

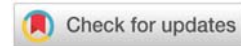


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Research Article

Epidemiology of drug-resistant tuberculosis in Bahrain, five years review

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Abstract

Introduction: Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide, drug resistance is one of the major contributors to that. No existing published data about the burden of Multi-Drug Resistant (MDR) TB in the kingdom of Bahrain, the aim of our study is to estimate the prevalence of MDR TB in the kingdom and to define its resistance profile.

Materials and methods: Retrospective observational study of patients with clinical diagnosis of TB between January 2014 and December 2018, cases with positive MTB culture were included for further analysis based on the results of phenotypic drug susceptibility testing to first line antituberculous. Result of molecular testing (MTB PCR & rifampicin resistant gene) were also retrieved and included in the analysis.

Results: During the study period, the incidence of TB in Bahrain have dropped 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 clinical diagnosis of TB, out of which; Five hundred and eighty eight (59%) had confirmed positive culture of Mycobacterium Tuberculosis (MTB).

MDR TB was identified among 15 out of the 588 positive isolates (3%). Majority of MDR (12cases ,80%) were Non Bahraini and 10 cases, (67%) were males, pulmonary involvement encountered among 11 cases (73%).

Discussion: Our rate of MDR is comparable to other reported data among neighboring Arabian Gulf countries who illustrated an average of 4% MDR-TB prevalence. Similar prevalence rate was estimated among European countries (3.8%).

Among other drug resistance pattern, isoniazid monoresistant was the most predominant resistant pattern among our population, it account for 9% among all tested isolates, this in agreement with most other previous studies among different population.

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

Introduction

Tuberculosis (TB) remains a major public health concern worldwide with attributable morbidity and mortality despite all enormous efforts [1,2], drug resistance is one of the major contributors to that.

The World Health Organization (WHO) declared multi-drug resistant TB (MDR-TB), defined as Mycobacterium tuberculosis resistant to isoniazid and rifampicin, as a public health crisis in 2013. Furthermore, the risk is aggravated with the emergence of extensively 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 20months or more [2], in addition to its financial burden, it is usually associated with a poor outcome and this have been documented in many published data that treatment success rates for drug-sensitive TB is significantly higher than that of MDR-TB with lower attributable mortality [5].

Obtaining precise figures about the global burden of MDR-TB is challenging, as drug susceptibility testing for MTB is not performed in many resource-limited settings on routine basis, in addition to the underreporting [6]. According to the available published data in WHO 2018 Global Tuberculosis Report, the



estimated worldwide prevalence of MDR is 3.5% of all new TB cases and 18% of previously treated cases with significant variability among different geographical regions where MDR rate is disproportionately higher in developing countries with high burden of the disease [6].

Optimizing an appropriate treatment regimen for MDR TB usually rely on patient history of previous treatment (for retreatment cases), results of susceptibility testing to other antituberculous drugs including second line agents in addition to local drug resistance patterns, hence it's very important to define our local resistant pattern of MDR in the kingdom of Bahrain.

No existing published data about the burden of MDR TB in the kingdom of Bahrain, the aim of our study is to estimate the prevalence of MDR TB in the kingdom and to define its resistance profile.

Materials and methods

Retrospective observational study of patients with clinical diagnosis of TB between January 2014 and December 2018.

In the kingdom of Bahrain; Public health directorate is responsible to collect data about all notified cases of TB from all governmental & private health care facilities through obligatory official notification from the treating clinician at the time of diagnosis. To ensure the efficiency of such reporting; all TB diagnostic mycobacteriology are centralized in the public health laboratory, also the supply of antituberculosis medication is restricted to the pharmacy of main governmental hospital where there is electronic notification from the pharmacy to the public health directorate for all cases on antituberculous therapy.

All this information are gathered, further tabulated & organized into the national TB surveillance database system in the public health.

Public health laboratory is the reference laboratory in the kingdom of Bahrain, where its mandatory to refer all clinical isolates with suspected TB for further identification & confirmation. All cases with suspected clinical diagnosis of TB will be processed routinely for Acid Fast Bacilli (AFB) smear, MTB culture and molecular testing by Gene X-pert for MTB Polymerase chain reaction (PCR) & rifampicin resistance gene. Cases with positive MTB culture will be further processed for phenotypic drug susceptibility testing to the 4 first line antituberculous medication (isoniazid, rifampicin, ethambutol and streptomycin), Pyrazinamide was not done on routine basis for all positive MTB isolates.

Data of the study were collected from all patients who had a clinical diagnosis of TB in Bahrain during the study period. Cases with positive MTB culture were included for further analysis based on the results of phenotypic drug susceptibility testing to first line antituberculous. Result of molecular testing (MTB PCR & rifampicin resistant gene) were also retrieved and included in the analysis. Patients with multiple positive TB cultures, the first positive culture was only included.

Results

Epidemiology of MDR TB & resistance to first line anti-tuberculous drugs

During the study period, the incidence of MTB in Bahrain have dropped 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 clinical diagnosis of TB; out of which; Five hundred and eighty eight (59%) had confirmed positive culture of MTB Table 1.

Table 1: Number & incidence of TB in Kingdom of 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 during the study period illustrated in Table 2, where the highest resistance pattern was documented against isoniazid (9%), followed by streptomycin (6%) then rifampicin (3%) and least for ethambutol (1%) Graph 1.

MDR TB was identified among 15 out of the 588 positive isolates (3%) by phenotypic drug susceptibility testing that illustrate resistance to both isoniazid & rifampicin. No details are available about treatment history of MDR cases to stratify them into new vs. retreatment cases. Majority of MDR (12 cases, 80%) were Non Bahraini and 10 cases, (67%) were males, pulmonary involvement encountered among 11 cases (73%).

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

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

As displayed in Table 2 below, The prevalence of resistant isolates & MDR TB was almost in the same range over the study period with minimal fluctuation spanning that period.

Discussion

Incidence of TB, as well as the prevalence of MDR TB showed great variability in different part of the world. Previous epidemiological data about TB in Bahrain revealed that Bahrain

**Table 2:** The prevalence of resistant isolates & 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%)

Graph 1: Average resistant rate of MTB to first line antituberculous (2014-2018).

Antituberculous Drug	isoniazid	Streptomycin	Rifampicin	Ethambutol	MDR
Percentage of resistance	9%	6%	3%	1%	3%

is considered as one of the low endemicity countries for TB with majority of TB patients (85%) are Non Bahraini [7].

Results of our study revealed MDR rate of 3% among all TB cases, which is comparable to other reported data among neighboring Arabian Gulf countries as published by Areeshi, et al., [8], who illustrated an average of 4% MDR-TB prevalence among 4 Arabian Gulf countries, with highest prevalence among UAE population (9.2%), followed by Kuwait (5.9%) and then Saudi Arabia (4.3%), whereas lowest prevalence rate was observed in Oman (1%).

Similar prevalence rate was estimated among European countries [9], as 3.8% among all TB cases, stratified into 15% among retreatment & 2.4% among new cases, while USA reported overall lower MDR prevalence rate of 1.2% [10].

Among other drug resistance pattern, isoniazid monoresistant was the most predominant resistant pattern among our population, it account for 9% among all tested isolates, this in agreement with most other previous studies among different population such as USA data [11], which showed comparable rate of INH monoresistant (9.3%) and other published studies in different geographical region including neighboring Arabian Gulf countries [11-13].

Rifampicin Resistance (RR) detection by molecular testing using Gene X-pert among our isolates was accurate predictor for MDR, 17 isolates were early identified by Gene X-pert as RR & the same isolates were confirmed later as rifampicin resistant by phenotypic drug susceptibility testing, out of these 17 isolates; two turn to be isoniazid sensitive, so were classified as rifampicin monoresistant while the remaining 15 (88%) were all confirmed as MDR by further phenotypic sensitivity testing (resistant to isoniazid and rifampicin).

Accordingly, in agreement with other previously published data [14], rapid testing for RR by molecular method is of great importance for early recognition of MDR for timely initiation of appropriate antituberculous therapy.

This study has some limitations, primarily related to its retrospective design. In addition, lack of information about

the status of MDR cases as being new cases or retreatment and the treatment outcome of those MDR patients which were missing as majority (80%) of cases were Non Bahraini and were repatriated according to our policy in Bahrain that all MDR TB cases are repatriated to their original countries after commencing them on appropriate antituberculous therapy & rendering them non infectious (by getting one negative MTB culture).

Other important limitation is lack of information about the susceptibility pattern of MDR cases to second line antituberculous drugs, indeed this should be considered as an important area of improvement in our national TB control program as it raised concerns about the need of performing routine susceptibility test of all MDR isolates to second line antituberculous drugs, which could be achieved either through upgrading of our public health lab capacity to perform such testing or to rely on linkage with a partner lab outside the country such as WHO Supranational Reference Laboratories in the region. Having such results of susceptibility to second line antituberculous drugs should be of critical value on individual case management to refine and optimize the antituberculous drug regimen & on a larger scale to have our national pattern of resistance for MDR to design the most appropriate empiric regimen for our population.

Conclusion

Incidence of MTB in Bahrain is dropping, our MDR TB rate is comparable to other reported data from developed countries & neighboring Arabian gulf countries.

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