percentage drug resistance for isoniazid was 3.4%-19.4%, 10.3% - 28.7%, 6.0%, 41% and 6.5% in Riyadh, Jeddah, Dammam, Gizan and Taif, respectively.⁷⁻¹⁷ Resistance to rifampicin was 0%-9.7%, 5.1%-23.4%, 0.2%, 20.0% and 15.3% for Riyadh, Jeddah, Dammam, Gizan and Taif, respectively. Resistance to streptomycin were 0.75%-12.5%, 7.7% - 22.7%, 0.7%, 26% and 15.9% for Riyadh, Jeddah, Dammam, Gizan and Taif respectively.⁷⁻¹⁷ Resistance for ethambutol was 0% -2.4%, 1.3%-6.9%, 3.9% and 4.0% for Riyadh, Jeddah, Gizan and Taif, respectively. Within the SDR-TB, resistance to isoniazid (3.4%-28.7%) was the most common, followed by resistance to rifampicin (0.2-23.4%), streptomycin (0.7%-22.7%) and ethambutol (0%-6.9%), respectively.⁷⁻¹⁷

For MDR-TB, defined by the WHO as resistance to at least isoniazid and rifampicin,⁶ the rates were 1.5% - 11.8%, 11.5% - 25.7%, 10.5%, 44% and 15.3% for Riyadh, Jeddah, Dammam, Gizan and Taif, respectively (Table 1).⁷⁻¹⁷ Most of the previous reports indicate that resistance to isoniazid and rifampicin was the most resistant combination, followed by resistance to isoniazid, rifampicin and streptomycin.

Discussion

According to a recent WHO report, the tuberculosis notification rates in Saudi Arabia decreased dramatically

From the Department of Biological and Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Abu-Amero: Department of Biological and Medical Research, MBC-03, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. E-mail: kamero@kfshrc.edu.sa.

Accepted for publication 15 May 2002. Received 27 October 2001.

TABLE 1. Summary of studies on anti-tuberculous drug resistance among *M. tuberculosis* isolates from different regions in Saudi Arabia (1979-1998).

Study Location	Year(s)	No. of isolates/patients	% Single drug resistance					Reference
			Isoniazid	Rifampicin	Streptomycin	Ethambutol	MDR-TB (%)	
Riyadh	1979-1982	1968	4.2	NR*	12.5	NR	3.7	8
Riyadh	1981-1982	47	7	9	NR	2	10.6	9
Gizan	1985	108	41	20	26	3.9	44	10
Taif	1986-1988	678	6.5	15.3	15.9	4	15.3	11
Riyadh	1986-1988	432	19.4	9.7	5.1	NR	11.8	12
Riyadh	1987-1997	670	3.4	0	0.75	0	1.5	13
Riyadh	1989-1994	289	7.2	3.1	3.5	2.4	3.8	14
Jeddah	1991	483	17.8	23.4	16.4	3.9	17.6	15
Jeddah	1993-1995	78	10.3	5.1	7.7	1.3	11.5	16
Dammam	1993-1996	411	6	0.2	0.7	0	10.5	7
Jeddah	1996-1998	101	28.7	20.7	22.7	6.9	25.7	17

*NR=not reported.

from 114 new cases per 100,000 in 1980 to 17 cases in 1999.¹⁸ This indicates a successful vaccination program and an effective tuberculosis eradication policy. Unlike the incidence rate, the prevalence of drug-resistant tuberculosis in Saudi Arabia is largely unknown, and this is due to the following facts: 1) only a few studies, mainly confined to large centers have been conducted; 2) most WHO reports regarding the global status of drug resistance have not reported data from Saudi Arabia; and 3) there is no reliable centralized data regarding drug resistant tuberculosis in Saudi Arabia. The Ministry of Health, the body responsible for collecting data on tuberculosis, such as new case notification and the status of drug resistance, does not have data regarding drug resistance other than what has already been published in the literature. This review attempts a thorough coverage of the literature published in the *Medline* (1966 - March 2002) concerning single- and multi-drug resistant tuberculosis in this country. To the best of my knowledge, such updated coverage has not been presented in any previous publication.

Reports concerning drug resistance from different regions in Saudi Arabia give a conflicting picture. Reports from the Jeddah area have shown an almost three-fold increase from 1991 to 1998.¹⁷ Exposure of the local population to the pilgrims (each year around 2 million pilgrims pass through Jeddah on their way to Makkah to perform Hajj; most of these pilgrims are from countries with a high prevalence of infectious diseases such as tuberculosis), expatriate workers and illegal immigrants have been suggested as causes for the high incidence to drug resistance around the Jeddah area.^{16,19} In fact, a recent report showed that tuberculosis was the most common cause of pneumonia requiring hospitalization among pilgrims in Makkah.²⁰ Resistance to isoniazid as a single drug was the most common. This was followed by resistance to rifampicin. Similar patterns of high resistance to isoniazid has been observed throughout Saudi Arabia (Table 1),²¹ which may be due to non-compliance or misuse as chemoprophylaxes.²²

In Riyadh, the MDR-TB ranged from 1.5% to 11.8% from 1979 to 1997 (Table 1). In one of the studies conducted at the Riyadh Armed Forces Hospital (covering 1987 to 1997), the authors reported a very low MDR-TB of 1.5%, which they attributed to the fact that their study population comprised mainly natives, and that the source of highly resistant tubercle bacilli observed in previous studies from the Kingdom could be from expatriates, especially those from the Indian subcontinent.¹³ This low rate of MDR was in contrast to two previous reports from the Riyadh area covering natives and the expatriate population, which reported relatively high MDR-TB rates of 10.6%⁹ and 11.8%¹², respectively.

There was one report from the city of Taif with a relatively high rate of MDR-TB compared to other areas in the Kingdom.¹¹ This high rate of MDR-TB (15.3%) in Taif was attributed to the possible role of non-compliance with anti-tuberculous treatment regimen. This was later confirmed in a study by Al-Hajjaj and Al-Khatim,²² in which the problem of non-compliance was investigated thoroughly. The authors concluded that non-compliance with anti-tuberculous treatment, despite a retrieval system being in operation, was the major cause for this high MDR-TB rate. The authors called for an urgent need for implementing a directly observed treatment short-course (DOTS) system in Saudi Arabia. In the last year, the Ministry of Health has established a National Tuberculosis Control Committee to put forward a proposed DOTS program that would be applicable to the Kingdom and to oversee its implementation.

In Dammam, there was one report concerning MDR-TB, which covered the 1993-1996 period. The MDR-TB reported from this area was 10.5%, which was relatively comparable to other MDR-TB rates from other areas in the Kingdom.⁷

In Gizan, the MDR-TB rate was extremely high (44%) compared to rates reported from other regions in the Kingdom.²³ The investigators attributed this to the fact that Gizan is very close to Yemen, which has been reported to

have one of the highest rates of active tuberculosis among Arab countries, and that workers moving across the border may be the cause for this high MDR-TB rate.

It was very difficult to draw a definite conclusion on the status of drug-resistant tuberculosis in this country based on these studies, for one or more of the following reasons: 1) most of the previous reports were conducted mainly in regional hospitals which have different native:immigrant ratios. Hospitals that treat high proportions of expatriates, may be the source of highly resistant tubercle bacilli and thus report high incidences of MDR-TB among their patients, as suggested by some of these studies; 2) some of the studies did not specify the site of *M. tuberculosis* isolation, i.e., pulmonary or extra-pulmonary; 3) almost all the studies failed to report patient compliance with treatment; 4) most studies also failed to differentiate between primary and acquired TB resistance in their studied population; 5) there is no standardized national TB treatment regime among hospitals in the Kingdom; and 6) some studies failed to report the method used for drug sensitivity testing. In addition, quality control methods among different laboratories is likely to have been variable, possibly affecting the accuracy of the results in some of the surveys.

Apart from possible variations in the population studied, geographical origin of the patients, site of *M. tuberculosis* isolation, and patient compliance with treatment, the actual explanation for this apparent discrepancy in prevalence of tuberculosis drug resistance remains unclear.

In conclusion, this study points to the need for developing a standardized national policy for the surveillance of drug resistant tuberculosis in Saudi Arabia. This can be achieved by establishing a network of national reference laboratories, using internationally accepted and standardized susceptibility methods. By establishing this system, the trend of resistance over time can be monitored in accordance with guidelines provided by the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD).³

References

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione M. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999;282:677-86.
2. Willcox PA. Drug-resistant tuberculosis: worldwide trends, problems specific to Eastern Europe and other hotspots, and the threat to developing countries. Curr Opin Pulm Med 2001;7:148-53.
3. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in resistance to antituberculosis drugs. World Health Organization/International Union Against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001;344:1294-303.
4. Cohn DL, Bustreo F, Raviglione MC. Drug resistant tuberculosis: review of the world situation and the WHO/IUATLD Global Surveillance Project. Clin Infect Dis 1997;24:121-30.
5. Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994-1997. WHO/IUATLD Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 1998;338:1641-49.
6. Schwoebel V, Lambregts van Weezenbeek CS, Moro ML, Drobniewski F, Hoffner SE, Raviglione MC, et al. Standardization of antituberculosis drug resistance surveillance in Europe. Recommendations of a WHO/IUATLD Working Group. Eur Respir J 2000;16:364-71.
7. Al-Rubaish AM, Madania AA, Al-Muhanna FA. Drug-resistant pulmonary tuberculosis in the Eastern province of Saudi Arabia. Saudi Med J 2001;22:776-9.
8. Al-Orainey IO. Resistance to antituberculosis drugs in Riyadh, Saudi Arabia. Tubercle 1989;70:207-10.
9. Shanks NJ, Khalifa I, Al-Kalai D. Tuberculosis in Saudi Arabia. Saudi Med J 1983;4:151-6.
10. Schiott C, Engbaek H, Vergmann B, Al-Motez M, Kassim I. Incidence of drug resistance amongst isolates of *Mycobacterium tuberculosis* recovered in Gizan area, Saudi Arabia. Saudi Med J 1985;6:375-8.
11. Jarallah JS, Elias AK, Al-Hajjaj MS, Bukhari MS, Al-Shareef HM, Al-Shammari SA. High rate of rifampicin resistance of *Mycobacterium tuberculosis* in the Taif region of Saudi Arabia. Tuber Lung Dis 1992;73:113-5.
12. Al-Orainey IO. Resistance to standard antituberculous drugs in Saudi Arabia. Saudi Med J 1989;7:363-8.
13. Al-Rasheed AM, Abu-Amro KK, Abdulsamad W, Alattayah S. Low prevalence of multi-drug resistance tuberculosis in Saudi patients: an eleven-year retrospective study (abstract). 20th Annual Congress of the European Society of Mycobacteriology, Lucerne, Switzerland (1999).
14. Ellis ME, Al-Hajjar S, Bokhari H, Qadri SH. High proportion of multi-drug resistant *Mycobacterium tuberculosis* in Saudi Arabia. Scand J Infect Dis 1996;28:591-5.
15. Zaman R. Tuberculosis in Saudi Arabia: initial and secondary drug resistance among indigenous and non-indigenous populations. Tuberculosis 1991;72:51-5.
16. Kinsara A, Gilpin C, Osoba A. Review of tuberculosis at the King Khalid National Guard Hospital, Jeddah, Saudi Arabia. Saudi Med J 1997;19:212-4.
17. Khan MY, Kinsara AG, Osoba AO, Wali S, Samman Y, Memish Z. Increasing resistance of *M. tuberculosis* to anti-TB drugs in Saudi Arabia. Int J Antimicrob Agents Chemother 2001;17:415-8.
18. Anonymous. WHO Report 2001. Global Tuberculosis Control. Communicable Diseases Publication, World Health Organization, Geneva (Switzerland), 2001.
19. Milaat WA, Ali A, Afif H, Ghabrah T. Epidemiology of tuberculosis in Jeddah region, Saudi Arabia. Saudi Med J 1994;15:133-7.
20. Al-Zaeer A, Mashlah A, Fakim N, Al-Sugair N, Al-Hedaithy M, Al-Majed S, et al. Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). J Infect Dis 1998;36:303-6.
21. Al-Kassimi FA, Abdullah AK, Al-Hajjaj MS, Al-Orainey IO, Bangboye EA, Chowdhury MN. Nationwide community survey of tuberculosis epidemiology in Saudi Arabia. Tuber Lung Dis 1993;74:254-60.
22. Al-Hajjaj MS, Al-Khatim IM. High rate of non-compliance with anti-tuberculosis treatment despite a retrieval system: a call for implementation of directly observed therapy in Saudi Arabia. Intern J Tuber Lung Dis 2000;4:34-49.
23. Al-Kassimi FA. Review of tuberculosis in Saudi Arabia. Saudi Med J 1994;15:192-5.