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Research Paper

The Prevalence of Antituberculosis Multidrug Resistance in Yemen 2013

Pharma

KEYWORDS : Tuberculosis; Drug sensitivity test;Multidrug resistance; Yemen

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ABSTRACT

Tuberculosis is an infectious disease caused by bacteria called Mycobacterium Tuberculosis. It primarily affects the lungs, but it can also affect organs in the central nervous system, lymphatic and the circulatory systems. An estimated 14 million people worldwide are infected with active tuberculosis (TB), which is a disease affecting mainly young adults. The vast majority of deaths from TB are in the developing world and TB is considered to be the second most contagious disease to cause fatalities in the world.The Incidence of tuberculosis (per 100,000 people) in Yemen was last reported 49 in 2010, according to a World Bank report published in 2012. Incidence of tuberculosis is the estimated number of new pulmonary, smear positive, and extra-pulmonary tuberculosis cases. The aim of this study to survey multidrug resistance tuberculosis (MDR TB) against four drugs used in Yemen (isoniazide, rifampicin, ethambutol and streptomycin) among new cases. Samples were collected from The National Tuberculosis Institute (NTI), Sana'a between Jan. and Sept. 2013. About 731 of 2226 of patients from different governances that referred to NTI were reported as Mycobacterium tuberculosis positive cultures.209 of 731 were showed mono or multidrug resistance, the others either negative or contaminated. 201 of 209 cultures were obtained from new cases and 8 previously treated. The prevalence of any resistance to four drugs was 63.7% (95 CI 58.1-71.3) among new cases compared with 25%(95CI 7.1-59.1) among previously treated cases. The prevalence of MDR TB was shown 41.3% (95 %CI 34.5-48.1) among new cases compared with 12.5% (95% 2.2-47.1). Conclusion: there is high prevalence of MDRTB developed worldwide in the last three yearsdeveloped between new cases. This estimates high prevalence problem not only in Yemen but around the world.

1. INTRODUCTION

Tuberculosis is a chronic disease caused by different strains of bacillus bacteria known as mycobacterium tuberculosis [1]. This infectious disease can be localized in the lung or spreads to affect other parts of body. Most of these cases are asymptomatic, but one of ten of infected cases may progress and can be fatal if not treated [2].

However, according to WHO reports in 2009 and 2010 found that "One third of the world's population is thought to have been infected with M. tuberculosis, with new infections occurring in about 1% of the population each year"[3,4].While, in 2007, about 13.7 million estimatedchronic active cases globally were recorded. Again in 2010, about 8.8 million new cases were reported with 1.5 million deaths, most of themwere reported in developing countries.[5,6].

Distribution of this disease is not uniform and equally, it differs from one area to other. Globally about 80% of population in Asia and Africa are positive tuberculin test, in contrast, the United States were reported only about 5-10% positive test. [1]. This variation referred to predisposing immune compromised diseases mainly AIDS.[7]

However, primary resistance occurs when a person becomes infected with a resistant strain of TB. A person with fully susceptible TB may develop secondary (acquired) resistance during therapy because of inadequate treatment, not taking the prescribed regimen appropriately (lack of compliance), or using low-quality medication [8]. Drug-resistant TB is a serious public health issue in many developing countries, as its treatment is longer and requires more expensive drugs. Moreover, multidrug resistant (MDR-TB) is defined as resistance to the two most effective first-line TB drugs: rifampicin and isoniazid. Extensively drug-resistant TB is also resistant to three or more of the six classes of second-line drugs [9].Totally drug-resistant TB, which was first observed in 2003 in Italy, but not widely reported until 2012, is resistant to all currently used drugs [10].

The estimated numbers of T.B cases in Yemen are 12000 that are mean 49 per 100,000 population and deaths in Yemen reached 2,251 or 1.72% of total deathsaccording to WHO statistics, 2012. The age adjusted death rate is 20.45 per 100,000 of population ranks Yemen number 70 in the world [11,12,13]

The aim of this study to survey the multidrug resistance tuberculosis (MDR TB) against four antituberculosis drugs used in Yemen (isoniazide, rifampicin, ethambutol and streptomycin) among new cases compared with previously treated onethrough measuring different parameters including: all referred clinical cases enrolled at The National Tuberculosis Institute (NTI), Sana'a –Yemen between Jan. andSep. 2013. Sputum test was done todifferentiate between positive and negative M. TB cases as well as drug sensitivity test to detect mono or multidrug resistance.

2. MATERIALS AND METHODS

2.1. Study design:

731positive sputum specimens of 2226 patients enrolled to NTI lab. between Jan.-Sep. 2013 from different centers and governorates in Yemen,including both sexes and different age groups were identified and cultured for DST. Drug sensitivity test was done to indicate mono or multidrug resistance tuberculosis (MDRTB). 209 casesof 731were shown mono or multidrug resistance tuberculosis (MDRTB). 201 of 209 were new cases and 8 previously treated. All patients were treated with the first line strategy including (isoniazide, rifampicin, ethambutoland streptomycin).

2.2. Methods

All sputum specimens were identified and DST done in the NTI. For isolation of culture, each specimen was treated with 4% NaOH to one volume of sputum and then homogenized by vigorous stirring. An aliquot of 0.1 ml of the specimen thus treated was inoculated into two tubes of 2% Kudoh media and incubated at 37C°. The culture was read in week 1 and after 4 weeks to detect rapid and slow growing, following which observations were made every week for 8 weeks until the result was recorded as negative. M. tuberculosis growing on media was differentiated from other mycobacteria by growth characteristics, colony morphology, the niacin test by a paper strip and the P-nitrobenzoicacid susceptibility test. DST was performed both at the National TB Reference Laboratory at the NTI, Sana'a City for confirmation. The proportion method was carried out for DST using Löwenstein-Jensen (L-J) medium at the NTI or Ogawa medium at the RIT. The critical proportion of resistance was 1% for all drugs; the critical concentration was as follows: 0.2 µg/ml for INH, 40 µg/ml for REP, 4.0 µg/ml for SM with L-J medium and 10µg/ml with Ogawa medium and 2.0 µg/ml for ETB with L-J medium and 2.5 µg/ml with

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Ogawa medium. A preliminary reading for DST was made at week 2,3 and finally after 4weeks. Resistance was expressed as the percentage of colonies that grew on the drug-containing medium compared to those on control medium. [14,15, 16]

2.3. Statistical analysis

The $\chi 2$ test was applied to compare two proportions and the t-test was applied to compare two means at a significance level of $P < 0.05$. Wilson's method for calculating 95%CI was applied for small frequency.10 Stata version 8.2 (Stata Corp, College Station, TX, USA) was used for statistical analyses.

3. RESULTS

Outcomes of this survey were shown high resistance development in the last years. MDRTB was high (41.3%) especially between new cases compared to (12.5%) between previous treated cases as shown in table (1). Most of these multidrug resistance were found between 15-44 productive age and was equally in both sexes as shown in table (2).

Table 1: Prevalence of drug resistance to anti-tuberculosis drugs in Yemen

	New cases		Previously treated cases		Total cases	
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI
Total strains included	717 (98.1)		14 (1.9%)		731(100)	
Total number of strains tested	201 (96.2)		8 (3.8)		209 (100)	
Susceptible to all four drugs	71 (35.3)	28.7 - 41.9	6 (75)	45 - 100	77 (36.8)	30.3 - 43.4
Any resistance	128 (63.7)	57.0 - 70.3	2 (25)	7.2 - 59.1†	130 (62.2)	55.6 - 68.8
PNB	2 (1)	0.3-3.6†	0	0 - 32.4†	2 (1)	0.3 - 3.4†
Niacin	2 (1)	0.3-3.6†	0	0 - 32.4†	2 (1)	0.3 - 3.4†
SM	46 (22.9)	17.1 - 28.7	0	0 - 32.4†	46 (22)	16.4 - 27.6
INH	98 (49.3)	42.3 - 56.2	2 (25)	7.1 - 59.1†	97 (46.4)	39.7 - 53.2
REP	93 (46.3)	39.4 - 53.2	1 (12.5)	2.2 - 47.1†	94 (45)	38.2 - 51.7
ETB	43 (21.4)	15.7 - 27.1	0	0 - 32.4†	43 (20.6)	15.1 - 26.1
Mono-resistance	45 (22.4)	16.6 - 28.2	1 (12.5)	2.2 - 47.1†	46 (22.0)	16.4 - 27.6
PNB	2 (1)	0.3-3.6†	0	0 - 32.4†	2 (1)	0.3 - 3.4†
Niacin	2 (1)	0.3-3.6†	0	0 - 32.4†	2 (1)	0.3 - 3.4†
SM	12 (6)	2.7 - 9.3	0	0 - 32.4†	12 (5.7)	2.6 - 8.9
INH	14 (7.0)	3.4 - 10.5	1 (12.5)	2.2 - 47.1†	15 (7.2)	3.6 - 10.7
REP	9 (4.5)	1.6 - 7.4	0	0 - 32.4†	9 (4.3)	1.6 - 7.1
ETB	6 (3)	0.6 - 5.4	0	0 - 32.4†	6 (2.9)	0.6 - 5.1
Multidrug resistance	83 (41.3)	34.5 - 48.1	1 (12.5)	2.2 - 47.1†	84 (41.2)	33.5 - 46.8
INH.REP	25 (12.4)	7.8 - 17.0	1 (12.5)	2.2 - 47.1†	26 (12.9)	8.3 - 17.6
INH.REP.ETB	24 (11.9)	7.5 - 16.5	0	0 - 32.4†	24 (11.5)	7.2 - 15.8
INH.REP.SM	21 (10.4)	6.2 - 14.7	0	0 - 32.4†	21 (10)	5.9 - 14.1
INH.REP.SM.ETB	13 (6.5)	3.1 - 10.0	0	0 - 32.4†	13 (6.2)	2.9 - 9.5

† Calculated by Wilson's method .INH: isoniazide, REP: rifampicin, ETB: ethambutol, SM: streptomycin

Table 2: prevalence of any resistance and MDR cases by sex andage in new cases (n=201)

n (%)		Any resistance				MDR				Total
		95%CI	Prevalence OR	P-value	n (%)	95%CI	Prevalence OR	P-value		
Sex					0.640				0.661	
	Female	64 (65.3)	55.9 - 74.7	1.15		42 (42.9)	33.1 - 52.7	1.13		98
	Male	64 (62.1)	52.8 - 71.5			41 (39.8)	30.4 - 49.3			103
	Total	128				83				201
Age group, years					<0.001				<0.001	
	0 - 14	0	0 - 35.4†			0	0 - 35.4†			7
	15 – 24*	37 (59.7)	47.5 - 71.9	1		24 (38.7)	26.6 - 50.8	1		62
	25 - 34	25 (37.9)	26.2 –49.6	0.41		19 (28.8)	17.9 - 39.7	0.64		66
	35 - 44	33 (100)		0		24 (72.7)	57.5 - 87.9	4.22		33
	≥ 45	33 (100)		0		16 (48.5)	31.4 – 65.5	1.49		33
	Total	128				83				201

***Reference group, † Calculated by Wilson's method**

4. DISCUSSION

About 14 million around the world are infected with tuberculosis according to the 2012 statistics especially in adult group. In Yemen, about 12,000 people are infected with this disease and 1400 are die from it [17]. Bad habits of khat chewing and water pipe smoking for long khat session are among the most risk factors in transmission of this infectious disease in Yemen. They use the same pipe for all the khat chewier in the same room. Some studies found that khat has immunemodulating effect that may increase the susceptibility to infectious disease [18, 19]. Tuberculosis is a most infectious disease caused by bacterial infection called mycobacterium. It is mainly affected pulmonary area and transmitted from person to other via infected droplet [20]. It affects mostly young person. About 95% are died in developing countries. When person is affected by this type of bacteria, it takes months to appear the symptoms. Through this period he becomes highly contagious source [21].

This study focused on the prevalence of mono and/or multidrug resistance TB against antituberculosis strategy in Yemen 2013. First line including INH, rifampicin, ethambutol and streptomycin is still the most efficacious treatment in Yemen up to 2010. In addition, some studies found that the annual risk of tuberculosis infection was low in Yemen in 2009 compared with that done in 1991through tuberculin survey [22]. Incontrast, the last three years showed rapidly developed resistance against this strategy in Yemen.

Outcomes of this work revealed that there is a high rate of resistance developed against mono (22.4%) and multidrug antituberculosis (41.3%) between new cases compared with previously treated one. It was seen that cases that developed monodrug resistance against rifampicin and INH more susceptible to develop multidrug resistance.

Multidrug resistance is caused by organism that developed resistance against INH and rifampicin either during treatment or due to infection caused by drug-resistant type. These forms not respond to the usual duration of treatment but need longer time. This may increase the incidence of toxicity, cost and patient compliance [18].

However, adult group especially that ranged between 15-24 (59.7%) and 35-44 years in both sexes showed high prevalence of developing resistance especially in Yemen. This may relates to debatable mismanagement of patient that found difficulty to continue treatment and the ease in development of resistance. In addition, the use of improper antibiotics or inadequate dose or infected by already resist organism all these are causes of developing drug resistance. This situation threatens the public health in Yemen and gives a chance to develop multidrug resistance against first line antituberculosis and failure of new cases treatment successfully [16]. WHO is warning the world from the development of MDR antituberculosis through the few years forthcoming. So development of TB Partnership Global Plan is very important to estimate the expected cases and treat them successfully.

However, according to the key findings of WHO, 2011about 3.7% around the world have MDR TB especially between new cases compared with previous treated one. They found that 9% of MDRTB may have also resisted to two other classes of drug[20]. These findings are supported our prevalence outcomes with high percentage of MDRTB over that recorded by WHO especially between middle age productive group.

In addition, WHO takes practical steps and effective to reduce the MDRTB development through providing evidence-based policies, new strategies to prevent and control TB disease. Engage the partnership of TB Global plan that need to treat the new cases very effectively. However, they also monitor the global TB programs and support the new researches in this manner through advisement and generosity fund [23].

5. CONCLUSION

There is high prevalence of MDRTB developed worldwide in the last three years especially in Yemen. This estimates public health problem not only in Yemen but around the world. The high burden countries should make and activate the TB partnership Global Plan to detect and treat successfully the new cases.

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7. CONFLICT OF INTEREST

There is no conflict of interest.

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