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Review article

Middle East *Mycobacterium tuberculosis* Antibiotic Resistance: A Systematic Review and Meta-Analysis

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Background: The global control of the drug resistance tuberculosis has remained as major challenge. The present study was the first review study in the Middle East region in order to determine levels of *Mycobacterium tuberculosis* resistance to the first-line anti-TB drugs among both new and previously treated cases.
Materials and Methods: The computer-assisted search was performed by using PubMed, Google Scholar, Scopus databases and related keywords. Within the time span of 1981-2014, a total of 480 articles were collected on the antibiotic resistance rates of *M. tuberculosis* in different countries of the Middle East region. About 63 relevant articles were selected by applying inclusion and exclusion criteria.
Results: By using meta-analyses, we determined mono drug resistance, any drug resistance, and multidrug resistance (MDR-TB) rates in both new and previously treated TB patients living in different parts of the Middle East. Other aspects related to patients, antimicrobial resistance, and methods used to assess the resistance rate were also analyzed.
Conclusion: The present study revealed that in comparison with the global average rate, the prevalence rate of drug resistant TB, especially MDR-TB, may be increasing in the Middle East. Therefore, in order to prevent the spread of drug-resistant isolates, detecting primary resistance to anti-TB drugs with the use of new rapid diagnostic methods is necessary.

Keywords: Mycobacterium tuberculosis, Antibiotic resistance, Middle East

1. Background

Mycobacterium tuberculosis (*M. tuberculosis*) is considered as a major cause of morbidity and mortality in humankind and has remained as a significant increasing concern for global public health in the 21st century (1-2). Tuberculosis (TB) is an infectious disease caused by bacterium *M. tuberculosis* (tubercle bacillus). The tubercle bacillus has latently infected one-third of the global population (2). According to the latest World Health Organization (WHO) estimation, there were 9 million new TB cases in 2013 with 1.5 million TB deaths in the world (3). Short course chemotherapy (SCC) of the first-line drugs, which is the treatment regimen recommended by WHO for new TB cases, is consisted of using 2 months of isoniazid, rifampicin, and pyrazinamide, plus a fourth drug (streptomycin or ethambutol), followed by 4 months of isoniazid and rifampicin (or alternatively, 6 months of isoniazid and ethambutol or thiacetazone) (4). But recently, the prevalence rate of multidrug-resistant strains of *M. tuberculosis* (MDR-TB) resistant to at least isoniazid and rifampicin has provided difficulties for TB control strategies (5). As the treatment, MDR strains require the use of second-line drugs that are much more toxic, expensive, and less effective than first-line drugs and need longer treatment period (about18.5months) (2, 6-7). Therefore, it is essential to perform drug susceptibility testing in order to detect and treat single drug resistant TB and prevent the emergence and spread of other forms of drug resistance (MDR, XDR and TDR) in new TB cases and also optimize the treatment (1,7).

TB is still one of the most common health problems in developing countries such as the Middle East countries. The Middle East is a region that covers S.W. Asia and N.E. Africa, stretching from the Mediterranean Sea to Pakistan and Afghanistan. Endemic countries with high burden of TB, Afghanistan and Pakistan, and high burden of MDR-TB, Iraq, are located in this region of the world (8). The trends in the incidence of TB and the emergence of MDR-TB isolates in the Middle East countries are different. In 2011, the incidence of TB per 100000 populations in the Middle East countries including Iran, Kingdom of Saudi Arabia, Turkey, Egypt, Syria, Israel, Afghanistan, Pakistan, Iraq, Yemen, United Arab Emirates, Qatar, Oman, Lebanon, Kuwait, Jordan, and Bahrain were 21, 14, 20, 16, 17, 5.8, 189, 275, 45, 48, 1.8, 40, 11, 16, 24, 5.8, and 18, respectively (9). In this year, the estimated MDR-TB cases among notified pulmonary TB cases in eastern Mediterranean countries was 17000, 7.8% for new TB cases and 21% for previously treated TB cases (9). Our systematic review of the published literature with the estimations for incidence rate of mono and any drug resistance and then meta-analysis of obtained data provided better evidence than surveillance estimations of anti-TB drug resistance reported by the World Health Organization.

2. Objectives

To the extent of our knowledge, this is the first systematic review study on antibiotic resistance of *M. tuberculosis* in the Middle East region. The purpose of this paper was to evaluate the prevalence rate of anti-tuberculosis drug resistance to the first- line drugs both in new and previously treated TB cases and also assess some aspects related to antimicrobial resistance, including: 1) year and area of research, 2) number of TB positive patients (sex and mean age) and strains tested, 3) methods used for drug susceptibility testing (DST), and 4) site of disease by using a systematic review and meta-analysis.

3. Materials and Methods

3.1. Search strategy and evaluation criteria

In this systematic review, we performed the computer-assisted search by using the electronic databases of PubMed, Scopus, and

Google Scholar in order to find published English language literature on antibiotic resistance in *M. tuberculosis* in the Middle East from 1981 to 2014. The authors used the medical terms including "antibiotic resistance", "*M. tuberculosis*", "Middle East", and "country of origin" for collecting a list of original research articles. Hand searching of reference lists was performed to identify any additional studies which might have been missed. Some limits were incorporated for the exclusion of irrelevant electronic search and repeated articles in databases. Inclusion criteria for the original articles to be included in our review after title, abstract, and full text review of articles, which should have been matched with our review, were consisted of: 1) being published in English language, 2) assessing drug susceptibility patterns of *M. tuberculosis* against first-line drugs (rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin), 3) investigating MDR-TB suspected patients.

Exclusion criteria for the original articles to be excluded from our review were consisted of: 1) availability only with their native language, 2) availability only with their abstract, 3) investigating patients suspected to XDR and TDR-TB, 4) assessing drug susceptibility patterns of *M. tuberculosis* against second-line drugs, 5) containing data of the combined prevalence rate of drug resistance regardless of prior drug treatment, and 6) being review articles. Duplicate studies were discussed, and only the most recent reports were included in our systematic review.

3.2. Quality criteria

Based on eight main quality criteria proposed by Loney *et al*, relevant articles were investigated (Table 1).

3.2.1. Characteristics of the target population

To extract the following data, all studies conducted in the Middle East region were assessed with regard to the target population characteristics, including: 1) their geographical area, 2) age, 3) sex, 4) type of patients (new/retreatment cases), 5) site of TB infection (pulmonary/extra-pulmonary specimens), and 6) clinical characteristics of patients.

3.2.2. Characteristics of sampling

To extract the following data, all of the studies conducted in the Middle East region were assessed with regard to the sampling characteristics, including: 1) sampling methods, 2) type of sample (pulmonary/extra-pulmonary specimens), 3) sample size/strains, and 4) number of patients.

3.2.3. Characteristics of antibiotic resistance of M. tuberculosis

To extract the following data, all of the studies conducted in the Middle East region were assessed with regard to the antibiotic resistance characteristics of *M. tuberculosis*, including: 1) the frequency of drug resistance to first-line anti-TB drugs (rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin) both in new cases and previously treated TB cases, and 2) the frequency of MDR.

3.2.4. Laboratory diagnosis and antibiotic susceptibility testing methods

To extract the following data, all of the studies conducted in the Middle East region were assessed with regard to the laboratory diagnosis of *M. tuberculosis* and drug susceptibility testing (DST) methods, including 1) biochemical tests, and 2) common methods for the performance of *M. tuberculosis* drug susceptibility testing.

3.3. Definitions

In the present study, we defined mono drug resistance, any drug resistance, and MDR-TB as resistance to a single first-line drug, to one or more first-line drug, and to at least INH and RMP, respectively (8). Also, patients with TB who had never received anti-TB drug or treated for less than 1 month were defined as new TB cases, and patients with previous history of receiving anti-TB treatment for at least 1 month were defined as previously treated TB cases (8). In drug susceptibility testing methods, *M. tuberculosis* was considered as a resistant isolate, when bacterial growth was 1% or more on the medium containing antibiotic compared to antibiotic-free medium.

3.4. Statistical analysis

The frequency of drug resistance was expressed as percentage. We pooled data across studies using random effects model due to heterogeneity of the included studies. Heterogeneity was assessed by Cochran's Q test ($p< 0.05$ was considered statistically significant) and I^2 index. Meta-analyses were done for each country separately, and for different categorical variables, sub-group analyses were done to explore the effect of the variables on the resistance frequency. For publication bias evaluation, funnel plots were used. All analyses were done by CMA version 2.

4. Results

A total of 480 articles were collected on antibiotic resistance of *M. tuberculosis* in different countries of the Middle East region from 1981 to 2014. After screening, 82 papers were selected based on inclusion and exclusion criteria. In the present study, articles were selected from 17 Middle Eastern countries, there were 20 studies from Iran, 13 studies from Kingdom of Saudi Arabia, 17 studies from Turkey, 3 studies from Egypt, 1 study from Syria, 2 studies from Israel, 12 studies from Pakistan, 2 studies from Iraq, 1 study from Yemen, 2 studies from United Arab Emirates, 2 studies from Qatar, 2 studies from Oman, 3 studies from Lebanon, 1 study from Kuwait, and 1 study from Jordan. No study was found from Afghanistan and Bahrain. Out of 82 articles, 19 articles were excluded from the meta-analysis because they were duplicate publications of the same affiliation. Table 1 represents the year of research and the number of strains tested, the study location, the methods used to assess the resistance rate, the prevalence rate of drug-resistant TB, and other aspects related to patients, including the number of *M. tuberculosis* positive patients (new or previously treated TB cases), their age, sex, and site of disease. Table 2 shows the prevalence rate of mono drug resistance, any drug resistance, and MDR-TB both in new and previously treated TB patients in different countries of the Middle East. Based on the obtained results in Table 2, countries with shared geographical borders such as Iran, Turkey, and Pakistan have similar drug resistance profile. Table 3 shows the overall antibiotic resistance pattern in the Middle East region. The number of the studies that contained data of mono, any, and multidrug resistance is presented in this table for both new and retreated TB cases. Also, for assessing heterogeneity of the studies included, we used the I^2 index and Cochran's Q test that show high heterogeneity between studies. Figure 2 is the funnel plot of the meta-analysis for detecting the presence of publication bias and assessing its impact on the analysis in both new and previously treated TB cases. The funnel plot shows some asymmetry which could be due to possible publication bias. Distribution of single, any, and MDR-TB among new TB cases in different countries of the Middle East are shown in Figure 3. Drug resistance rate has not been evaluated completely in many countries such as Bahrain and Afghanistan, so it cannot fully be generalized to the country level and the Middle East region. Ultimately, Figure 4 presents the forest plot of the meta-analysis on mono drug resistance, any drug resistance, and MDR-TB in both new and previously treated TB patients. It has been arranged based on country, type of patients (new or previously treated), type of antibiotic resistance, event rate for each study as number (percent), and 95% confidence interval.

Table 1. Prevalence of antibiotic resistance among new and previously treated TB cases in the Middle East region.

First author (Ref)	Year	Method (s)	Area-City	Patients (n)	Clinical characteristics of patients	Strains (n)	New TB cases				Previously treated TB cases				Site of disease	Mean age	Sex M/F
							Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)	Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)			
Nasiri (8)	2010-12	Proportion method	Iran-Five cities	6426	Mycobacteriology center, Baqiyatallah hospital, Tehran	252	252	24	41	16	NA	NA	NA	NA	Pulmonary-TB/extra-pulmonary- TB	11-80	NA
Haeili (10)	2010-12	Proportion method	Iran-Five cities	NA	Tehran University of Medical Sciences	291	291	29	NA	15	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary-TB	9-88	NA
Namaei (11)	2001-2	Proportion method	Iran-Mashhad	2682	Mashhad University of Medical Sciences	105	105	20	31	1	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	56.6	55/ 60
Mohajeri (12)	2011-12	Proportion and microdilution methods	Iran-Kermanshah	130	Kermanshah University of Medical Sciences	112	112	15	NA	16	NA	NA	NA	sit	Pulmonary-TB	NA	64/ 48
Bahrmand (13)	1998-9	Proportion method	Iran-Tehran	774	Pasteur Institute of Iran	563	563	47	87	23	NA	NA	NA	NA	Pulmonary-TB	1-85	380/ 394
Heidarnejad (14)	1999-2000	Proportion method	Iran-Tabriz	165	Tabriz University of Medical Sciences	155	148	NA	25	NA	7	NA	NA	1	Pulmonary-TB	44	92/ 73
Farnia (15)	2006-7	Proportion method	Iran-Tehran	NA	NRITLD	258	NA	NA	NA	NA	258	20	22	72	Pulmonary-TB/ extra-pulmonary- TB	42.5	147/ 111
Taghavi (16)	2008-9	Proportion method	Iran-Tehran	96	NRITLD	96	96	30	30	36	NA	NA	NA	NA	Pulmonary-TB	50	53/ 43
Farazi (17)	2011-12	Proportion method	Iran-Arak	120	Arak University of Medical Sciences	115	103	13	31	NA	12	3	NA	NA	NA	52.23	56/ 59
Sharifi (18)	2009-10	Proportion method	Iran-Yazd	31	Yazd University of Medical Sciences	31	31	NA	10	2	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Naserpour-Farivar (19)	2001-3	Proportion method	Iran-Zahedan	84	Bou-Ali hospital of Zahedan	84	84	NA	32	14	NA	NA	NA	NA	NA	NA	NA
Metanat (20)	2007-8	Proportion method	Iran-Zahedan	88	Zahedan University of Medical Sciences	88	78	NA	9	9	10	NA	NA	4	pulmonary TB	15-94	35/ 53
Al-Rubaish (21)	1993-6	Bactec system	KSA-Dammam	411	King Fahad Hospital of the University, Al-Khobar and the Dammam Chest Hospital	NA	411	29	43	11	NA	NA	NA	NA	pulmonary TB	NA	NA
Al-Tawfiq (22)	1989-2003	Disk method	KSA-Dhahran	279	Dhahran Health Center, Saudi Aramco Medical Services Organization	279	279	86	78	2	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	49	133/ 146
Khan (23)	1996-8	Bactec system	KSA-Jeddah	101	King Khalid National Guard Hospital	101	101	69	30	21	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	NA	39/ 35

Table 1. (Continued)

First author (Ref)	Year	Method (s)	Area-City	Patients (n)	Clinical characteristics of patients	Strains (n)	New TB cases				Previously treated TB cases				Site of disease	Mean age	Sex M/F
							Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)	Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)			
Kordy (24)	1981-2003	Bactec system	KSA-Riyadh	764	King Faisal Specialist Hospital and Research Centre	764	714	35	54	12	50	3	11	7	NA	47	NA
Asaad (25)	2009-11	Proportion method	KSA-Najran	80	Chest and Fever Hospital and King Khalid Hospital	68	68	50	26	14	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Varghese (26)	2002-5	Bactec system	KSA- Nine provinces	NA	Nine provinces	151	103	88	NA	15	48	4	NA	44	Pulmonary-TB/ extra-pulmonary- TB	NA	103/ 48
Al-Awaidy (27)	1994-5	Bactec system	KSA-Riyadh	NA	Sahari Chest Hospital	362	362	57	45	NA	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Al-Orainey (28)	1986-8	Bactec system	KSA-Riyadh	432	Chest Diseases Centre and King Khalid University Hospital	432	340	30	39	NA	92	11	53	NA	Pulmonary-TB/ extra-pulmonary- TB	35	242/ 190
AL-HAJJAJ (29)	1996-7	NA	KSA-Riyadh	231	Riyadh Tuberculosis Center	231	NA	NA	NA	NA	231	56	91	4	Pulmonary-TB	35.9	173/ 58
Al-Hajoj (30)	2009-10	Bactec system	KSA-13 provinces	2235	King Faisal Specialist Hospital and Research Centre	1904	1609	193	264	29	295	97	188	47	Pulmonary-TB/ extra-pulmonary- TB	NA	1195/ 702
Moaddab (31)	1999	Proportion method	Turkey-Istanbul	91	Cerrhapasa Medical Faculty Hospital	91	38	8	12	1	42	11	24	5	Pulmonary-TB	NA	NA
BALCI (32)	1995-9	Bactec system	Turkey-Gaziantep	2798	Clinical microbiology laboratory of Gaziantep University Hospital	264	264	47	106	52	NA	NA	NA	NA	NA	47	NA
Kilicaslan (33)	1999	Proportion method	Turkey-Istanbul	3351	Central Microbiology Laboratory of the Istanbul Union Against Tuberculosis	1370	1046	136	209	33	324	46	131	60	Pulmonary-TB	35.7	1141/229
Karabay (34)	NA	Proportion method	Turkey-Trakya	NA	Medical Faculty of Trakya University	214	118	18	30	NA	96	25	75	NA	Pulmonary-TB	44.6	192/ 22
BULUT (35)	2004-7	Bactec system	Turkey-Tokat	300	Faculty of Medicine, Gaziosmanpaşa University	241	241	28	48	11	NA	NA	NA	NA	NA	5-78	151/ 90
Surucuoglu (36)	1997-2003	Bactec system	Turkey-Manisa	NA	Celal Bayar University Hospital	355	297	NA	75	13	58	NA	26	13	Pulmonary-TB	NA	273/ 82
Tahaoglu (37)	1992	Proportion method	Turkey-Istanbul	785	Pulmonary department of the Siireyyapaga Center for Chest Diseases and Thoracic Surgery	NA	525	86	140	12	260	49	139	35	Pulmonary-TB	38	NA
Kartaloglu (38)	1999-2000	Bactec system	Turkey-Istanbul	365	Gata Camlica Chest Diseases Hospital	365	365	69	87	10	NA	NA	NA	NA	Pulmonary-TB	25.5	352/ 13
Komurcuoglu (39)	1999-2004	Proportion method/ Bactec system	Turkey- Izmir	387	Izmir Training Hospital for Chest Diseases and Chest Surgery	297	231	8	18	5	53	12	31	6	Pulmonary-TB	23.7	387/0

Table 1. (Continued)

First author (Ref)	Year	Method (s)	Area-City	Patients (n)	Clinical characteristics of patients	Strains (n)	New TB cases				Previously treated TB cases				Site of disease	Mean age	Sex M/F
							Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)	Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)			
Kisa (40)	1998-2001	Bactec system	Turkey-Ankara	470	Mycobacteriology Laboratory of Gulhane Military Medical Academy	470	470	47	70	8	NA	NA	NA	NA	Pulmonary-TB	30.5	NA
Agarwal (41)	2000-7	Bactec system	Turkey-Malatya	NA	Turgut Ozal Medical Center, Inonu University	397	397	NA	114	18	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	33.9	238/ 159
Kayhan (42)	2005-10	Bactec system	Turkey-Samsun	16932	Samsun Chest Diseases and Thoracic Surgery Hospital	1607	1607	251	537	63	NA	NA	NA	NA	Pulmonary-TB	NA	1218/ 389
Karagoz (43)	2005	Proportion method	Turkey-Istanbul	1513	Sureyyapasa Chest Diseases and Thoracic Surgery Training Hospital	1513	1277	134	209	41	236	30	81	31	Pulmonary-TB	37.3	857/ 656
Erturan (44)	1992-2002	Bactec system	Turkey-Istanbul	27436	Department of Microbiology and Clinical Microbiology	1843	1843	230	594	283	NA	NA	NA	NA	NA	NA	NA
Abd-El Aal (45)	2014	Indirect NRA	Egypt-Mansoura	123	Mansoura University Hospitals and Mansoura Chest Hospital	67	27	4	11	NA	40	6	24	NA	Pulmonary-TB	41.1	51/ 16
Abdel Aziz (46)	2002	NA	Egypt-NA	NA	NA	849	632	NA	193	14	217	NA	148	83	Pulmonary-TB	NA	NA
Rahmo (47)	2003-5	Proportion method	Syria-All Syrian provinces	88	Ministry's central laboratory	88	NA	NA	NA	NA	88	18	NA	55	Pulmonary-TB	34.5	63/ 25
Abdel Aziz (46)	2000	NA	Israel-NA	NA	NA	277	253	NA	79	36	24	NA	10	5	Pulmonary-TB	NA	NA
Gilad (48)	1992-7	Proportion method	Israel-Negev	249	Clinical Microbiology Laboratory of the Soroka Medical Center	249	249	32	71	21	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	52	138/ 111
Ayaz (49)	2006-9	Proportion method	Pakistan-Karachi	1229	Marie Adelaide Leprosy Centre	1004	846	128	180	21	158	19	54	22	Pulmonary-TB	32.3	531/ 473
Butt (50)	2000-2	Bactec system	Pakistan-Rawalpindi	1359	Armed Forces Institute of Pathology	325	325	48	21	91	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	NA	NA
Ghafoor (51)	2010	Bactec system	Pakistan-Rawalpindi	4050	Department of Microbiology, Armed Forces Institute of Pathology	689	689	171	386	132	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	NA	388/ 310
Abdullah (52)	2011	Agar dilution method	Pakistan-Karachi	NA	Pathology Department, Dow Medical College,Dow University of Health Sciences	84	84	NA	NA	4	NA	NA	NA	NA	NA	15-58	39/ 45
Javaid (53)	2008	Proportion method	Pakistan-Peshawar	122	NA	119	119	8	15	3	NA	NA	NA	NA	Pulmonary-TB	NA	53/ 66
Iqbal (54)	2000-3	Proportion method	Pakistan-Lahore	894	Tuberculosis ward/OPD of Mayo and other major hospitals of Lahore	894	498	66	185	60	396	87	247	92	Pulmonary-TB/ extra-pulmonary- TB	15-60	NA

Table 1. (Continued)

First author (Ref)	Year	Method (s)	Area-City	Patients (n)	Clinical characteristics of patients	Strains (n)	New TB cases				Previously treated TB cases				Site of disease	Mean age	Sex M/F
							Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)	Case (n)	Mono-R (n)	Any-R (n)	MDR-TB (n)			
Irfan (55)	2004	Proportion method/ Bactec system	Pakistan-Aga Khan	216	Clinical Microbiology Laboratory of The Aga Khan University	216	80	NA	31	8	136	NA	107	98	NA	NA	NA
Javaid (56)	NA	Proportion method/ Bactec system	Pakistan-Punjab	430	Centers in Lahore, Multan and Rawalpindi	387	387	28	42	4	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Javaid (57)	2005	Proportion method	Pakistan-Karachi	140	Diagnostic centers in Karachi	130	130	10	15	2	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Nema (58)	2005-6	Proportion method	Iraq-All over the country	411	Institute of tuberculosis and chest disease in Baghdad	411	NA	NA	NA	NA	411	103	213	52	Pulmonary-TB	34	311/ 100
Merza (59)	2008-9	Proportion method	Iraq-Dohuk	86	NTP center of Dohuk province	53	38	1	4	3	15	1	8	7	Pulmonary-TB	49.10	37/ 16
Al- Akhali (60)	2004	Proportion method	Yemen-All over the country	790	National TB Reference Laboratory at the NTISana'a City	563	510	33	49	15	53	4	11	6	Pulmonary-TB	NA	NA
AL-Zarouni (61)	2004-8	Bactec system	UAE-Sharjah	1810	Department of Laboratory Sciences, Al-Qassimi Hospital	312	312	NA	109	15	NA	NA	NA	NA	NA	36	230/ 82
Alfaresi (62)	2001-8	Disk method	UAE-Abu Dhabi	43	Mycobacteriology laboratory of the Emirati Hospital	43	43	NA	10	7	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	NA	34/ 9
Abdel Aziz (46)]	2001	NA	Qatar-NA	NA	NA	284	284	NA	28	1	NA	NA	NA	NA	Pulmonary-TB	NA	NA
Abdel Aziz (46)	2001	NA	Oman-NA	NA	NA	183	171	NA	9	0	12	NA	7	7	Pulmonary-TB	NA	NA
Wright (63)	2006	NA	Oman-NA	NA	NA	164	150	NA	10	2	14	NA	6	5	NA	NA	NA
Hamze (64)	2004-5	Bactec system	Lebanon- All Lebanese provinces	NA	Laboratory of the hospital at the Middle East Health Centre in Bsalim/Metin in Lebanon	87	87	4	21	6	NA	NA	NA	NA	Pulmonary-TB	10-77	62/ 25
Hamze (65)	1994-5	Bactec system	Lebanon-Beirut	NA	American University of Beirut Medical Center and Islamic hospital in Tripoli	96	78	8	15	5	18	10	18	6	Pulmonary-TB/ extra-pulmonary- TB	NA	64/ 32
Araj (66)	2002-4	Bactec system	Lebanon- Beirut	245	Private or public sector in the different health regions	206	190	19	36	2	16	1	7	10	Pulmonary-TB	13-79	124/ 82
Mokaddas (67)	1996-2005	Bactec system	Kuwait-NA	NA	All major government/private hospitals in Kuwait	5399	5399	NA	673	48	NA	NA	NA	NA	Pulmonary-TB/ extra-pulmonary- TB	NA	NA
Wright (63)	2004	NA	Jordan-NA	NA	NA	141	111	NA	36	6	30	NA	25	12	NA	NA	NA

Abbreviations: Any-R: Any drug resistance,Mono-R: Mono-drug resistance, MDR: Multi-Drug Resistance, NA: Not Available,M/F: Male/Female, KSA: Kingdom of Saudi Arabia, Indirect NRA: Indirect Nitrate Reductase assay,UAE: United Arab Emirates, NRITLD:National Research Institute of Tuberculosis and Lung Disease.

Table 2: Antibiotic resistance rate in different countries of the Middle East region.

	New TB cases			Previously treated TB cases		
Country	**Mono-R (95% CI)**	**Any-R (95% CI)**	**MDR (95% CI)**	**Mono-R (95% CI)**	**Any-R (95% CI)**	**MDR (95% CI)**
Iran	14.4% (9-22.1)	23.3% (17.6-30.1)	9.6% (4.6-19.1)	12.7% (3.7-35.3)	8.5% (5.7-12.6)	28.1% (23.1-33.7)
KSA	27% (13.8-46.1)	17% (12-23.4)	4.9% (1.8-12.9)	16.5% (9.7-26.8)	45.9% (30.1-62.7)	21.5% (4-64.4)
Turkey	13.4% (11.5-15.5)	23.8% (19.8-28.2)	4.2% (2.4-7.2)	18.6% (14.5-23.5)	52.2% (41.6-62.5)	15.4% (12.7-18.6)
Egypt	14.8% (5.7-33.5)	31.8% (25.7-38.7)	2.2% (1.3-3.7)	15% (6.9-29.6)	66.8% (60.7-72.5)	38.2% (32-44.9)
Israel	12.9% (9.2-17.6)	29.9% (26.1-34.1)	11.2% (6.6-18.3)	NA	41.7% (24.1-61.7)	20.8% (8.9-41.3)
Pakistan	12.4% (8.7-17.3)	20.8% (11.6-34.5)	6.2% (3.2-11.6)	16.8% (9.1-29.1)	59.4% (35.9-79.2)	33.4% (10-69.3)
Iraq	2.6% (0.4-16.5)	10.5% (4-24.9)	7.9% (2.6-21.8)	17.9% (5.3-45.8)	51.9% (47.1-56.6)	25% (5.4-65.8)
Yemen	6.5% (4.6-9)	9.6% (7.3-12.5)	2.9% (1.8-4.8)	7.5% (2.9-18.4)	20.8% (11.9-33.7)	11.3% (5.2-23)
UAE	NA	30.9% (20.9-43)	8.7% (2.5-26.3)	NA	NA	NA
Qatar	NA	9.9% (6.9-13.9)	0.45% (0-2.5)	NA	NA	NA
Oman	NA	6% (3.8-9.2)	1% (0.3-3.3)	NA	50% (31.5-68.5)	46.4% (26-68.2)
Lebanon	8.9% (6.1-13)	20.4% (16.5-24.9)	4.2% (1.5-10.7)	25% (1.9-85.3)	81% (90-99.5)	47.5% (21.8-74.7)
Kuwait	NA	12.5% (11.6-13.4)	0.9% (0.7-1.2)	NA	NA	NA
Jordan	NA	32.4% (24.4-41.7)	5.4% (2.4-11.5)	NA	83.3% (65.7-92.9)	40% (24.3-58.1)
Syria	NA	NA	NA	20.5% (13.3-30.2)	NA	62.5% (52-72)
Afghanistan	NA	NA	NA	NA	NA	NA
Bahrain	NA	NA	NA	NA	NA	NA

Abbreviations:Mono-R: Mono-drug resistance,Any-R: Any drug resistance, MDR: Multi-Drug Resistance, NA: Not Available, KSA: Kingdom of Saudi Arabia, UAE: United Arab Emirates,CI: Confidence Interval.

Table 3. The overall antibiotic resistance pattern in the Middle East region.

New TB cases					Previously treated TB cases				
Type of drug resistance	**Number of studies**	**Percent of drug resistance (95% CI)**	**Heterogeneity**		**Type of drug resistance**	**Number of studies**	**Percent of drug resistance (95% CI)**	**Heterogeneity**	
			I^2 (%)	***P* value**				**I^2 (%)**	***P* value**
Single drug resistance	41	14.7% (12.2- 17.5)	94.8	0.00	**Single drug resistance**	22	17.9% (14.6-21.7)	82.1	0.00
Any-drug resistance	55	20.8% (18-24)	96.6	0.00	**Any-drug resistance**	26	50.5% (43.2-57.8)	93.1	0.00
Multi-drug resistance	52	5% (3.7-6.8)	96.0	0.00	**Multi-drug resistance**	27	26.6% (19.9-34.4)	93.6	0.00

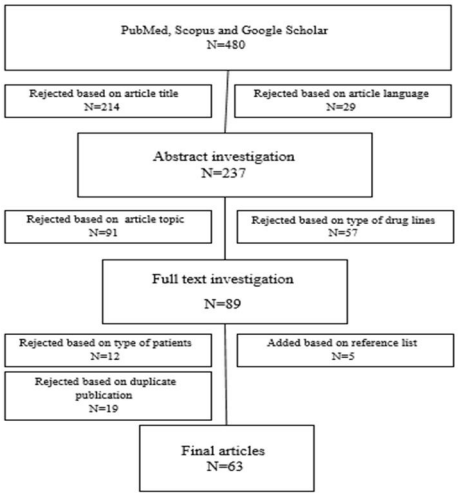

Fig 1. Flowchart of full search strategy.

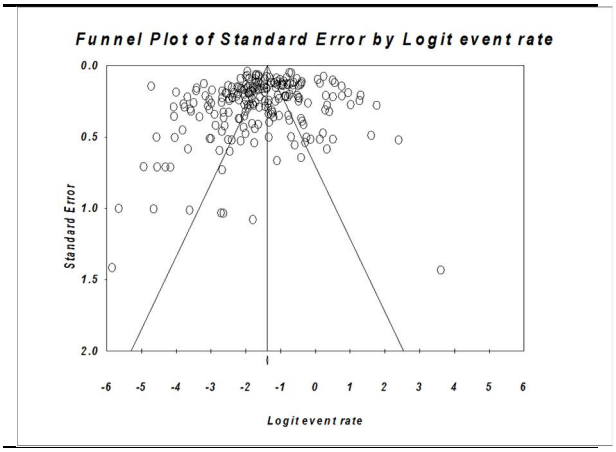

Fig 2. Funnel plot of the meta-analysis on mono drug resistance, any drug resistance, and multidrug resistance in new and previously treated TB patients. Note slight asymmetry of the plot which could be due to possible publication bias.

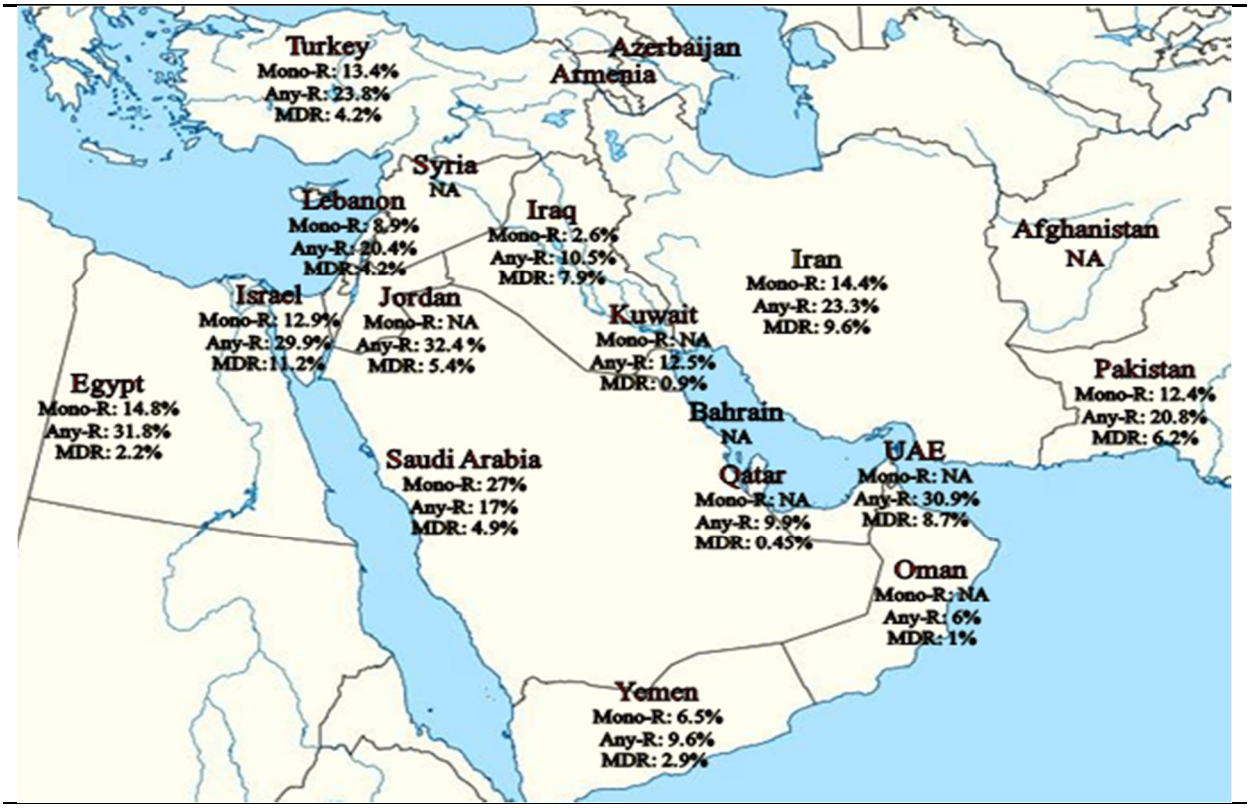

Fig 3. Distribution of mono, any, and multidrug-resistant TB among new TB cases in different countries of the Middle East.

5. Discussion

Our study is the first comprehensive systematic review for the estimation of the prevalence rate of drug-resistant TB in the Middle East region. After reviewing the collected data, it was revealed that methods used for assessing the *M. tuberculosis* antibiotic susceptibility were different in countries of the Middle East (Table 1). According to our data, it was revealed that the proportion method was constantly used to determine the antibiotic susceptibility in the Middle East region.

In the present study, the resistance of *M. tuberculosis* to a single first-line drug was detected in 14.7% (95% CI: 12.2% to 17.5%) of the new TB cases in the Middle East. The highest and the lowest mono drug resistance rate in new cases were detected in KSA (27%, 95% CI: 13.8% to 46.1%) and Iraq (2.6%, 95% CI: 0.4% to 16.5%), respectively. In previously treated TB cases in the Middle East, the resistance rate to a single first-line drug was found in 17.9% (95% CI: 14.6% to 21.7%) of the patients. Among the Middle Eastern countries, the highest prevalence rate of resistance to a single first-line drug was found in retreatment patients in Lebanon (25%, 95% CI: 1.9% to 85.3%), and the lowest rate was found in Yemen patients (7.5%, 95% CI: 2.9% to 18.4%). It seems that there is a strong correlation

between mono drug resistance and the emergence of MDR-TB, particularly in isoniazid and rifampicin, which are the other forms of TB with more difficult treatment. So an urgent need to control the mono drug resistance in new TB cases and to treat these patients is felt.

The resistance to one or more first-line drugs was found in 20.8% (95% CI: 18% to 24%) of the new TB cases and 50.5% (95% CI: 43.2% to 57.8%) of the previously treated TB cases in the Middle East. Jordan had the highest prevalence rate of resistance to one or more first-line drug both in new and previously treated TB cases, 32.4%(95% CI: 24.4% to 41.7%) and 83.3% (95% CI: 65.7% to 92.9%), respectively. However, the lowest proportion in new and previously treated cases was detected in Oman (6%, 95% CI: 3.8% to 9.2%) and Iran (8.5%, 95% CI: 5.7% to 12.6%), respectively. For the new TB cases, our results are in agreement with other studies conducted in China (17.9%), Philippines (20.5%), India (21.3%), Norway (22·3%), Lithuania (24·2%), Peru (23·2%), and Northern Mariana Islands (22·2%,) (63). But for previously treated TB cases, similar results have been shown in the studies conducted in Thailand (50.5%), Latvia (52·7%), Guatemala (54·8%), and Ethiopia (48.7%) (63).

Drug-resistant TB is prevalent in different parts of the world, and according to the global reports, it was estimated that 3.5% of the new and 20.5% of the retreated TB patients had MDR-TB in 2013 (3). Compared with the global reports on TB in 2014, the prevalence rate of resistance to at least INH and RMP, MDR-TB, was found in 5% (95% CI: 3.7% to 6.8%) of the new TB cases and 26.6% of the retreatment cases (95% CI: 19.9% to 34.4%) in the Middle East, which shows increasing trend. High and low levels of resistance to at least INH and RMP among new cases were found in Israel (11.2%, 95% CI: 6.6% to 18.3%) and Qatar (0.45%, 95% CI: 0% to 2.5%), respectively. The MDR-TB rate in our study was high compared with the previous reports of WHO from the Middle East (9). Also, the prevalence rate of MDR-TB in new and retreated cases in the Middle East was high in comparison with what has been reported from other parts of the world, for example, African region (1.9% and 9.4%), region of the Americas (2.1% and 11.5%), South-East Asia region (2.1% and 17.2%), and Western Pacific region (4.9% and 23.2%), and was low in comparison with what has been reported from European region (12.1% and 36.5%) for new and retreated cases, respectively (68). In general, the prevalence rate of drug resistance is likely to change substantially during the course of the review (1981-2014). Therefore, because there are high MDR-TB burden countries in the Middle East and with regard to our results on the incidence rate of MDR-TB, in order to control the emergence of more MDR-TB and to reduce its impacts on public health, management of drug-susceptible or mono drug resistance TB is important.

Limitations

The main limitation of this review study which might have affected the meta-analysis results were consisted of: 1) not finding any study on *M. tuberculosis* resistance in Bahrain and Afghanistan, so it cannot completely represent the prevalence rate of drug resistance in the Middle East level, 2) the presence of articles with their native language, 3) exclusion of some articles from the study because of containing data from the combined prevalence rate of drug resistance (i.e. the prevalence rate of drug resistance among all cases of TB, regardless of prior drug treatment), 4) Immigration and mass gatherings because the prevalence rate of drug resistance of *M. tuberculosis* in many countries of the Middle East such as Iran, KSA, and Iraq is clearly influenced by immigrant workers and foreigners visiting Islamic rituals, 5) heterogeneity, we observed the great heterogeneity (high I^2 index) among the included studies for the pooled estimations of single drug resistance, any drug resistance, and MDR-TB in both new and previously treated cases, which could be due to differences in various countries, year and methods used between studies, and 6) evidence of possible systematic error (publication bias).

6. Conclusion

In sum, across 17 countries from the Middle East, the authors reported wide differences in the prevalence rate of mono, any, and multidrug resistance in both new and previously treated TB patients. The present systematic review showed high levels of drug-resistant TB, especially MDR-TB, which may be increasing in both groups of TB patients in the Middle East. Hence, in order to gain a more effective TB control, identifying individuals with TB signs and symptoms by new rapid diagnostic methods, performing drug susceptibility testing, detecting primary resistance to the first-line anti-TB drugs, providing effective treatment to prevent the emergence of other forms of drug resistance are needed.

Abbreviations

NC-MR: New case-Mono drug resistance, NC-AR: New case-Any drug resistance, NC-MDR: New case-Multidrug Resistance, PT-MR: Previously treated-Mono drug resistance, PT-AR: Previously treated-Any drug resistance, PT-MDR: Previously treated -Multidrug Resistance, CI: Confidence Interval.

Conflict of Interests

None declared.

Acknowledgments

None declared.

Authors' Contribution

Mohammad Derakhshan designed the study, Farzad Khademi wrote the manuscript and analyzed the data, Arshid Yousefi-Avarvand collected the data, Hamid Vaez edited the article and Ramin Sadeghi analyzed data.

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Group by Case/Resistance	Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value
Egypt-NC-AR		0.318	0.257	0.387	-4.984	0.000
Egypt-NC-MDR		0.022	0.013	0.037	-14.013	0.000
Egypt-NC-MR		0.148	0.057	0.335	-3.229	0.001
Egypt-PT-AR		0.668	0.607	0.725	5.143	0.000
Egypt-PT-MDR		0.382	0.320	0.449	-3.429	0.001
Egypt-PT-MR		0.150	0.069	0.296	-3.917	0.000
Iran-NC-AR		0.233	0.176	0.301	-6.709	0.000
Iran-NC-MDR		0.096	0.046	0.191	-5.507	0.000
Iran-NC-MR		0.144	0.090	0.221	-6.684	0.000
Iran-PT-AR		0.085	0.057	0.126	-10.644	0.000
Iran-PT-MDR		0.281	0.231	0.337	-6.971	0.000
Iran-PT-MR		0.127	0.037	0.353	-2.861	0.004
Iraq-NC-AR		0.105	0.040	0.249	-4.049	0.000
Iraq-NC-MDR		0.079	0.026	0.218	-4.084	0.000
Iraq-NC-MR		0.026	0.004	0.165	-3.563	0.000
Iraq-PT-AR		0.519	0.471	0.566	0.775	0.438
Iraq-PT-MDR		0.250	0.054	0.658	-1.228	0.219
Iraq-PT-MR		0.179	0.053	0.458	-2.204	0.027
Israel-NC-AR		0.299	0.261	0.341	-8.736	0.000
Israel-NC-MDR		0.112	0.066	0.183	-7.060	0.000
Israel-NC-MR		0.129	0.092	0.176	-10.108	0.000
Israel-PT-AR		0.417	0.241	0.617	-0.813	0.416
Israel-PT-MDR		0.208	0.089	0.413	-2.656	0.008
Jordan-NC-AR		0.324	0.244	0.417	-3.620	0.000
Jordan-NC-MDR		0.054	0.024	0.115	-6.819	0.000
Jordan-PT-AR		0.833	0.657	0.929	3.285	0.001
Jordan-PT-MDR		0.400	0.243	0.581	-1.088	0.277
KSA-NC-AR		0.170	0.120	0.234	-7.676	0.000
KSA-NC-MDR		0.049	0.018	0.129	-5.554	0.000
KSA-NC-MR		0.270	0.138	0.461	-2.323	0.020
KSA-PT-AR		0.459	0.301	0.627	-0.468	0.640
KSA-PT-MDR		0.215	0.040	0.644	-1.344	0.179
KSA-PT-MR		0.165	0.097	0.268	-5.178	0.000
Kuwait-NC-AR		0.125	0.116	0.134	-47.307	0.000
Kuwait-NC-MDR		0.009	0.007	0.012	-32.513	0.000
Lebanon-NC-AR		0.204	0.165	0.249	-10.316	0.000
Lebanon-NC-MDR		0.042	0.015	0.107	-6.040	0.000
Lebanon-NC-MR		0.089	0.061	0.130	-10.886	0.000
Lebanon-PT-AR		0.810	0.090	0.995	0.755	0.450
Lebanon-PT-MDR		0.475	0.218	0.747	-0.163	0.871
Lebanon-PT-MR		0.250	0.019	0.853	-0.753	0.451
Oman-NC-AR		0.060	0.038	0.092	-11.660	0.000
Oman-NC-MDR		0.010	0.003	0.033	-7.253	0.000
Oman-PT-AR		0.500	0.315	0.685	-0.002	0.998
Oman-PT-MDR		0.464	0.260	0.682	-0.309	0.757
Pakistan-NC-AR		0.208	0.116	0.345	-3.772	0.000
Pakistan-NC-MDR		0.062	0.032	0.116	-7.771	0.000
Pakistan-NC-MR		0.124	0.087	0.173	-9.685	0.000
Pakistan-PT-AR		0.594	0.359	0.792	0.775	0.438
Pakistan-PT-MDR		0.334	0.100	0.693	-0.897	0.370
Pakistan-PT-MR		0.168	0.091	0.291	-4.438	0.000
Qatar-NC-AR		0.099	0.069	0.139	-11.118	0.000
Qatar-NC-MDR		0.004	0.000	0.025	-5.635	0.000
Syria-PT-MDR		0.625	0.520	0.720	2.320	0.020
Syria-PT-MR		0.205	0.133	0.302	-5.139	0.000
Turkey-NC-AR		0.238	0.198	0.282	-9.797	0.000
Turkey-NC-MDR		0.042	0.024	0.072	-10.859	0.000
Turkey-NC-MR		0.134	0.115	0.155	-21.667	0.000
Turkey-PT-AR		0.522	0.416	0.625	0.396	0.692
Turkey-PT-MDR		0.154	0.127	0.186	-14.543	0.000
Turkey-PT-MR		0.186	0.145	0.235	-9.751	0.000
UAE-NC-AR		0.309	0.209	0.430	-3.016	0.003
UAE-NC-MDR		0.087	0.025	0.263	-3.490	0.000
Yemen-NC-AR		0.096	0.073	0.125	-14.918	0.000
Yemen-NC-MDR		0.029	0.018	0.048	-13.341	0.000
Yemen-NC-MR		0.065	0.046	0.090	-14.839	0.000
Yemen-PT-AR		0.208	0.119	0.337	-3.956	0.000
Yemen-PT-MDR		0.113	0.052	0.230	-4.748	0.000
Yemen-PT-MR		0.075	0.029	0.184	-4.818	0.000

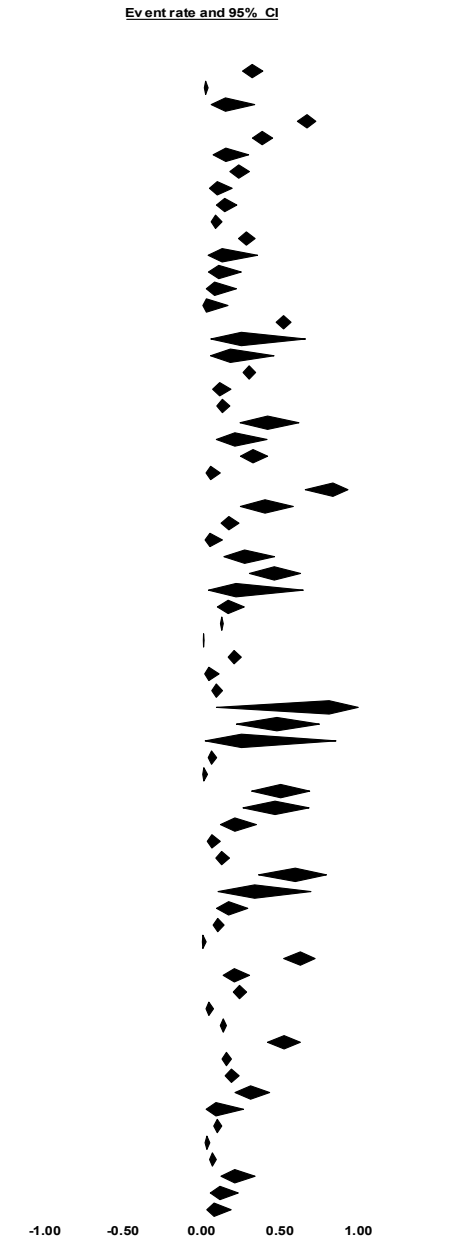

Fig 4. Forest plot of the meta-analysis on mono drug resistance, any drug resistance, and multidrug resistance in new TB patients in each of countries of the Middle East region. **Abbreviations:** NC-MR: New case-Mono-drug resistance, NC-AR: New case-Any drug resistance, NC-MDR: New case-Multi-drug Resistance, PT-MR: Previously treated-Mono-drug resistance, PT-AR: Previously treated-Any drug resistance, PT-MDR: Previously treated -Multi-drug Resistance, CI: Confidence Interval

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