Epidemiology of Drug-resistant Tuberculosis, A Five Year Review

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Objective: To evaluate the prevalence of multidrug-resistant tuberculosis (MDR TB) and to define its common resistance profile.

Design: A Retrospective Study.

Setting: Ministry of Health, Bahrain.

Method: All cases of clinically diagnosed TB between January 2014 and December 2018 were included in the study. Patients with positive culture were included for further analysis based on the results of phenotypic drug susceptibility to first-line anti-tuberculous drugs. Results of molecular testing Mycobacterium Tuberculosis Polymerase Chain Reaction (MTB PCR) and rifampicin-resistant gene were included in the analysis. All data were retrieved form the national public health data system and public health reference laboratory.

Result: During the study period, the incidence of TB in Bahrain decreased from 17 per 100,000 population in 2014 to 11 per 100,000 population in 2018. A total of 946 patients were diagnosed as TB, out of which, 588 (59%) had confirmed positive culture of MTB.

MDR TB was identified among 15 (3%) out of the 588 positive isolates. Isoniazid monoresistant was the most predominant resistant pattern among our population, it accounted for 53 (9%) among all tested isolates.

Conclusion: Incidence of MTB in Bahrain is decreasing. The MDR TB rate is comparable to other reported data from developed countries.

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Tuberculosis (TB) remains a major public health concern worldwide with attributable morbidity and mortality; drug resistance is one of the major contributors[1-2].

WHO defined multi-drug resistant TB (MDR-TB) as Mycobacterium tuberculosis (MTB) resistant to isoniazid and rifampicin, as a public health crisis in 2013. Furthermore, the risk is aggravated with the emergence of extensive drug-resistant TB (XDR-TB), defined as resistant to isoniazid, rifampicin, one fluoroquinolone, and one second-line injectable drug[3,4]. MDR-TB treatment requires the use of toxic and expensive medications for 20 months or more[2]. In addition to its financial burden, it is usually associated with a poor outcome[5].

The global burden of MDR-TB is challenging, as drug susceptibility testing for MTB is not performed in many resource-limited settings, in addition to underreporting[6]. The estimated worldwide prevalence of MDR is 3.5% of all new TB patients and 18% of previously treated with significant variability among different geographical regions where MDR rate is disproportionally higher in developing countries with high burden of the disease[6].

An appropriate treatment regimen for MDR TB usually relies on patient history of previous treatment (for retreatment group), and result of susceptibility to other anti-tuberculous drugs including second-line agents, in addition to local drug resistance patterns; therefore, it is very important to define the local resistant pattern of MDR.

To our knowledge, there is no existing published data about the burden of MDR TB in Bahrain.

The aim of our study is to evaluate the prevalence of MDR TB in Bahrain and to define its resistance profile.

METHOD

A retrospective study of patients with a clinical diagnosis of TB between January 2014 and December 2018 was performed.

All patients with a suspected clinical diagnosis of TB were processed routinely for Acid-fast Bacilli (AFB) smear, MTB culture and molecular testing by Gene X-pert for MTB Polymerase chain reaction (PCR) and rifampicin resistance

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gene. Patients with positive MTB culture were further tested for phenotypic drug susceptibility testing to the 4 first-line anti-tuberculous medication (isoniazid, rifampicin, ethambutol, and streptomycin). Pyrazinamide was not done for all positive MTB isolates.

The data were collected from all patients who had a clinical diagnosis of TB in Bahrain during the study period. Patients with positive MTB culture were included for further analysis based on the results of phenotypic drug susceptibility to first-line anti-tuberculous. Results of molecular testing (MTB PCR and rifampicin resistant gene) were included in the analysis. For patients with multiple-positive TB cultures, only the first positive culture was included.

RESULT

During the study period, the incidence of MTB in Bahrain decreased from 17 per 100,000 population in 2014 to 11 per 100,000 population in 2018. A total of 946 patients were reported to the public health with the clinical diagnosis of TB; 588 (59%) had confirmed positive culture of MTB, see table 1.

Table 1: Number and Incidence of TB in Bahrain (2014-2018)

Year	Incidence (/100,000 population)	Number of clinical TB	Number of culture-positive MTB
2014	17	222	164
2015	18	250	136
2016	11	153	106
2017	12	170	79
2018	11	151	73
Average / Total	**13.8 (average)**	**946 (total)**	**558 (total)**

The average resistance of MTB isolates to the first-line agents revealed that the highest resistance was against isoniazid 53 (9%), followed by streptomycin 35 (6%), rifampicin 18 (3%) and the least was ethambutol 6 (1%), see tables 2 and 3.

Table 2: Average Resistant Rate of MTB to First Line Anti-tuberculous (2014-2018)

Anti-tuberculous Drug	isoniazid	Streptomycin	Rifampicin	Ethambutol	MDR
Percentage of resistance	9%	6%	3%	1%	3%

MDR-TB was identified among 15 (3%) out of the 588 positive isolates by phenotypic drug susceptibility testing, which illustrates resistance to both isoniazid and rifampicin. No details were available about the treatment history of MDR cases to classify them into new versus retreatment cases. The majority of MDR (12 patients, 80%) were non-Bahraini; 10 patients (67%) were males. Eleven (73%) patients had pulmonary involvement.

Six (40%) out of the fifteen MDR isolates showed full resistance to the four tested first-line agents (isoniazid, rifampicin, ethambutol, and streptomycin), three (20%) MDR isolates were sensitive to ethambutol but resistant to streptomycin, while the remaining six MDR isolates (40%) were sensitive to both ethambutol and streptomycin.

No results were available about susceptibility testing of MDR isolates to second-line anti-tuberculous drugs as such testing is not part of routine TB diagnostic protocol in our public health laboratory.

The prevalence of resistant isolates and MDR-TB during the study period were similar with minimal fluctuation.

DISCUSSION

The incidence of TB, as well as the prevalence of MDR-TB, showed great variability in different parts of the world. Previous epidemiological data revealed that Bahrain is considered one of the low endemicity countries for TB; the majority of the TB patients (85%) were non-Bahraini[7].

In this study, MDR rate was 3% among all TB patients, which is comparable to other reported data among neighboring Arabian Gulf countries where an average of 4% MDR-TB

Table 3: The Prevalence of Resistant Isolates and MDR TB

Year	Isoniazid resistant Number (%)	RIF Resistant Number (%)	Ethambutol Resistant Number (%)	Streptomycin Resistant Number (%)	MDR Number (%)	Resistant to any first line antiTB	Resistant to all 4 first line drugs	Sensitive to all 4 first line drugs
2014	13/164 (8%)	6/164 (4%)	3/164 (2%)	8/164 (5%)	5/164 (3%)	38/164 (23%)	1/164 (1%)	126/164 (77%)
2015	14/136 (10%)	3/136 (2%)	2/136 (1%)	7/136 (5%)	2/136 (1%)	48/136 (35%)	2/136 (1%)	88/136 (65%)
2016	12/106 (11%)	3/106 (3%)	2/106 (2%)	11/106 (10%)	3/106 (3%)	17/106 (16%)	2/106 (2%)	89/106 (84%)
2017	3/79 (4%)	1/79 (1%)	0/79 (0%)	7/79 (9%)	1/79 (1%)	14/79 (17%)	0/79 (0%)	65/79 (83%)
2018	7/73 (10%)	4/73 (5%)	1/73 (1%)	4/73 (5%)	4/73 (5%)	27/73 (37%)	1/73 (1%)	46/73 (63%)
Total / Average	49/558 (9%)	17/558 (3%)	8/588 (1%)	37/588 (6%)	15/588 (3%)	144/558 (26%)	6/558 (1%)	414/558 (74%)

prevalence among 4 Arabian Gulf countries; the highest was in UAE population (9.2%), followed by Kuwait (5.9%) and Saudi Arabia (4.3%). The lowest prevalence rate was observed in Oman (1%)[8].

A similar prevalence rate was estimated among European countries; 3.8% among all TB patients, 15% among retreatment and 2.4% among new patients[9]. Meanwhile, the USA reported an overall lower MDR prevalence rate of 1.2%[10].

Isoniazid monoresistant was the most predominant resistant pattern among our population, it accounted for 9% among all tested isolates. This is similar to most other previous studies among different populations such as the USA, which showed a comparable rate of INH monoresistant (9.3%) and other regions including neighboring Arabian Gulf countries[10-13].

Rifampicin resistance (RR) detection by molecular testing using Gene X-pert among our isolates was an accurate predictor for MDR; 17 isolates were identified early by Gene X-pert as RR and the same isolates were confirmed later as rifampicin-resistant by phenotypic drug susceptibility testing. Of these 17 isolates, two were isoniazid sensitive; therefore, they were classified as rifampicin monoresistant while the remaining 15 (88%) were confirmed as MDR by further phenotypic sensitivity (resistant to isoniazid and rifampicin). Accordingly, rapid testing for RR by molecular method is of great importance for early recognition of MDR for timely initiation of appropriate anti-tuberculous therapy[14].

This study had some limitations due to its retrospective design. In addition, lack of information about the status of MDR patients. Non-Bahrainis are repatriated to their original countries after commencing appropriate anti-tuberculous therapy and rendering them non-infectious (after one negative MTB culture).

Another limitation was the lack of information about the susceptibility pattern of MDR cases to second-line anti-tuberculous drugs. This should be considered as an important area of improvement in the national TB control program, which could be achieved either through upgrading the public health lab capacity to perform such testing or linked to a partner lab outside the country such as WHO Supranational Reference Laboratories in the region.

CONCLUSION

The incidence of MTB in Bahrain is decreasing; our MDR TB rate is comparable to other reported data from developed countries and neighboring Arabian Gulf countries.

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REFERENCES

1. Daniel TM. The History of Tuberculosis. Respir Med 2006; 100(11):1862-1870.
2. World Health Organization. Geneva. Global Tuberculosis Report 2017. http://www.who.int/tb/publications/global_report/en/ Accessed in October 2017.
3. Dheda K, Gumbo T, Gandhi NR, et al. Global Control of Tuberculosis: From Extensively Drug-Resistant to Untreatable Tuberculosis. Lancet Respir Med 2014; 2(4):321-338.
4. Zignol M, Dean AS, Falzon D, et al. Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. N Engl J Med 2016; 375:1081.
5. Rajbhandary SS, Marks SM, Bock NN. Costs of Patients Hospitalized for Multidrug-Resistant Tuberculosis. Int J Tuberc Lung Dis 2004; 8(8):1012-1016.
6. World Health Organization. Global Tuberculosis Report 2018. http://www.who.int/tb/publications/global_report/en/ Accessed on 01 October 2018.
7. Bahrain Health Statistics. Health Statistics 2017. http://intranet.health.gov.bh/Docs/Statistics/Health Statistics2017/Chapters/PublicHealth_MoH2017.pdf Accessed on 01 October 2018.
8. Areeshi MY, Bisht SC, Mandal RK, et al. Prevalence of Drug Resistance in Clinical Isolates of Tuberculosis from GCC: A Literature Review from January 2002 to March 2013. J Infect Dev Ctries 2014; 8(9):1137-1147.
9. European Centers for Disease Prevention and Control. Tuberculosis Surveillance and Monitoring in Europe 2019. https://ecdc.europa.eu/sites/portal/files/documents/tuberculosis-surveillance-monitoring-Europe-2019-20_Mar_2019.pdf Accessed on 29 July 2019.
10. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2013. US Department of Health and Human Services, Atlanta, GA 2013. http://www.cdc.gov/tb/statistics/reports/2013/pdf/report2013.pdf Accessed on 29 July 2019.
11. Gegia M, Cohen T, Kalandadze I, et al. Outcomes among Tuberculosis Patients with Isoniazid Resistance in Georgia, 2007-2009. Int J Tuberc Lung Dis 2012; 16(6):812-816.
12. Ormerod LP, Horsfield N, Green RM. Can a Nine-Month Regimen be used to Treat Isoniazid Resistant Tuberculosis Diagnosed after Standard Treatment is started? J Infect 2001; 42:1–3.
13. Bang D, Andersen PH, Andersen AB, et al. Isoniazid-Resistant Tuberculosis in Denmark: Mutations, Transmission and Treatment Outcome. J Infect 2010; 60:452–457.
14. Steingart KR, Schiller I, Horne DJ, et al. Xpert(R) MTB/RIF Assay for Pulmonary Tuberculosis and Rifampicin Resistance in Adults. Cochrane Database Syst Rev 2014; (1):CD009593.