Factors associated with patient and health system delay in diagnosis and commencement of treatment for pulmonary tuberculosis in the Middle East and North Africa (MENA)

Systematic Review

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SUMMARY OF CONTENT

This MPH dissertation undertakes a systematic review on factors associated with patient and health system delay in diagnosing and commencing treatment for pulmonary tuberculosis in Middle East and North Africa (MENA). The dissertation is composed of three main parts: namely parts A, B and C.

Part A is the research protocol, which give brief background to research topic and the process of this review. This systematic review aims to assess factors associated with patient and health system delay for diagnosis and initiation of treatment of pulmonary tuberculosis in Middle East and North Africa (MENA).

Part B elaborates on the background and highlights the importance of this research by examining the existing theoretical and empirical literature relevant to the topic.

Part C presents the entire research project in a format suitable for PLOS journal submission. The background of this research project is summarized and the results are presented and discussed.

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PART A: PROTOCOL

LIST OF ABBREVIATIONS

AFB	Acid Fast Bacilli
DOTS	Directly Observed Treatment Short Course
HIV	Human Immune Deficiency Virus
MDR	Multi Drug Resistant
MDGs	Millennium Development Goals
MENA	Middle East and North Africa
NGOs	Non - Governmental Organizations
NTP	National TB Control Programme
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
ART	Anti-Retroviral Therapy
CPT	Cotrimoxazole Preventive Therapy
TBMUs	Tuberculosis Management Units
WHO	World Health Organization

OPERATIONAL DEFINITIONS

1- **Tuberculosis suspect**. Any person who presents with symptoms or signs suggestive of TB. The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

2- **Bacteriologically confirmed case of TB**: A patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic test (such as Xpert MTB/RIF).

3- **Clinically diagnosed case of TB:** A patient who does not fulfil the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

4- **Smear positive pulmonary TB (PTB) patients:** patients with two or more sputum smears positive for AFB (acid fast bacilli) or one sputum positive for AFB and radiological abnormalities consistent with active TB as determined by the treating medical officer or one sputum positive for AFB and culture positive for AFB.

5- **Smear negative PTB patients:** Patients with three smears negative for AFB and radiological abnormality consistent with active TB or failure to respond to antibiotic trials.

6- **Case of pulmonary TB (PTB):** Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs. Tubercles intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tubercles pleural effusion, without radiographic abnormalities in the lungs, constitute a case of extra-pulmonary TB. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of pulmonary TB.

7- **Case of extra-pulmonary TB (EPTB):** Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

8- **New case of TB**: A patient who has never been treated for TB or has taken anti-TB drugs for less than one month.

9- **Previously treated case of TB**: A patient who has been treated for one month or more with anti-TB drugs in the past. Re treatment cases are further classified by the outcome of their most recent course of treatment into four categories: 1. Relapse patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection). 2. Treatment after failure patients have previously been treated for TB and their most recent course of treatment failed i.e. they had a positive sputum smear or culture result at month 5 or later during treatment. 3. Treatment after loss to follow-up patients have previously been treated for TB and were declared ‗lost to follow-up' at the end of their most recent course of treatment. 4. Other previously treated patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

10- **Case of multidrug-resistant TB (MDR-TB)**: MTB that is resistant to two first-line drugs: isoniazid and rifampicin.

11- **TB health facility** is defined as any health institution with health care providers formally engaged in any of the following TB programme functions (DOTS): referring patients with presumptive TB or confirmed TB cases, laboratory diagnosis, TB treatment and patient support during treatment.

12- **Patients' delay:** The time interval between date of onset of TB symptoms and first presentation to a professional health provider.

13- **Health system's delay:** The time interval between date of first presentation of patients to a professional health provider and initiation of treatment.

14- **Diagnostic delay:** The time interval between the onset of TB symptoms and diagnosis of TB.

15- **Treatment delay:** The time interval between date of diagnosis and initiation of treatment.

16- **Total delay:** The time interval between date of onset of TB symptoms and initiation of treatment.

17- **Non-formal health providers:** These include traditional health providers, local injectors and drug retail outlets.

18- **Formal health providers**: Professional health providers working in modern health facilities i.e. hospitals, health centres, clinics owned by the government or the private sector.

19- **Self-treatment:** Any kind of self-prescribed treatment taken by patients for their illness.

20- **Case detection rate:** is calculated as the number of new cases reported to NTPs in a given year divided by estimated incidence for the same year. The CDR is thus a ratio rather than a rate, but in the context of this indicator the term ‗rate' has become standard terminology.

1. BACKGROUND

Globally, tuberculosis (TB) is second to HIV/AIDS as a cause of illness and death of adult (1)(2)]. In 2013, an estimated 9.0 million people had TB with 1.5 million deaths (including 360 000 of whom were HIV-positive)(3). TB occurs in every part of the world, the largest number of new TB cases occurred in the South-East Asia and Western Pacific Regions, accounting for 56% of the new cases (1)(3). The efforts through effective diagnosis and treatment had succeeded to save 37 million lives between 2000 and 2013 (3). However the death from the disease is still unacceptably high given the fact that deaths from TB are preventable (3) . With strong TB control programme many of these deaths could be avoided.

1.1Problem statement

The goal of Tuberculosis control is to stop disease transmission, thereby reduce mortality and morbidity rates (4)(5). Identification of transmission determinants such as number of incident infectious cases and durations of their infectiousness is mandatory to effectively control, since without detection the smear–positive index case is found to infect around 30%–40% of his contacts (6)(7). Early case detection and proper treatment will reduce the time of infectiousness of this case in the community and hence the number of new individuals exposed and infected (7). On the other hand, delay in case detection which eventually cause delay in diagnosis may worsen the disease, increase the risk of death and enhance tuberculosis transmission in the community. Unfortunately, in developing countries early case detection of TB had never gained its expected place in the strategies of national tuberculosis control programmes, in spite of the scale up of quality-assured TB services in line with the Stop TB Strategy (8).

In developing countries, almost all national tuberculosis control programs depends on passive case detection which is based on diagnosing infectious cases whom present themselves to the health facilities (8). This type of case detection is known to be influenced by factors such as patient motivation, the degree of diagnostic suspicion by health workers and the quality of laboratory facilities (9)(10). In fact passive case detection by definition is considered to be a major source of delayed diagnosis (11). These delays may be attributed to both patients as well as the health care system (11).

The patients may delay seeking help or the health care system may delay in suspecting and investigating for TB. Patient‘ delay is the period between onset of TB symptoms to first visit to any

health provider (health seeking period) (7). The health seeking is a very complicated process and is influenced at many levels by patient‘s socio-economic factors, social interactions, and the health system related factors (6). on the other hand, the Health system‘ delay: Period from the date of the patient's first contact with the health care service to the initiation of treatment (7). This period is influenced by several factors such as; prevalence of TB, accessibility of health facilities, patient‘s socio-demographic characteristics, symptoms on presentation, presence of refined suspicion index, infrastructures and organization of the health system (6). TB control programs must understand the reasons behind these delays in order to achieve their goals successfully (7). However in almost all MENA countries, the national TB control programmes are able to detect on average one third of smear-positive tuberculosis cases (7). The remaining two thirds will thus continue to transmit TB infection in the community until detected by other health sectors (7).

The Middle East and North Africa region (MENA), is an economically diverse region comprising both the oil-rich economies in the Gulf and the countries that are resource-scarce in relation to population, such as Egypt, Morocco, and Yemen [14,15]. The World Bank‘s account of the MENA region covers the 21 members of the Arab League, and Iran, Israel, and Turkey [16]. The region is known for its unusual cultural homogeneity represented in its linguistic, religious, socio-cultural, and historical references [17]. The Arab spring phenomenon has been impacted these countries in the last half decade and draw marked changes in the Health Delivery.

1.2 Justification for this review

Three earlier systematic reviews have addressed the delay of TB diagnosis and treatment [18-20]. However, none of these reviews were specific to the MENA region or are in need of updating since the time of publication. We will be conducting this review to summarize the most recent evidence for factors associated with both patient and health system delay in diagnosis and commencing treatment for PTB in the MENA region.

1.3 Research question:

What are the factors associated with patient and health system delay for diagnosis and treatment of tuberculosis in Middle East and North Africa (MENA)?

2. OBJECTIVES:

2.1 Primary Objectives:

- To study factors associated with patient and health system delay for diagnosis and initiation of treatment of pulmonary tuberculosis in Middle East and North Africa (MENA).

2.2 Secondary Objectives:

- To determine the magnitudes and contributions of patient period in the total pre-treatment period.
- To determine the magnitudes and contributions of health system period in the total pre-treatment period.
- To determine the magnitudes of total delay.

3. METHODS

3.1 Criteria for considering studies for this review

3.1.1 Types of studies:

Observational studies: case control studies, cross sectional studies and population based studies. In case of Randomized control trials (RCTs), cluster-randomized control trials (cRCTs), controlled before-and-after studies (CBAs) and cohort studies (prospective and retrospective) studies, we will only use baseline population data.

3.1.2 Type of Participants:

TB patients (or suspected TB patients) defined as:

1. All chest symptomatic individuals with cough ≥2 weeks and suspected for TB,
2. Pulmonary TB (PTB) patients (smear-negative, new smear positive or re-treatment patients),
3. Pulmonary and extra-pulmonary TB (EPTB) (if data were presented for PTB separately).

3.1.3 Types of outcome measures:

3.1.3.1 Primary outcome:

1. Factors associated with patient and health system delay

3.1.3.2 Secondary outcome:

1. Patient delay, defined as the time interval from onset of TB symptoms to first visit to any health provider.
2. Health system delay, defined as the time interval from the first health provider visit to initiation of treatment such as:
    - Diagnostic delay is the time interval between the onset of symptoms and labeling of the patient as tuberculosis patient (tuberculosis diagnosis).
    - Treatment delay is time interval between tuberculosis diagnosis and initiation of anti-tuberculosis.
3. Total delay is the time interval from the appearance of major of TB symptoms to initiation of treatment.

3.2 Search methods for identification of studies:

A comprehensive search to identify both published and unpublished articles with the relevant studies with no language and time limit will be performed. The search strategies for electronic databases will incorporate both medical subject headings (MeSH) and free-text terms and will be adapted to suit each individual database using applicable controlled vocabulary (see appendix 1).

3.3 Electronic searches

Relevant studies will be searched for and identified from electronic databases including; Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, CINAHL, Psychlnfo, Scopus, Index Medicus for the Eastern Mediterranean Region (IMEMR), (Africa-wide) allied health and Google scholar.

In addition, we will identify conference proceedings and reference lists of relevant articles.

3.4 Data collection

3.4.1 Selection of studies:

Two authors will screen titles and abstracts to select potential eligible studies. Thereafter, the full text of potentially eligible studies will be obtained and the final selection for inclusion into the review will be conducted by two independent authors. Any disagreements regarding inclusion of studies will be resolved by discussion or by consulting a third author. A PRISMA flow chart will be used to

summarize the search and selection of studies for the review. A table of all included studies will be included in the final review and the reasons for exclusion of studies will also be documented.

3.4.2 Data extraction and management:

Data will be extracted from selected studies independently by two authors using standardized data extraction forms (see Appendix 2). Disagreements on study selection and data extraction will be resolved by consensus between the two review authors, failing which a third author will arbitrate. Prior to use, the extraction form will be piloted on at least five studies identified randomly from the list of included studies. For each study report, we will extract available information on the setting, method of obtaining the study sample, sample characteristics, study design, data collection method, measure of the dependent variable, data source(s), data collection method(s) and instrument, and findings. Findings will include all variables tested for an association with delay.

3. 5 Data analysis and synthesis:

We will express the result of each study as a risk or an odd ratio with its corresponding 95% confidence interval for dichotomous data or mean difference with its standard deviation for continuous data. We will group studies that compare broadly similar types of outcome to get feasible results on an overall estimate of effect. Random effects meta-analysis will be preferred due to anticipated heterogeneity in study results. We will derive SEs where studies have provided the corresponding numerator and denominator for delay of TB prevalence estimates. We will consider non-overlapping CIs as an indication of statistically significant differences. Prevalence of TB delay from different studies will be pooled in a meta-analysis using Review Manager 5.3. If we encounter variation in reported outcome measures between studies, we will not pool the results but summarize the findings in a narrative format.

3. 5.1 Assessment of risk of bias in included studies:

The quality assessment tool by Hoy et al. 2012 [21] for observational studies that are modified by Werfalli and colleagues [22] to allow for a composite score that assist with relative comparison between the studies will be applied a to all screened full reports in order to code eligibility decisions and to assess study quality and agreement between investigators. The scoring system tool categorizes high risk studies as those with an overall score of 0-5 points, moderate risk as 6-8 and low risk >8 points see table 1.

Table 1: Quality assessment tool [21] modified by [22]	
Items	**Quality Score**
External Validity	(4 points)
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
Internal Validity	(6 points)
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)

Overall score	**Quality**
0-5 points	**Low Risk:** Further research is very unlikely to change our confidence in the estimate
6-8 points	**Moderate Risk:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate
>8 points	**High Risk:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

3. 5.2 Assessment of heterogeneity:

We anticipate substantial variation in study results due to differences in study designs, populations, and onset of symptoms, first appropriate health care provider, definition of TB delay used by authors and health system status (also TB transmission and burden in different countries). We will examine statistical heterogeneity between study results using the Chi-squared test of homogeneity (with significance defined at the alpha-level of 10%), and quantify any statistical heterogeneity between study results using the I-squared statistic [23].

3. 5.3Dealing with missing data:

If necessary, we will contact the corresponding authors of included studies to give us any missing data. We will describe missing data for each included study and discuss the extent to which the missing data could alter our results.

3. 5.4 Sub-group analyses

Subgroup analyses may be conducted if possible, taking into account but not limited to age, gender, socioeconomic characteristics, attitudes and beliefs of the target population toward TB, definition of delay, HIV/TB co-burden, setting of the studies and country income status. We will use the Chi2 test for subgroup differences to test for subgroup interactions.

3. 5.5 Grading the quality of evidence

The GRADE approach will be used to assess the quality of evidence related to each of the outcomes. The GRADE approach will assess the quality of evidence as very low, low moderate or high, with implications on how confident we can on the results and if further research is likely to change the results [24].

4. ETHICS

Systematic reviews draw on publicly available secondary data and, therefore do not require formal ethical review [25]. It is noted that ethical research, even if secondary research, relies on scientific validity. The study will be guided by experts with knowledge of content and methodology. The results of this review will be available online through the university library. The review will also be written up for submission to a peer reviewed journal.

5. FUNDING

No funding is expected for this review.

6. DISSEMINATION

The study will be disseminated by peer-review publication and conference presentation.

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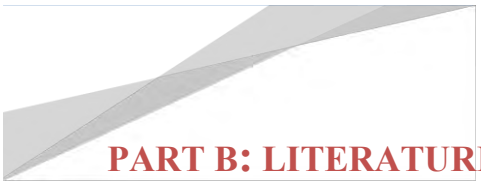

PART B: LITERATURE REVIEW

INTRODUCTION

Tuberculosis (TB) remains one of the world‘s deadliest communicable diseases [1-4]. In 2013, about 64 per cent of the estimated nine million people who have developed TB were detected as newly diagnosed cases. It is estimated that this figure omitted about 3 million cases that were either not detected, or not reported to national TB programs (NTPs) [4]. This problem related to the low detection rate of TB is one of the major difficulties confronting TB control worldwide. In almost all Middle Eastern and North African (MENA) countries, the national TB control programmes can identify on average one-third of smear-positive TB cases [5]. The remaining two-thirds will thus continue to transmit TB infection in the community until detected by other health sectors. This overview precedes the systematic review and is structured according to the following sections:

- Background, health systems status, disease burden and TB situation in the MENA region.
- TB control: goals, target, and challenges.
- The challenge of low case detection rate in developing countries.
- The health seeking behaviour among TB patients.
- Overview of TB delay and its consequences.
- Levels of delay in the diagnosis and treatment of TB (total, patient and health system delays).
- Certain factors associated with delay in TB diagnosis and treatment

SEARCH STRATEGY

Articles used in this overview were obtained from scholarly resources, such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Google Scholar (http://www.scholar.google.co.za/). A wide range of keywords such as tuberculosis, epidemiology, tuberculosis delay and case finding for TB without language restriction were used to retrieve relevant articles for each topic. We searched the literature between 1995 -2015, we choose this period because the issue of TB delay has gained considerable attention within the last 20 years.

1. OVERVIEW OF THE MENA REGION

1.1 Background

The Middle East and North Africa region (MENA) is an economically diverse region comprising the oil-rich economies in the Gulf and countries that are resource-scarce in relation to population, such as Egypt, Morocco, and Yemen [6,7]. The World Bank's account of the MENA region covers the 21 members of the Arab League (Algeria, Bahrain, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, The United Arab Emirates and Yemen), Iran, Israel, Armenia, Azerbaijan, Georgia and Turkey [8-10] (Figure B1). The region, known for its unusual cultural homogeneity, is represented in its linguistic, religious, socio-cultural, and historical references [10]. Also, the region is at the intersection of the trade routes connecting Europe and China, India and Africa, and all the cultures of the Mediterranean basin. The area accounts for 7 per cent of the world's population numbering 351.4 million in 2014 [11].

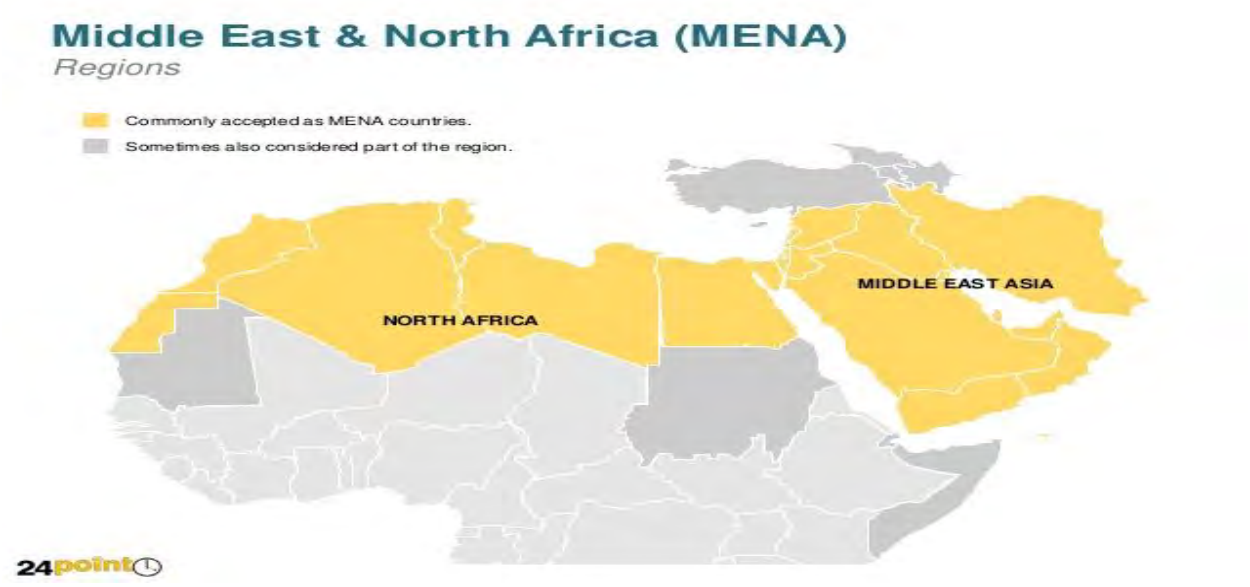

Figure B1: Middle East and North Africa map (Resource reproduced from slide share available at http://www.slideshare.net/Presentationsat24point0/map-of-mena-14114848. According to World Bank, countries in orange are commonly accepted as MENA's countries whereas countries in grey (Turkey, Armenia, Azerbaijan, Georgia, North Sudan, Somalia and Mauritania) are only sometimes accepted. However, for this review, we considered all the countries on the map to be eligible.

The region has one of the fastest-growing populations in the world with higher birth rates than death rates. The demographic projection articulates that the region's youth population (up to 24 years old)

will grow steadily by about 2 million by the end of 2015, then increase by about 10 million between 2015 and 2030 [11]. Many countries adopted active population policies that contribute significantly to reducing the fertility rates, starting from a regional average of over six births per woman in 1980 to below four in 2003 [12]. This decline in fertility rates does not avoid the problem that despite mortality rates, the region is challenged by a rapidly expanding youth population and a smaller growth rate in the ageing population [12]. Another challenge related to demographic transition is the population movement. Conflicts, wars, natural disasters and political instability have led to displacement, forced migration and outpourings of refugees. In relation to TB, these demographic transitions virtually ensure that the number of TB cases will increase over the coming years [13].

The regional epidemiological transitions result from the effects of rapid urbanisation, changes in tobacco consumption, diet and decreasing burden of communicable diseases with an increase in chronic diseases and injuries [12]. In terms of smoking, the age-standardized prevalence of current tobacco smoking in persons aged 15 years and over in the region is 39 per cent ranging from 15.3 per cent in Morocco to 53.9 per cent in Lebanon. Furthermore, smoking-related mortality rates are expected to rise to 9·5 per cent in 2020 from the current estimate of 2.4 per cent [14]. Further changes in nutrition have led to the region being challenged by the high prevalence of individuals suffering from stunting, iron-deficiency anaemia and morbid obesity. Road traffic related mortality is among the highest in the world (26·4 per 100 000 population compared with 19 per 100 000 for the world as a whole) [12]. The disease burden is discussed later in this chapter.

Both demographic and epidemiological transition increased the demand for many services such as educational and health services at all levels and will place enormous pressure on existing systems. Furthermore, threats from rapid urbanization, smoking, malnutrition and overpopulation, together with migration, political instability, rising unemployment and low economic growth (in most of the region‘s countries) must be considered. The impact of these factors on the health of populations in general and TB, in particular, is unimaginable. Consequently, there is an urgent demand for stronger public health systems that encompass the needs and expectations in terms of both quality and quantity. Fortunately, in the wake of the Arab Spring, the demands for greater accountability and more responsive public service delivery echoed across the Region [15].

The Arab revolution that started in December 2010 called for freedom, social justice and improved accountability for a dignified life and well-being. This phenomenon, recognizable in the name of the Arab Spring, impacted almost all MENA‘s countries and caused marked changes in the qualities of life [16]. Although most attention focuses on security and political developments, there are substantial consequences for population health. These include immediate problems, such as violent deaths and injuries, population displacement and damage to essential

infrastructures. Longer-term weaknesses still to be debated in the political changes include high unemployment, the low status of women, erosion of already weak welfare systems and rising food prices. The health system in the region is expected to be severely devastated by the crises now and in the coming years [16]. Indeed, all these problems provide an environment where TB is very likely to occur [17,18]. It is vital to establish structures to contain the potential increase in numbers of TB in these circumstances and prevent a repeat of the mistakes made in countries that have undergone similar rapid political transition [16].

1.2 Public health care System in the region

All aspects of health systems are suffering from the pressure placed upon them by the continuously increasing demands due to demographic and epidemiologic transitions with technological advances and rising public expectations. The political instability contributed to emergency situations (the sectarian war and Arab spring), and economic sanctions have stretched resources beyond the systems' ability to cope, quality is reduced and services defined as ―below standard." [19]. However, most countries in the MENA region are in the process of making an attempt to reform their health care systems in a responsible manner. Unfortunately, most are financially motivated rather than needs driven and are based on the United States or European models that are not contextualized to meet the needs of the countries concerned. This has led to the rapid and unregulated expansion of the private sector in these countries focussing mainly on curative medicine, but not preventive medicine or a public health agenda. Limited resources available for badly needed public health programmes are further squeezed as a result [19].

WHO states that there are six elements necessary to create a health system: leadership and governance, health care financing, health workforce, medical products and technologies, information and research and, service delivery [20]. These elements are essential to achieve the goals of a health system for better health, awareness and response to the needs of the communities and financial protection against high medical service costs (Figure B2). Jabbour et al. 2012 examined the health system based on these elements and concluded that the health system in the region is very poor and does not meet the basic criteria (ensuring equity, universality, comprehensiveness and free service at point of delivery [21]. The current health system in the region is not satisfactory and lacks the commitment to promote the equity. Furthermore, in countries where the health system has been destroyed, the opportunities for an equitable health system is very limited. In those countries where the health system is progressing towards universal coverage (being able to provide health services to its citizens) i.e. Gulf countries, the migrant domestic and expatriate individuals are excluded [21].

The issue of health equity is mainly associated with health care financing. Despite the fact that most MENA countries are classified as middle-income countries, their health systems are not delivering results proportionate to wealth levels [22]. Government financing for health is very low; the World Bank reports that MENA countries have some of the lowest levels of government spending on health care.

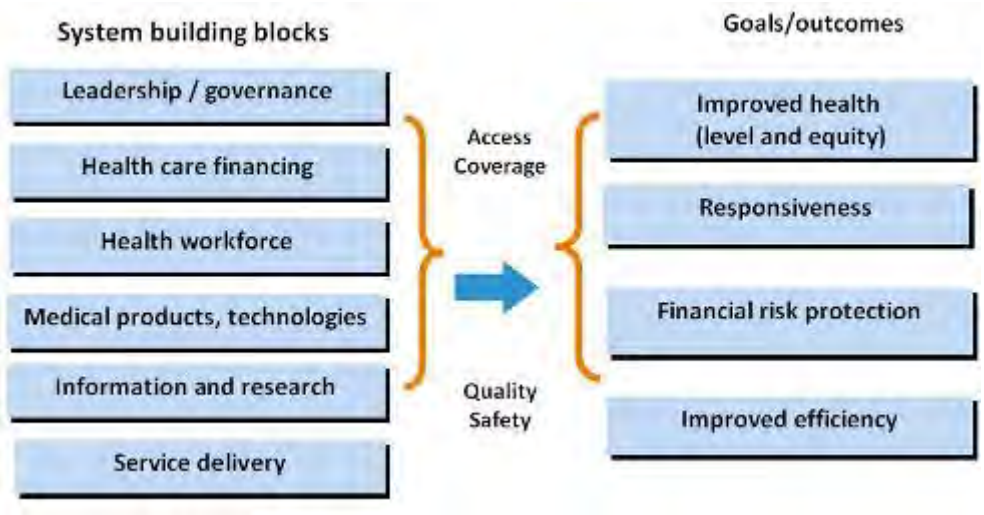

Figure B2: This conceptual WHO Health Systems Framework illustrates the building blocks for a good health system and the outcomes that might be achieved if these blocks were implemented. Source; WHO/WPR 2014

On average, MENA governments spend 8.2 per cent of their budget on health care compared to 80 per cent on the military forces in some countries. For instance, in 2011, Saudi Arabia and the United Arab Emirates, considered as wealthy countries, spent 2.3 per cent and 4.1 per cent respectively of their gross domestic product (GDP) on health care. This resulted in high costs for families in the region who have to pay almost 40 per cent of all health care costs [22].

It is significant that the issue of the delays in the diagnosis of TB, particularly in the health system and this contribution to the total delay in these cases could help analyse the quality of the health system. For example, three studies conducted in different time periods in Turkey found that delayed action in the health system it‘s the main source of TB delay in identifying the disease early and making it more treatable [23-25]. Health care providers were slow to suspect TB and the tools available for its investigation and diagnosis are often underutilized. Another multicentre study [5] identified on average five health care providers in the region available to TB patients for treatment (range= 2-12) and a minimum of two visits to each patient before a diagnosis of TB is confirmed. Also, the accessibility of the health facility was another significant predictor of delay in Egypt, Syrian Arab Republic and Yemen, where patients travel for more than half an hour to reach the health facility. These poor quality services by the public health system force patients to seek alternative care at private health care providers, including homeopaths or traditional healers [5].

1.3 Public health service delivery in the region

Regrettably, none of MENA‘s countries can be defined as having a well-developed public health delivery system. They are at different stages in the development of their public health infrastructures and capabilities and there are variations between countries in terms of their capabilities. Nevertheless, addressing inadequate capacity and insufficient resources allocated to preventive health services or a wider public health agenda in comparison to acute services, despite the major public health challenges mentioned, is not stated as a problem in the region [19]. Table B1 summarizes variations among some MENA‘s countries concerning:

- **Service or academic orientation public health:** Academic public health deals with teaching and research, supporting service departments of public health at the national and local levels and complementing the service of public health to provide high-quality delivery for the nation.
- **The level of function:** As noted on the Table B1 according to the World Bank, the overall level of function in the region is poor. However, some countries are in the process of improving this, but there are many obstacles faced by these countries in constructing better public health capabilities. These include long-term public health initiatives created by politicians and policymakers who may be more interested in quick and immediate returns that can translate into political gain. Lack of reliable data on population, lifestyles, behaviours, risk factors, and the activities and performance of the health system are further obstacles to designing relevant and timely interventions.
- **Funding for public health function** there are variations in the type of funding available to the public health service. In some countries, it is part of the general allocation to health and cannot be defined separately while in the other countries it is well defined (see Table B1). Furthermore, epidemiological and public health research is almost non-existent in most countries due to a lack of funds. This reduces the ability of both academic and service departments in their attempts to address the nation‘s health problems and achieve the best solutions based on the evidence.
- **Higher medical training for public health practitioners:** The development of the Arab Board of Medical Specializations (a residency programmes for training in most medical and surgical specialties) in 1970s by the Council of Arab Health Ministers is one of the most significant efforts to establish, apply, maintain and monitor high standards for medical specializations. Currently, 14 of the 24 MENA countries participate in the Arab Board

training and residency programme (Table B1). The countries that are not part of the Arab Board are running their systems that are possibly similar to the Arab Board [19].

In spite of these difficulties, there are some impressive efforts in progress to strengthen the health system and the delivery of these services in the region. The public health systems have been reviewed by WHO, the World Bank, the Arab Board, United Nations Children's Fund (UNICEF), the European Union, the US Agency for International Development, the UK Department for International Development, as well as other international and national organizations. As a result, there is financial and technical support being made available to strengthen the system‘s function [19].

Table B1: Public Health Infrastructure and Function in MENA/EM Countries

Country	Infrastructure	Function	Funding	Training
Bahrain	Academic + service	Medium	Not well defined	Arab Board
Djibouti	Service	Weak	Not known	—
Egypt	Academic + service	Relatively strong	Generally not well defined	1. Academic diplomas 2.Plan for Egyptian National Board 3. Arab Board
Iran	Academic + service	Strong	Defined	Academic diplomas, master's, PhD
Iraq	Service + academic	Relatively strong	Some public, health services defined separately	1. Arab Board 2. Iraqi National Board 3. Academic diplomas, master's, PhD
Jordon	Academic + service	Weak	Not well defined	1. Arab Board 2. Jordanian National Board, 3. Academic diplomas, master's, PhD.
Kuwait	Service	Strong	Defined	1. Arab Board, 2. Academic
Lebanon	Academic	Weak	Not well defined	1. Arab Board, 2. Academic diplomas, master's, PhD
Libya	Academic	Weak	Not well defined	Arab Board
Morocco	Academic + service	Medium	Defined	Specializations diploma
Oman	Service	Developing	Defined	Arab Board
Qatar	Service	Developing	Defined	Arab Board
Saudi Arabia	Service + academic	Medium	Defined	1. Arab Board, 2. Saudi National Board
Sudan	Academic	Weak/limited	Not well defined	1. Arab Board (but no Community Medicine as yet), 2. Academic
Syria	Academic (in the process of developing service public health)	Weak	Not well define	1. Arab Board 2. Low professional diploma, 3. Academic diplomas
Tunisia	Academic + service + research	Strong	Defined	1. Tunisian National Board, 2. Academic diplomas, master's, PhD.
United Arab	Service	Strong	Well defined	Arab Board
West Bank	Academic + service	Developing	Not well defined	1. Academic diplomas, 2. Some trainees were offered places on the Arab Board in other Arab countries.
Yemen	Academic + service	Not known	Not known	1. Arab Board 2. Academic diplomas, master's
No available information for Algeria and Somalia Adapted from [19]				

1.4 Disease burden in the region

The MENA region faces problems related to disease that can be divided into two parts; the declining burden of communicable diseases (CDs) and an increasing burden of non-communicable diseases (NCDs). Figures reveal that the CDs declined from 40 per cent in 2000 to 29 per cent in 2010, while the NCDs rose from 45 per cent to 53 per cent over the same period [26].

NCDs are the cause of many more premature deaths and disabilities (also known as disability-adjusted life years or DALYs) than in the past as shown in Figure B2 below [27]. Approximately, 65 per cent of the region‘s deaths among people aged 45-60 are due to cardiovascular diseases and cancer. According to WHO Global Status Report on NCDs in 2010, NCD deaths in the region are expected to increase by 20 per cent by 2020 if the trend is not reversed or at least stopped [28]. The main risk factors responsible for NCDs include tobacco consumption, unhealthy diet, physical inactivity and harmful alcohol consumption [28]. According to the WHO, the national health systems capacity for prevention and control of chronic diseases in the region is insufficient due to limited resources, fragmented and uncoordinated approaches to chronic care, low commitment to prevention, lack of surveillance systems, absence of clear policies and inadequate treatment guidelines [12].

As previously mentioned the health care systems in the region focus mainly on acute care, where the patients who present at the hospital are usually severely ill or suffering from long-term complications. The health system responds by treating and discharging the patients, and if needed, the patients may be offered a follow-up appointment. In reality, these chronic conditions require a coordinated, comprehensive system that integrates acute and chronic care effectively [12]. In order to overcome this problem, a few countries such as Morocco have developed a long-term care strategy for diabetic patients. The solution for meeting the increasing demand for NCDs care in the twenty-first century will be the associating of public health to health care, and the provision of individual care in a manner that impacts population health [12].

In regard to CDs, approximately all MENA‘s countries have achieved high rates of immunization coverage (80 to 100 per cent) for all vaccine-preventable diseases and made good improvements according to survival indicators. According to UNICEF and World Bank, the infant mortality rate has declined from 44 deaths per 1 000 live births in 2004 to 21.3 deaths per 1 000 live births in 2013 and the life expectancy at birth has increased from about 68 years in 2004 to an average of 72 years in 2013 [29,30]. However, newer CDs such as HIV/AIDS are emerging and will provide new challenges.

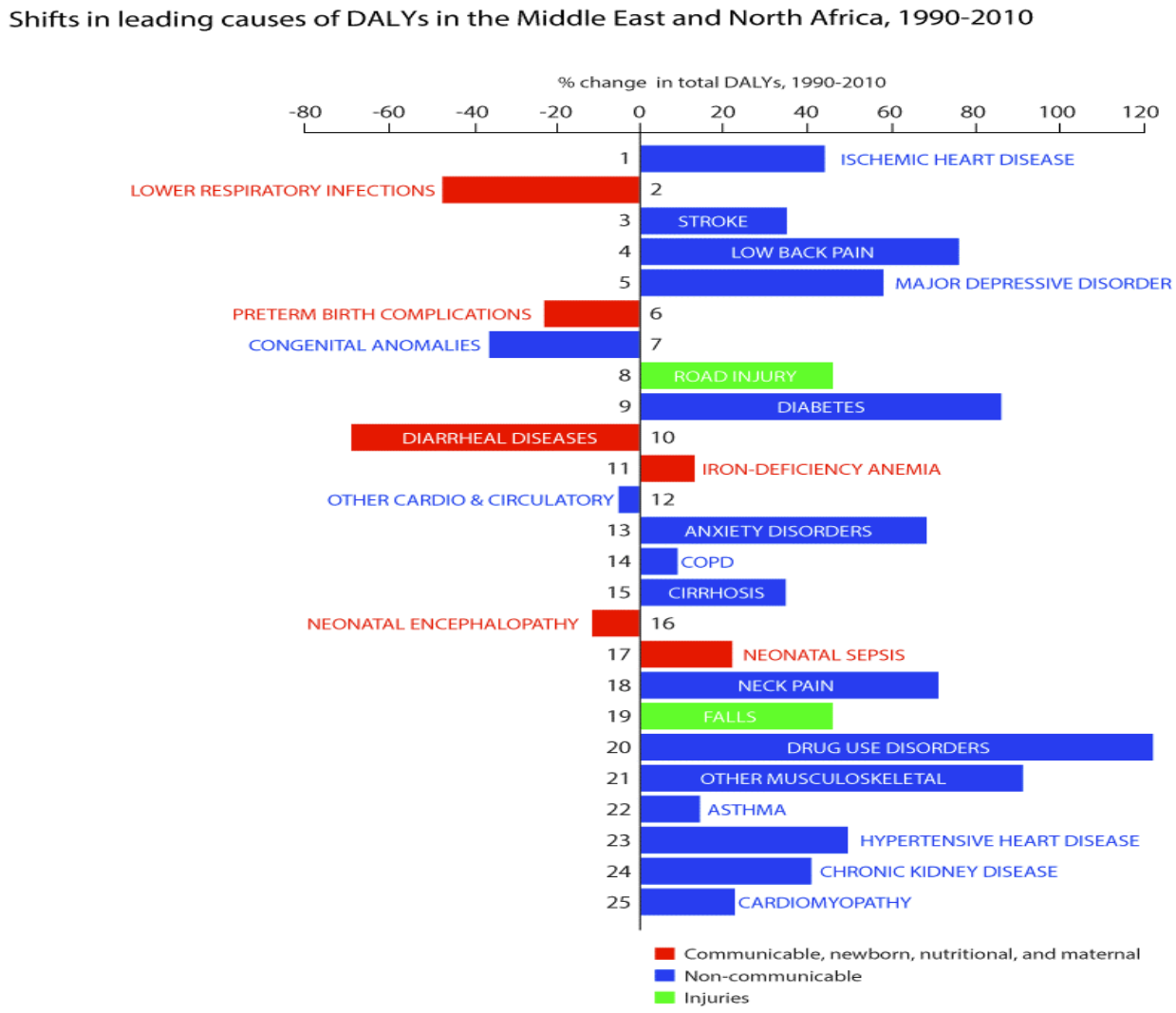

Figure B3; DALYs in the Middle East and North Africa, source Institute for Health Metrics and Evaluation (IHME). Resource reproduces from http://www.humanosphere.org/basics/2013/09/visualizing-the-burden-of-disease-in-the-middle-east-and-north-africa/. Bars on the right show the percentage by which DALYs have increased since 1990 and bars on the left show the per cent by which DALYs decreased. Most communicable diseases declined between 1990 and 2010, as shown by the red bars. And the non-communicable diseases and injuries increased as shown in blue and green bars respectively.

1.5 HIV/AIDS in the region

The MENA region accounts for only 2 per cent of the estimated global number of people living with HIV [31]. In 2014, there were 240 000 (150 000-320 000) people living with HIV in the region and 12 000 (5300–24 000) AIDS-related deaths [32]. However, recent estimates show that MENA is one of two regions with the fastest growing numbers related to the HIV epidemics. Between 2001 and 2014, there was a 26 per cent increase in the diagnosis of new HIV infections and AIDS-related deaths more than trebled in the region. This could be attributed to many causes and the most significant of these is the lack of availability of treatment (14 per cent) [32]. In addition, insufficient commitment, stigma, discrimination and inappropriate laws continue to obstruct the work carried out for those living with HIV and people on the margins in the MENA region [31]. There is also a shortage of data on HIV in countries across the region, as only four countries have effective HIV surveillance systems enabling them to track their epidemics. This makes it difficult to get an accurate picture of the situation, both regionally and nationally [33].

HIV/AIDS among TB patients is a useful indicator of the maturity of the HIV epidemic in a given setting because it reflects the presence of advanced HIV or AIDS cases in the population [33]. TB is considered a leading cause of death in HIV-infected patients and accounts for 25 per cent of HIV-related deaths [1,3,4,34]. The issue of TB diagnosis and treatment delays in HIV co-infected patients is addressed in many studies, especially in countries where HIV is prevalent [35,36]. However, it is difficult to make any conclusions in this regard in the MENA region due to the scarcity of HIV statistics.

OVERVIEW ON TUBERCULOSIS EPIDEMIOLOGY

1.1 BACKGROUND

Human TB is caused by infection with *Mycobacterium tuberculosis*, which is acid-fast bacilli and a member of Mycobacterium complex. Broadly, TB can be classified into two main types: Pulmonary TB, which is the most common and involves the lung parenchyma and/or *hilar* lymph nodes. Extra-pulmonary TB can present with, or without, the pulmonary form; it affects many organs or tissues other than the lung parenchyma, such as the pleura, meninges, extra-pulmonary lymph nodes, intestines, kidneys and bones. Individuals with pulmonary TB produce airborne droplets while coughing, sneezing, or talking. Inhaled infectious droplets lodge in the alveoli where the bacilli are taken up by macrophages. Then there will be a series of reactions that result in either containment of the infection or progression to active disease [37].

Inside macrophages, M. tuberculosis replicates slowly but continuously, and spreads through the lymphatic system to the *hilar* lymph nodes. Thereafter, a process called phagocytosis occurs, where the phagocytes (neutrophil and macrophages) engulf many of the bacteria and TB-specific lymphocytes destroy the bacilli and normal tissue. This immune reaction will result in the forming of granulomas (which are new tissue masses of live and dead bacilli surrounded by a protective wall of macrophages) that will limit the further replication and spread of bacilli. Unless a later defect occurs in cell-mediated immunity, the infection remains within the granulomas [37]. The bacteria remain dormant and in this stage it is called a Latent TB infection.

The cases with latent TB infection don‘t show any symptoms related to TB but come up positive in Tuberculin Skin Tests (TST) and Interferon-Gamma Release Assays (IGRA) blood tests. Cases with latent TB infection can progress to full-blown TB disease through either endogenous reactivation of the latent bacilli, or exogenous reinfection with a new strain. In the absence of other predisposing conditions, only about 5 per cent of infected people develop the progressive primary disease within five years of infection [37].

In cases where the immune response are not able to contain the replication of Mycobacterium, primary progressive TB disease will develop with symptoms (mainly coughing with night sweats for more than two weeks) and become a source for transmitting the disease within the community.

2.2 TB Transmission

Tuberculosis transmission depends upon exposure to tubercle bacilli. There are three major factors that determine the risk of becoming exposed:

1) The number of incidents of infectious cases in the community. The higher the number of these cases, the higher the risk of transmission [38].
2) The number and nature of interactions between a TB case and a susceptible contact per unit of time of infectiousness. This is influenced by many factors. These include population density (low levels of infectiousness in rural settings), family size, climatic conditions (low TB transmission in a warm climate because people stay in well-ventilated places) and age of the patient. The latter affects the pattern of social participation; all age groups socialize together and this may introduce TB transmission among specific age group [38].
3) The duration of infectiousness. A period of two months is enough for the infection to spread to domestic contacts. In addition, without treatment, 50 per cent of TB patients will die within five years and on average, the patient who is the source of infection will infect 10 to 15 people per year (WHO 2014). Most transmission of TB occurs between the appearance of a cough and initiation of treatment [38]. The patient becomes more contagious as the delay progresses, the length of which is positively associated with the bacillary number in sputum smear [39].

2.3 Risk factors for TB

There are numerous risk factors associated with the development of TB such as the presence of HIV infection, underlying health conditions such as diabetes mellitus and cancer, close contact with TB infected individuals, age (with the young and elderly being particularly vulnerable due to weak immunity), smoking, alcoholism and poverty [40].

2.4 TB Diagnosis

A complete history, physical examination, tuberculin skin test, acid-fast bacillus (AFB) smears, chest X-rays and sputum culture are used to diagnose TB. During the taking of the history, the patient may reveal contact with someone who has been diagnosed with TB. The health provider needs to take a

full medical history including the duration of symptoms, any other medical conditions and a history of medical problems and diagnoses [41]. The tuberculin test measures the delayed hypersensitivity response to an injection of purified protein derivative by producing a local skin reaction within 48 to 72 hours of injection into the skin of an infected person. The tuberculin skin test is a great diagnostic tool as a screening test, as a strong positive skin reaction indicates the presence of viable tubercle bacilli in the body [42]. Sputum specimens will be checked under a microscope for rapid diagnosis and culture. Smears are taken to check for acid-fast bacilli that have a waxy capsule, which is stained with difficulty using red dyes that give the bacilli red look when examined under the microscope. Culture examination is more accurate than microscopy but it takes much longer to obtain results, usually about six weeks [4]. A chest X-ray of a person infected with TB may reveal lesions in the upper lobes of the lungs and useful for the evaluation of patients who have negative sputum smears to confirm pulmonary TB and identify other abnormalities that may be responsible for the symptoms [4].

2.5 TB Globally

Globally, TB is second to HIV/AIDS as a cause of illness and death of adults [1-3,34]. In 2013, an estimated nine million people were infected with TB resulting in 1.5 million deaths (including 360 000 of whom were HIV-positive)[4]. TB occurs worldwide. The largest number of new TB cases were identified in South-East Asia and Western Pacific Regions, accounting for 56per cent of the new cases [1,4]. The efforts made for effective diagnosis and treatment have succeeded in saving 37 million lives between 2000 and 2013 [4]. However, the death from the disease is still unacceptably high, given the fact that deaths from TB are preventable [4,43]. Many of these deaths could be avoided with a stronger and more efficient TB control programme.

2.6 TB in MENA region

According to World Bank estimates, this region is responsible for about 6–7 per cent of the global burden of TB [44]. In 2013, the estimated number of incident TB cases in the region was 40 per 100,000 people. The incidence of TB is calculated by the estimated number of new pulmonary, smear positive and extra-pulmonary tuberculosis cases. The rate of decline of patients with TB has reduced very slowly with less than 1 per cent per year from 1990 [45][1]. However, ten countries have reduced their numbers of individuals with TB to rates of less than 25 per 100 000 populations in 2010, compared to only one country in 1990. According to WHO, seven countries (Sudan, Morocco,

[1] Eastern Mediterranean Region (EMR) is one of WHO‘s six regions include all MENA countries plus Afghanistan and Pakistan. We exclude the data for these countries from the final figures.

Somalia, Iraq, Egypt, Islamic Republic of Iran and Yemen) were responsible for 95 per cent of the TB burden in the region in 2010 [45].

Related to multi-drug resistance TB (MDR/TB), the region has very low rates of MDR about 3.5 per cent, however, it is estimated that 12 per cent of MDR-TB cases have been identified and 72 per cent of these cases is on treatment on 2013 [45]. Furthermore, since 1994 only eight countries in the region have reported MDR/TB data from areas representing only 22 per cent of all tuberculosis cases. The primary limiting factor to expanding survey coverage is the high number of countries currently facing conflict and complex emergency situations [46].

The national governmental contribution to NTPs budgets varied in different countries. In Djibouti, Somalia and Southern Sudan, NTPs relied entirely on external donors such as the Global Fund to Fight AIDS, TB and Malaria (GFATM). In countries from the Gulf Cooperation Council (GCC), the governments are responsible for all the NTPs budgets while in the remaining countries, the governmental financial contribution ranged from 30 per cent to 50 per cent of the planned budget [46]. In terms of TB treatment, all countries in the region use standardized treatment regimens in line with the internationally recommended guidelines. Additionally, all countries have DOTS in place, at least during the intensive phase, for all patients in all centres, except for Jordan, Saudi Arabia, Sudan and Yemen, where DOTS was not uniformly carried out for all patients [45].

In all countries in this region, sputum smear microscopy was the basis of diagnosis of pulmonary tuberculosis and was provided free of charge at all diagnostic centres. According to [46], 18 countries reported a laboratory network coverage for direct smear microscopy within the recommended level of one laboratory per 50 000–250 000 of the population. All countries, except Djibouti and Somalia, reported having culture laboratories. External quality assessment for culture laboratories was reported to be 100 per cent in six countries. All countries in the area, except Djibouti, occupied Palestinian territory and Somalia, had drug susceptibility testing laboratories.

2.7 TB CONTROL

The control of TB depends on whether the transmission cycle can be interrupted by decreasing numbers of infectious cases by effective case-finding complemented by high cure rates [4]. By reducing the infectious period through prompt intervention with appropriate chemotherapy, it decreases the possibilities that members of the community continue to be exposed to infection [38]. Many strategies and intervention had been developed globally and sometimes contextualized to serve the national needs and fulfil these goals. Some adopted the global TB strategy and significant progress is being made on its implementation [46].

2.7.1 The Stop TB strategy

The Stop TB Strategy is the global TB strategy developed by WHO for the period 2006−2015 within the framework of the Millennium Development Goals (MDGs)[4]. The goal of this strategy is to achieve 2015 global targets for reduction in the burden of disease caused by TB. These targets can be translated to a reduction in the frequency of the disease, and that prevalence and mortality rates should be halved by 2015 compared to 1990 levels. The achievement of these targets will be discussed later under TB in MDGs. One of the major components of this strategy is pursuing high-quality DOTS expansion and enhancement.

2.7.2 Directly Observed Treatment Strategy (DOTS)

In 2009, coverage of DOTS in the region was reported to be 97 per cent [46]. Five countries did not achieve 100 per cent coverage: Iraq (87 per cent), Pakistan (99 per cent), occupied Palestinian territory (45 per cent), Sudan (91 per cent) and United Arab Emirates (20 per cent). The DOTS is a treatment intervention that focuses on the prompt treatment of symptomatic cases with short-course chemotherapy administered under direct observation of health providers [4]. The overall goal of this strategy is to reduce transmission of tuberculosis in the community through early detection of smear-positive tuberculosis cases and rapid administration of the full-course treatment. The DOTS strategy demands political commitment, case detection by sputum smear microscopy and mostly occurs among self-referring symptomatic patients. A standard short-course chemotherapy is administered under the correct conditions including directly observed therapy, ensuring regular drug supplies and a standard recording and reporting system, which includes the evaluation of the treatment outcome [47].

This goal translated into the detection of at least 70 per cent of estimated infectious cases and secured a treatment success rate of 85 per cent among detected cases by 2005 [48]. Disappointingly by the end of 2005, only 32 per cent of the estimated cases were detected through DOTS [48]. Currently, the DOTS strategy continues to struggle to resolve the problem of low detection rates by closing the gap between the number of notified cases and estimated incident cases [1]. The issue of low detection rate will be discussed in details later in this research. In the MENA region, there was a significant decline in TB prevalence and TB-related mortality compared with a baseline in 1990, but the Millennium Development Goals (MDGs) targets were not reached [4].

2.7.3 TB in the MDGs

The MDGs are the eight international development goals that were identified as reliable following the Millennium Summit of the United Nations in 2000. All 189 United Nations member states at the time, and at least 23 international organizations, committed to help achieve the Millennium Development Goals by 2015 [49]. TB was included as part of MDG 6 with targets that include five indicators that are TB incidence, TB mortality, TB prevalence, case detection rate for new cases and the treatment success rate for new TB cases [4]. The MDG target of the TB incidence rate falling by 2015 has been met worldwide in all six WHO regions (Table B2). The target to reduce TB mortality by 50 per cent has been met in three regions, Americas, South-East Asia and Western Pacific Regions. The African, Eastern Mediterranean and European Regions are unlikely to reach the target. The target of a 50 per cent reduction in TB prevalence has been achieved only in the Americas and the Western Pacific Regions and from the other regions only South East Asia Region appears on track to reach the target. The Targets for the treatment success rate among new TB cases and the case detection rate (notifications of new and relapse cases divided by estimated incidence) were not set for 2015. Treatment success rates were above 85 per cent globally in 2012 and the case detection rate was 64 per cent in 2013 [4].

The United Nations Summit for the adoption of the post-2015 development agenda will take place in September 2015 in New York. The post-2015 development agenda includes the Sustainable Development Goals (SDGs) with targets set for 2030. One of these goals, ―Ensure healthy lives and promote well-being for all at all ages", includes a target to ―end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases" by 2030.

Table B2: Progress towards 2015 targets set within the MDG framework. Adapted from WHO 2014 global TB report.

MDG FRAMEWORK: INDICATORS AND TARGETS					
Indicator	TB incidence rate	TB prevalence rate	TB mortality rate	TB case detection rate	TB treatment success rate
Target	Incidence rate falling	50% reduction compared with 1990	50% reduction compared with 1990	Not set	Not set
Global	Met	Not in track	Not on track	64 (61–66)	86
AFR	Met	Not on track	Not on track	52 (46–57)	81
AMR	Met		Met	77 (73–80)	76

EMR	Met	Not on track	Not on track	58 (49–71)	87
EUR	Met	Not on track	Not on track	80 (77–84)	75
SEAR	Met	Not on track	Met	62 (59–65)	88
WPR	Met	Met	Met	83 (79–88)	92
AFR; African, AMR; Americas, EMR; Eastern Mediterranean, EUR; European, SEAR; South-East Asia, WPR; Western Pacific On track means that the indicator will likely be achieved by the end of 2015 based on the current predicted trend.					

2.7.3.1 Post-2015 TB strategy

Currently, the transition between the MDGs that established in 2000 and a post-2015 development framework are in progress. Within this framework, the WHO developed a post-2015 strategy that targets to end the global TB epidemic by 2035 [4]. Similarly, global targets are a 95 per cent reduction in the number of TB deaths and a 90 per cent reduction in cases, compared with a baseline of 2015 [4] see Table B2.

Table B2: the post-2015 TB strategy (adapted from WHO 2014 global report p. 19)

VISION	A TB-free world — Zero deaths, disease and suffering due to TB
GOAL	End the global tuberculosis epidemic
MILESTONES FOR 2025	— 75% reduction in TB deaths (compared with 2015) — 50% reduction in TB incidence rate (less than 55 TB cases per 100 000 population) — No affected families facing catastrophic costs due to TB
TARGETS FOR 2035	— 95% reduction in TB deaths (compared with 2015) — 90% reduction in TB incidence rate (less than 10 TB cases per 100 000 population) — No affected families facing catastrophic costs due to TB
PRINCIPLES	1. Government stewardship and accountability, with monitoring and evaluation 2. Strong coalition with civil society organizations and communities 3. Protection and promotion of human rights, ethics and equity 4. Adaptation of the strategy and targets at country level, with global collaboration
PILLARS	1- Integrated, patient-centred care and prevention 2. Bold policies and supportive systems 3. Intensified research and innovation

2.8 TB INTERVENTIONS

TB control can be categorized broadly into four major interventions:

2.8.1 Treatment of Tuberculosis

An intervention that focuses on two broad aims; firstly to reduce the risk of death and restore health and curing patients and secondly, to reduce the risk of transmission in the community [38]. Treatment intervention is the most widespread method for TB control and it has two main fundamentals parts, case finding and case holding [50]. For this to occur, it is essential to maintain a high suspicion index by health providers [51], timely initiation of proper treatment and increase patient‘s awareness and health worker‘s readiness to control the spread of TB. Social and cultural factors in the control process and their contribution must also be considered [47].

2.8.2 Active Case Finding and Treatment of Smear-Positive Tuberculosis

The main objectives of this approach is to ensure early detection of active TB in order to reduce the risk of poor disease outcomes and the adverse social and economic sequences, as well as help to reduce the transmission of TB. However, this strategy requires a special effort by the health care system to increase the detection of TB in a given population.

Broadly, there are two major means of active case finding. Mass mini radiography for population screening and population surveys using TB symptoms to screen patients (symptomatic screening) [52]. The mass radiography showed 90 per cent detection of active TB cases and 85 per cent of inactive TB cases. But, this needs huge investment and is extremely expensive. Symptomatic screenings are less costly to implement, but may detect only 70 per cent of prevalent cases, depending on the target groups and the methods used to elicit symptoms [52].

Active case finding are criticised in many debates and was abandoned in 1974 by WHO‘s Steering Committee in TB due to cost and that it frequently leads to poor treatment compliance [53]. Furthermore, active case finding is difficult on a large scale and requires the investment of extensive human and financial resources in identifying a relatively small number of cases. Also, there is no universal consensus on the impact of active case finding on TB incidence [54]. Many mathematical models have examined this relationship with the same conclusion.

One of these models modelled active case-finding approaches after considering costs and prevalence in different regions of the world. The authors concluded that ACF strategies combined with DOTS would yield enormous benefits in areas with high TB prevalence, and many deaths could be prevented [54]. However, recently published cluster-randomized control trial (c-RCT) used ACF revealed contradictory results [55]. This c-RCT was undertaken with South African gold miners and aimed to interrupt TB transmission by means of mass symptomatic screening. In regards to TB incidence, the trial showed similar TB rates in the intervention and control clusters. The incidence of TB was 3.02 per 100 person-years in the intervention cluster and 2.95 per 100 person-years in the control clusters

and the authors concluded that mass screening had no significant effect on TB control in gold miners [55].

2.8.3 Preventive therapy

2.8.3.1 Preventive therapy for contacts of tuberculosis patients

This intervention defined as preventative treatment that aims to prevent infection with TB bacilli from occurring through contact with TB patients and adults in the general population [38]. Success of this intervention must combine two elements that are the active tracing of contacts and prophylaxis treatment. In practice, contact investigation to identify recent infection has been limited to children within the household, which restricts the comprehensiveness of this intervention [47]. The usefulness of this intervention among the adult population with latent infection is also expected to have a protective efficacy of 60-80 per cent, depending on the duration of therapy [56]. The main limitations facing this intervention are partial uptake and compliance with prophylaxis agents [56].

2.8.3.2 Preventive therapy in people with HIV infection

This intervention is defined as treatment of a sub-clinical, latent *Mycobacterium tuberculosis* populations in the human host and is given to reduce the risk of progression to clinically overt TB [38]. Preventive chemotherapy for six to twelve months using isoniazid is effective but operationally inefficient. In adults, there is the danger of mono-therapy of clinically active TB, which might not be recognized if mycobacterial culture facilities and chest radiography procedures are not routinely available [38]. This is of particular concern in HIV-infected patients who would be most likely to benefit because they frequently have active TB not identified on sputum smear microscopy alone [47,56]. Preventive chemotherapy is an individual intervention and does not appear to have as great an epidemiologic impact as chemotherapy for TB [38]. Even if precautions could be taken to prevent unintentional mono-therapy for patients with active TB, it remains an inefficient tool that reaches only a fraction of persons infected with M. tuberculosis [38].

2.8.4 Vaccination with Bacilli Calmette-Guerin (BCG)

Vaccinations aim at reducing the risk of progression from infection to disease. Consequently, its effect is expected to be similar to that of the strategy to reduce the prevalence of infection [38], but it is not considered to have a great epidemiological impact on TB transmission. The vaccine effectiveness is up to 80 per cent for disseminated TB, mainly TB meningitis in childhood, but not PTB in adolescents and adults [52].

2.9 CERTAIN CHALLENGES TO TB CONTROL

2.9.1 Limitations of Passive case finding

Currently, the principal means of controlling transmission and reducing incidence in developing countries relies on the passive case finding approach [4]. This method is based on diagnosing infectious cases who present at the health facilities using sputum smear microscopy [57]. This type of case detection is effective in patients with pronounced symptoms but less effective in early diagnosis for people with less obvious symptoms.

Another shortcoming of this approach is the difficulty in detection of patients with sputum-smear-negative TB. This point is highly important, because as the numbers of undetected smear-negative PTB increase, their contribution to the total burden of TB and total transmission also increases. Consequently, this becomes one of the major forces driving the epidemic [58].

Passive case finding is influenced by factors such as patient motivation, the degree of diagnostic suspicion by health workers and the quality of laboratory facilities [59,60]. Therefore, it is considered to be a major source of delayed diagnosis discussed in detail in the following sections.

2.9.2 Low TB Case detection rate

A low detection rate of TB is one of the major difficulties confronting TB control worldwide. Globally, ―the number of TB cases diagnosed and notified per 100 000 population remained relatively stable between 1990 and 2000, rose sharply between 2000 and 2008, and subsequently slowly started to fall" [4]. In 2013, about 64 per cent of the estimated 9 million people with TB were notified as being newly diagnosed cases. This is estimated to have left about 3 million cases that were either:

- Not diagnosed (due to poor access to health care and/or failure to detect cases when people visit health care facilities), or
- Diagnosed, but not reported to national TB programmes, such as the failure of reporting cases diagnosed in the private sector (NTPs)[4].

According to the World Bank, the TB Case Detection Rate (CDR) for ―all forms" of TB in the region was 70 per cent in 2013 (Figure B3) [44]. This rate varied across the countries in the region where some countries corresponded to higher rates such as in Turkey, Yemen, Tunisia and Morocco 88 per cent, 88 per cent, 87 per cent and 85 per cent respectively. The countries with very low rates are Iraq and UAE, 57 per cent and 50 per cent respectively. The remaining countries vary between 65 per cent

and 73 per cent [44]. It must be noted that these CDRs are for all forms of TB, i.e. Pulmonary TB (PTB) both smear positive and negative, Extra-pulmonary TB (EPTB), relapse forms and etcetera. Regrettably, there is no recent data for CDRs in smear -positive TB in the region.

The WHO 2008 report noted that, while the CDR for all forms is currently up to date, the NTPs in the region could detect on average one-third of smear-positive pulmonary TB cases. The remaining two-thirds will thus continue to transmit TB infection in the community until identified by other health sectors [5]. This is very alarming because infectiousness is higher among smear positive PTB cases where the proportion of contacts found infected at the time of diagnosis of a smear-positive index case is between 30–40 per cent. If the case are not detected and adequate treatment provided, the circle of susceptible contacts will widen [5]. The delay of case detection is one of the major challenges and obstacles faced by NTPs in all areas and will be discussed further in this chapter.

WHO developed two initiatives to solve the problem of low detection rate are the public-public and public-private mix (PPM) initiatives [4]. The involvement of all public, voluntary, corporate and private providers through PPM approaches is one of the chief components of TB strategy. Globally, many countries have implemented PPM initiatives and in most of these, PPM initiatives contributed about 10–40 per cent of total notifications.

In the MENA region, the NTPs started collaborating with key non-programme health care providers, including prison services, university hospitals, health insurance organizations, nongovernmental organizations and the private sector. The NTPs in Egypt and northern Sudan have identified or recruited a full-time individual in their central unit who is responsible for public-private mix-related issues. In Egypt, Islamic Republic of Iran, Jordan, southern Sudan and the Syrian Arab Republic the proportion of cases detected by non-programme providers constituted one-third or more of the total TB cases discovered. Whereas, in Iraq, northern Sudan and Yemen this proportion is less than 10 per cent [46].

These two problems (passive case finding and low case detection rate) contribute critically to the problem of delay diagnosis and initiation of treatment in TB and will be further discussed.

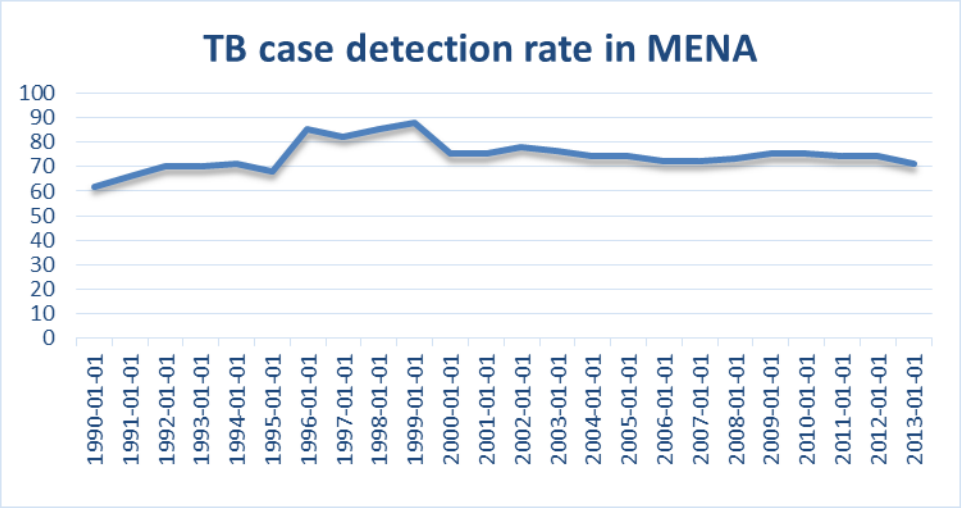

Figure B3: shows the TB case detection in MENA between 1990 and 2013. The CDR increased by only 10% from that in 1990. Resource; World Bank available on https://www.quandl.com/data/WORLDBANK/MEA_SH_TBS_DTEC_ZS-Middle-East-North-Afric

2. DELAY IN THE DIAGNOSIS AND TREATMENT OF TB

Despite the advances and decentralizing of TB diagnosis and treatment, the pool of undetected TB cases still remains large in many countries. This is particularly among the high-risk groups such as those with HIV, close contacts of TB patients, miners, prisoners, intravenous drug users, homeless people and others [58]. The delays in detecting and diagnosing TB cases leads to higher risk of death, exacerbates the course of the disease and high financial consequences [58]. In addition, delayed diagnosis increases the duration of infectiousness, enhances transmission, especially in poor living and working conditions (overcrowding and inadequately ventilated environments), and expands the disease epidemic [5,58,61,62]. Furthermore, the patient becomes more contagious as the delay progresses, which can positively associate with the bacillary number in the sputum smear [39].

Therefore, TB controls to stop disease transmission through early diagnosis and immediate initiation of treatment are vital and examining the reasons for delays in detection and treatment are significant for TB control programmes in improving their strategies. These delays may be attributed to patients and the health care system [57]. The patients may delay seeking help, or the health care system may delay in investigating for TB. Therefore, focusing on patient and health system factors associated with delays in detection of TB is important for identifying points of intervention for TB control [36,63,64].

3.1 Consequences of TB Delay

Several studies studied the consequences of delaying the diagnosis and treatment of TB [51,61,62,65-67]. Their results can be summarized as:

2.1.1 Community-related consequences

Delay in the diagnosis and treatment, especially in active cases, enhances transmission within the community [5,38,57,68]. As mentioned earlier, the transmission of TB from an infectious person depends on three major factors. These factors concern the relationship between time and degree of infectiousness together with the number of available susceptible contacts and the time from onset of infectious disease to diagnosis [38]. Accordingly, the risk of becoming exposed is greater if the number of infectious cases increases and the duration of infectiousness is prolonged. Without treatment, a person with active PTB can infect on average 10 to 15 persons a year [69]. In particular, a study from California found that during the delay, patients exposed an average of eight contacts [62].

This would be higher in settings where there is problems related to overcrowding and higher social capital. Moreover, the study by Rao et al. (1999) found that management delays (from admission to treatment initiation) result in an average of 23.9 health care workers being exposed. As a consequence, the subsequent evaluation of each of these workers adds substantially to the overall costs of hospitalization [51].

2.1.2 Patient-related consequences

Many studies [62,65-67] but not Rao et al. (1999) conclude that delay in the diagnosis and treatment exacerbates the course of the disease and increases the risk of death, especially where there is HIV co-infection. A hospital based study conducted by Rao et al. (1999) in the United States found the delay to worsen the course of the disease but not related to TB mortality rates [51]. This contradiction could be attributed to the low incidence of HIV co-infection in the population studied by Rao et al. (1999) whereas, the rest of these studies were conducted in high HIV prevalence settings.

Another patient related consequence is financial as patients spend more money on consultation either with health care providers or traditional healers, and buying non-effective/relevant treatment. Also, absenteeism from work due to illnesses might affect the needs of the patient‘s family.

3.2 Levels of delay in the diagnosis and treatment of tuberculosis

Most studies divide the pre-treatment period into two main time frames: a period before the patient presents to a health care provider and after the patient‘s first contact with a health provider until diagnosis and initiation of anti-TB treatment.

3.2.1 Total diagnostic delay

The total diagnostic delay is defined as the period related to both patient and health care provider before diagnosis and initiation of treatment [5]. There are many factors influences this delay period mainly the health seeking behaviour among the patient. Health seeking behaviour is very complicated process and governs by so many factors. Understanding of these factors could reduce delay to diagnosis, improve treatment compliance and improve health promotion strategies in a variety of contexts [70]. These factors have been examined under so many situations by deferent behavioural models from social psychology, medical sociology and medical anthropology [70]. One of these models is the Andersen‘s Behavioural Model of Health Care Utilization that initially developed in the late 1960. The model suggests that people‘s use of health services is a function of their predisposition

to use services. In which, factors which enable or hinder use, and their need for care, providing a way to conceptualize these variations in utilization rates and consumption of medical resources [71]. In this model, use of health care services is a function of 3 main domains: need, enabling, and predisposing factors. Need factors, account for the majority of the explained variability in physician use, include the individual‘s perceived health care need and other indicators of their health status. Enabling factors include items such as the individual‘s income, health insurance status, and access to a source of regular care. Finally, predisposing factors include demographic variables, socioeconomic status, attitudes, and beliefs [71]. This categorization will be used in the next section when analysing the factors for TB delay.

The length of total diagnostic delay varied with a range from 30 days in the Philippines [50] to 136 days in Tanzania [72]. In most MENA‘ countries, the mean diagnostic delay ranged between one and a half months to four months [5]. The length of the diagnostic delay was 46 days in Iraq[5], 53 in Sudan[47] 57 in Egypt [5], 46 in Morocco [73], 59.2 in Yemen [5], 79.5 in Somalia [5], 77.6 in Syrian Arab Republic [74], 127 in Islamic Republic of Iran [5], and 78.5 in Turkey [25].

3.2.2 Patients delay

There is no obvious consensus regarding the definition of patient delay. The WHO definition of patient delay is the time interval from the appearance of the major pulmonary symptoms of the disease until the first visit to a medical care centre [5]. There are some differences in the use of this definition that may be due to different descriptions of what is meant by the health system and who represents medical care and the TB symptoms. For example, a study conducted in New York defined patient delay as the period from the onset of any TB or non-TB symptoms to the first visit to a medical centre [75]. This definition was considered inaccurate according to the WHO as it defines the TB suspect case as any person who presents with symptoms or signs suggestive of TB. The most common symptom of PTB is a productive cough for more than two weeks, possibly accompanied by other respiratory symptoms (shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue)[76].

Another definition, applied in Gambia, was the period between the onset of pulmonary symptoms of TB and first consultation with any person which included traditional healers, market drug sellers, pharmacists, village health workers, friends and relatives as well as medical staff [77]. This yields the shortest delay ever documented (two days)[77]. Although different definitions for the patient delay

seem ambiguous, these discrepancies enrich the outcome of studies conducted and made their conclusions more specific and focused [47].

The specific period to be considered as a patient delay likewise seems unclear. Some researcher considered 30, 45 or 60 days as a significant delay period while others choose their cut-off point based on physician‘s clinical practices and experience [78]. Patient delay is considered to be the main contributor to total delay in some studies [5,50,75,77,79-81]. This point is highly significant when detailing TB control interventions especially in resource-limited settings where the main focus should target this period more than the health system one.

Numerous factors are identified as contributors to delay in seeking health services. One of the most important is the effect of stigmatisation of TB mediated denial and concealment of TB diagnosis, especially among women. Also, anxiety regarding high costs for diagnosis and treatment (perceived barriers) especially among men and that the standard of health facilities did not meet expectations of appropriate health services in terms of resources and staff competence [47]. There is a vicious circle of repeated consultations with a multitude of healthcare providers without a correct diagnosis that plays a major role in the delay in many countries [63].

3.2.3 Health systems delay

The gold standard definition of health system delay is considered as the time interval between the date of the first presentation of patients to a professional health provider and initiation of treatment [5]. However, different definitions were used in the literature by many researchers like ―the time interval from the first consultation until date of TB diagnosis” [82]. The shortcoming of this definition is obvious. TB diagnosis, although an important component in TB control, is not the end goal of TB control programmes. Getting diagnosed is not a guarantee of starting and being treated. The time between being diagnosed and commencing treatment for some patients is very long [37].

Another study used the definition of the time from the first visit to a health provider to diagnosis [77]. The author defined the health provider to be ―any person consulted by the patient about his/her sickness who gave or prescribed something (whatever the form) for treatment. These included traditional healers, market drug sellers, pharmacists, village health workers (VHWs), friends and relatives as well as medical staff”. This broad definition yielded the longest health system period ever documented (10.8 weeks)[77].

The lack of definitions to specify an accepted period of delay between TB diagnoses and start of treatments plays an important role in terms of what is considered as a health system delay. Some studies considered 7 days, others 10 days, 14 days, or based on physician‘s practices when the physician choose their delay cut-off point [78].

The shortest health system delay was documented in the USA with a mean period of 6 days [75]. The longest delay was documented in Gambia (10.8 weeks) [77]. Based on systematic review of 58 studies globally, the contribution of health provider‘s period in the total diagnostic delay was varied. As a result of using different definitions, studies stated that health provider delay was the main contributor to the total delay, but not in all studies [63]. For example, studies from Ethiopia, Gambia and Ghana [77,82,83] found that the health provider delay is the main contributor to the total diagnostic delay; these studies included part of patient‘s delay within the definition of health system delay. The study from the Gambia [77] assumed that traditional healers or family members could be health providers. In the Ethiopian study [82], a health provider was defined as anyone who gave the patient something as medication.

The delay within the health system is influenced by several factors such as prevalence of TB, accessibility of health facilities, patient‘s socio-demographic characteristics, symptoms on presentation, presence of refined suspicion index, infrastructures and organization of the health system [47].

3.3.4 Certain factors associated with delay in TB diagnosis and treatment

Rural and urban settings: Studies from Botswana [1], the Gambia [15], Tanzania [14], Ghana [22] and Korea [25], showed that the delay were significantly longer in rural areas. In Somalia, living in the suburbs and rural areas was associated with double the risk of delay compared to urban areas [5].

Age of the patient: TB represents a markedly aging epidemic, with a progressive increase in the notification rate with age and a peak among those aged ≥65 years old in the Eastern Mediterranean Region [4]. A review found 56/58 studies documented that older patients (>40 years) were at a much higher risk of TB diagnostic delay compared with those younger than 40 years [63]. According to a South African study, this can be attributed to coexisting medical conditions in the elderly persons, such as heart diseases and chronic chest problems, which may contribute to the difficulty of diagnosing TB, and can thus result in delayed diagnosis and treatment [84].

Gender of the patient: In 2012, an estimated 33% of incident TB (2.9 million cases) occurred among women worldwide [85]. Although the global case notification rate of TB is lower for women than

men, TB is among the top three (the other two being maternal related deaths and HIV) killers among women aged 15 to 44 years [86]. Diwan V one of the first researchers considering TB control as a gender issue [87], fortified a gender-based approach to TB control with the idea that would promote understanding biological variations, cultural differences, and even structural violence leading to poverty, inadequate health care resources and increased risk of tuberculosis and death [87]. Sociocultural structures are the main gender-specific barriers to accessing TB diagnostic and treatment services [88]. This review emphasized that women experienced barriers due to financial dependence, lack of physical independence, the de-prioritization of their health in households, stigma within the household, relatively low general and TB-related literacy, and the expectation that an ill wife must take care of her husband, but not vice versa [88]. On the other hand, men primarily experienced community-based stigma and work-related financial and physical barriers, which reflect their higher status/power and role as the primary earner [88]. In addition, gender-specific issues seem to impact marriage due to TB related stigma. For men diagnosed with TB, the potential inability to work and support the family appeared to be linked to reduced marriage likelihood [88]. Whereas women, diagnosed with TB, found to be faced with concerns regarding fertility before marriage, threats of divorce after marriage due to fear of contagion and the inability to perform household chores [88].

HIV status: In the MENA region, there are only 2% of the global estimated number of people living with HIV [31]. However recent estimates show that it is one of the two regions with the fastest growing HIV epidemics. Insufficient commitment, stigma, discrimination, and inappropriate laws continue to obstruct work with people living with HIV and people on the margins in the MENA region. Hence rapid actions to curb demand exceeding supply are highly recommended [31]. HIV/AIDS among tuberculosis (TB) patients is a useful indicator of the maturity of the HIV epidemic in a given setting because it reflects the presence of advanced HIV or AIDS cases in the population [33]. TB considered a leading cause in death of HIV infected patients and accounting for 25% of HIV related death [1,3,4,34]. The mortality rate and the incident rate of new AIDS-defining opportunistic infections were founded to be higher for HIV-TB-co-infected patients than for HIV-infected patients without active TB who were matched for CD4 cell counts [35].

The relative risk of TB doubles in the first year after HIV infection, when CD4 counts are still preserved, and continues to increase during the years after seroconversion as CD4 counts decrease [35]. HIV increases the risk of progression to active TB in both primary TB infection and the reactivation of latent TB [35]. The sub-optimal performance of traditional TB diagnostic tools, such as smear microscopy and chest X-ray (CXR), in HIV co-infected patients had led to relying on other laboratory methods such as culture. Culture however, has a lag time-to result of up to 6 weeks, thus creating a diagnostic delay and increased morbidity and transmission [35].

These are not the only factors that create diagnostic delay of TB among HIV patients. A South African study found that older patients with elevated viral load and on ART while diagnosed with PTB are at higher risk of TB diagnosis delay [84]. Another study from Peru, found that the principal reasons for treatment-seeking delays were lack of knowledge and confusion of TB symptoms, fear and embarrassment of receiving a TB diagnosis, and a patient tendency to self-medicate prior to seeking formal medical attention [89]. The median delay was 55 days (IQR = 20 – 302) in South Africa [84], 73 days in Mexico [90], and 41 days in Brazil [91].

The main interventions to reduce the burden of HIV in TB patients are HIV testing and provision of ART and CPT to those found to be HIV-infected [1]. The main interventions to reduce TB among people living with HIV are regular screening for TB and provision of isoniazid preventive therapy (IPT) to those without active TB who meet eligibility criteria [1].

Stigma: Stigma widely affects both genders and was reported as a major barrier to accessing TB diagnostic and treatment facilities. Several, especially qualitative, studies describe the effects of stigma and discrimination associated with TB. Social isolation of patients inside a family bond, where the patient may be forced to eat and sleep separately, or in the community, where the person may be avoided by former friends and acquaintances, was described as the main contributing factors to the stigmatization of TB patients in developing countries [92]. Patients often isolate themselves to avoid infecting others and to avoid uncomfortable situations such as being shunned or becoming the subject of gossip [92]. Communal lack of knowledge regarding TB transmission and the worry that TB is incurable or can be passed down to offspring lead to stigma that impasses the marital prospects of all TB patients, regardless of gender [88]. And it seems that stigma and health literacy are related. A higher degree of stigma was recorded in females compared to males in almost all MENA countries [5]. Concurrently, females were found to be at a significantly lower socioeconomic status and had poorer knowledge about TB compared to males in the region [5].In Yemen, Somalia, Syrian Arab Republic and Egypt, around 30%–40% of patients reported feeling ashamed of the diagnosis, and one quarter had to hide the diagnosis [5]. One quarter to 40% of patients agreed that tuberculosis affected social and marital relations, family responsibilities and work performance [5].

Education and Knowledge about TB: Patients who had limited knowledge about TB were more likely to delay seeking care. Many studies found strong association between knowledge and level of education. for example in Iraq the 64% of TB patients who had completed more than 9 years of education, had a satisfactory level of TB knowledge [5]. In contrast the level of TB knowledge found to be less than 30% in Tanzania with the majority of the patients having less than 9 years of education [72]. The percentage of patients in MENA countries with adequate TB knowledge , appears very low [5]. The source of this knowledge was found to be either friends of the patients, relatives or

fellow tuberculosis patients. However, in Egypt the media played a significant role where the main source of information about TB was documentary presentations by health staff of chest facilities [5].

Presenting symptoms: Atypical presentations of TB such as absence of cough together with negative sputum, extra-pulmonary TB, and absence of haemoptysis were associated with longer health system delay in USA, St. Louis, Missouri, Ghana, Ethiopia and Canada [51,61,75,83,93,]. Similarly failure to perform sputum examination, not having a chest radiograph at the first medical visit was associated with longer health system delay [51,61].

The vicious circle of repeated visits at the same level: Storla et al stated that approximately all the studies identified the problem of vicious circle of repeated consultations with a multitude of healthcare providers without a correct diagnosis as a major factor for delay [63].
Three groups of healthcare providers were particularly identified as sources of this vicious circle:

1) Primary-level government health posts, which have limited diagnostic facilities and poorly trained staff
2) Private practitioners with low awareness of TB and,
3) Unqualified vendors, quacks and traditional healers [63].

Self-medication: Patients who start the process of health seeking by visiting non-formal healthcare services or practicing self-medication had a longer delay for the diagnosis of TB, compared with those who initially seek formal healthcare services [82]. Study carried out in Thailand, highlighting the effect of the use of pharmacies on the delay in the diagnosis of TB. Had found that nearly 50% of patients had visited the pharmacy immediately after their onset of symptoms, while 12% of these patient who could recall details of this visit, indicated that the medication recommended was cough suppressants, mucolytic, bronchodilators and antibiotics, however, none were refer to a tuberculosis unit [94]. More than 94% of patients in Burkina Faso [63], about 50% in Pakistan [5] and 13% in Iraq [5] were found to practice repeated courses of nonspecific antibiotics immediately after the onset of symptoms.

4. CONCLUSION

Despite the MENA region having only 6% of the world‘s TB, several indicators such as overgrowing population, weak and devastating health systems as well as political and security instability in the MENA region might create opportunity for massive spreading of TB. Thus, there is a need for a comprehensive review of factors which may play a role in the spread of TB within this region. It is anticipated that this study, using rigorous methods of the systematic review process, will present a foundation towards efforts in containing the disease while, learning from other region‘s experience, so as to achieve satisfactory results in the MENA region.

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PART C: JOURNAL MANUSCRIPT

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
CDC	Centre for Disease Control
DOTS	Directly Observed Treatment Short Course
EMRO	Eastern Mediterranean Region Office
HIV	Human Immune Deficiency Virus
MDGs	Millennium Development Goals
MENA	Middle East and North Africa
NGOs	Non - Governmental Organizations
NTPs	National TB Control Programmes
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PTB	Pulmonary Tuberculosis
TB	Tuberculosis
TBMUs	Tuberculosis Management Units
UNAIDS	United Nations for AIDS program
WHO	World Health Organization

Factors associated with patient and health system delay in diagnosis and commencement of treatment for pulmonary tuberculosis in the Middle East and North Africa (MENA): A Systematic Review & Meta-Analysis.

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ABSTRACT

Background: The goal of Tuberculosis control is to stop disease transmission, thereby reducing mortality and morbidity rates. Early case detection and proper treatment will reduce the time of infectiousness in the community and hence the number of new individuals exposed and infected. Most transmissions occur between the onset of cough and initiation of treatment. Delay in case detection which eventually cause delay in diagnosis and treatment, may worsen the disease, increase the risk of death and enhance tuberculosis transmission in the community. Currently, there exists no comprehensive review of factors playing a role in the delay of diagnosis and treatment for pulmonary TB in the Middle East and North Africa regions (MENA).

Methods: we conducted a comprehensive literature search among the following databases,Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, CINAHL, Psychlnfo, Scopus, Index Medicus for the Eastern Mediterranean Region (IMEMR), (Africa-wide) allied health and Google scholar of original data from MENA's countries on patient or health system delay in TB diagnosis or treatment. Electronic searches were complemented by a hand search for reference lists of potentially included studies. Data were extracted, reviewed and rated using a single form by two reviewers independently. The quality of each study assessed in terms internal and external validity generalizability of the study results. We categorized patient and health system-related factors based on the predisposing, enabling or need as suggested by Anderson's behavioural model. Meta-analysis was conducted and subgroups were analysed according to the individual factors related to patient and health system delay.

Result: Our initial search yielded 303 articles from nine databases, from which 20 studies were identified as eligible. Fifteen assessed both patient and health system sources of delay, 4 Studies assessed patient delay only and 2 studies assessed total delay without demarcation between patient and health system delay. Eighteen of our included studies were cross-sectional and used consecutive patient sampling. Eleven studies had a low risk of bias, seven studies had a moderate risk of bias and five studies had a high risk of bias. Due to shortcomings on the quality of evidence on the observational studies the GRADE system produced a low quality of evidence for this review.

In all the studies, standard definition for patient delay was consistent; but not for health system delay where definitions varied considerably. Almost all the studies associated socio-demographic characteristics of the patients such as female gender and poverty with patient delay. Meta-analysis revealed that older age and low patient income were significantly associated with patient delay (OR, 1.49; 95% CI, 1.31 to 1.70) and (OR, 1.26; 95% CI, 1.09 to 1.45) respectively. Adequate TB knowledge, high TB perception, employment and a low crowding index were protective factors from

patient delay (OR, 0.72; 95% CI, 0.61 to 0.85), (OR, 0.60; 95% CI, 0.46 to 0.78), (OR, 0.83; 95% CI, 0.72 to 0.95) and (OR, 0.78; 95% CI, 0.64 to 0.94) respectively. Visiting a public facility first was the only enabling factor to be significantly inversely associated with patient delay in meta-analysis. Female gender was significantly associated with both patient and health system delay in the MENA region (OR, 1.24; 95% CI, 1.02 to 1.50), and (OR, 1.68; 95% CI, 1.18 to 2.38) respectively. HIV/TB co-burden and needs factors were rarely assessed.

Discussion: TB control programmes in the MENA region need to increase their efforts to reduce patient and health system delays in order to achieve their goals successfully. These findings highlight the necessity to raise the awareness about TB in the community and to build a good referral system and to develop interventions that understand the gender differences in the region. Research should lay emphasis on HIV and health system related factors and cohort studies to identify enabling and needs factors related to delay.

Keywords: Tuberculosis case finding, Delayed Diagnosis, tuberculosis control, Middle East and North Africa, health care–seeking behaviour, delivery of health care.

1. BACKGROUND

1.1 Description of the condition

Tuberculosis (TB) remains a major global health problem as an estimated 9.0 million people developed TB and 1.5 million died from the disease in 2013 [1]. Despite the advances in and decentralizing of TB diagnosis and treatment, the detection of TB cases has never reached its expected potential in many countries. For instance, in 2013, about 64 per cent of the estimated 9 million people who developed TB were identified as newly diagnosed cases. This is estimated to have left about 3 million cases that were either not detected, or not reported to national TB programs (NTPs)[1].

In almost all of the Middle East and North Africa (MENA) the problem of delayed detection is a major challenge confronting TB control in the region. As a result of these delays, the infected patient has a higher risk of death, exacerbation of the course of the disease and, terrible social and financial consequences. Moreover, this patient may increase the disease transmission within the community by infecting all his/her susceptible contacts. In particular, a study from California found that a delay of two months is enough to spread the disease to an average of eight contacts (2). This number will increase as delay progresses to reach 15 persons a year [1] and would be higher in settings of overcrowding and higher social capital. Moreover, the study by Rao et al.1999 [3] found that management delays (from admission to treatment initiation) will result in an average of 23.9 health care worker exposures. Thus, as the delay progresses, the epidemic is prolonged and expands. Therefore, to curb this and reduce poor disease outcome and adverse social and economic consequences, timely diagnosis and prompt initiation of anti-TB treatment is vital [4].

The most fitting approach to timely diagnosis is the active case finding which is based on mass screening for TB in a given population [4]. However, this approach is difficult on a large scale and requires a special effort by the health care system, such as investing extensive human and financial resources. This is the reason that all national TB programs (NTPs) currently rely on the passive case finding approach as the principal means of controlling transmission and reducing incidence in developing countries [1]. This approach is based on diagnosing infectious cases that present themselves to the health facilities using mostly sputum smear microscopy. Passive case finding by default is considered to be a major source of delayed diagnosis.

Reasons for delayed diagnoses can be attributed to patients as well as to the health care system [5]. The patients may delay in seeking help, or the health care system may delay in suspecting and investigating for TB. These two periods are influenced by numerous factors (see figure C1) such as socio-demographic characteristics, stigmatization effect of TB, fear of high individual expenses, symptoms on presentation, presence of refined suspicion index, infrastructures and organization of the health system. Therefore, Focusing on patient and health system factors associated with delays in detection is an important starting place in identifying points of intervention for TB control [6,7,8].

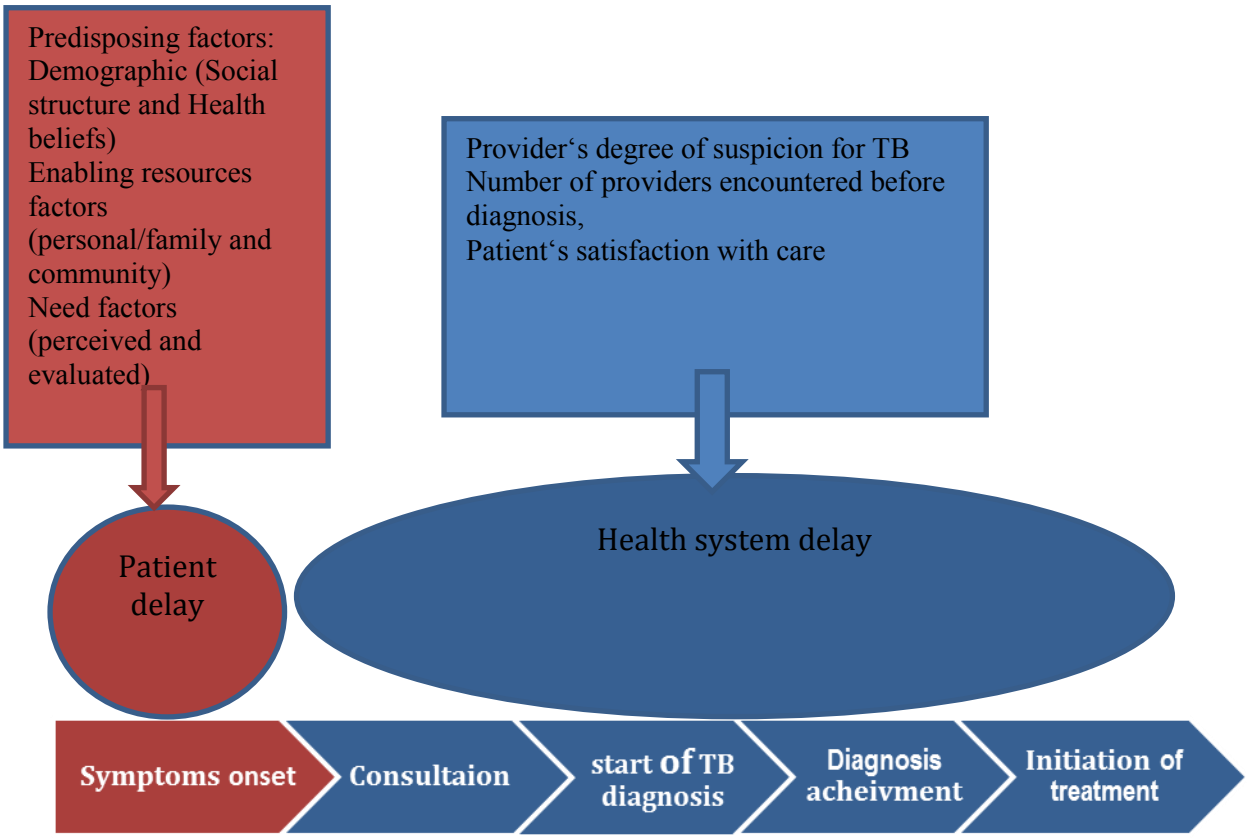


Figure C1: Conceptual framework (adapted form Yang et al.(2014)[11]) illustrating factors associated with patient and health system delay of TB diagnosis and initiation of treatment and TB care continuum from symptom onset to treatment initiation that were used to define delays that provides obstacles to TB control at the patient and health system level. Predisposing factors are factors that influence the initial performance of the behaviour. Enabling factors are those factors that make it possible or easier for individuals to enact the behaviour. Need factors are those factors that follow enactment of behaviour and influence continuation.

1.2 Why is it important to do this review?

Identification of the factors associated with TB delay has helped many regions to undertake measures to increase the effectiveness of their TB control programs; for instance, in 1994 the Centre for Disease Control (CDC) in the United States issued guidelines for preventing the transmission of TB in response to studies published on the issue of delay [9]. Implementation of these guidelines resulted in reversing the upsurge in reported cases of TB disease and a decline in case rates in the subsequent 10 years [9]. Through this review, we would like to instigate parallel results with regards to the MENA region.

There are four previous systematic reviews that have addressed the delay of TB diagnosis and treatment, however, none focused on the MENA region [6,7,10,11]. The systematic review by Thomas 2002 [10] and Storla 2007 [7] includes antiquated studies not applicable to current functioning NTPs. Finnie (2011) analysed factors associated with TB delay in high HIV/ TB co-burden areas in sub-Saharan Africa [6]. However, his review is not applicable to regions with a low HIV problem (i.e. MENA). Yang et al. (2014) included few studies from the MENA region, but their review was aimed at the gender differences in TB delay [11].

In the MENA region, several factors contribute to devastating the health system in general and TB-related services in particular. For instance, political instability contributes to emergency situations (the sectarian war and Arab spring) and economic sanctions have stretched resources beyond the systems' ability to cope, quality has deteriorated and many services defined as "low standard" [12].

In this study, the aim is to review systematically, all primary quantitative studies from countries in the MENA region which address factors associated with the delay in TB diagnosis and initiation of treatment. It is anticipated that this review will provide evidence for new or improved policies that incorporate an understanding of the current political situation, health system weakness and comorbidity patterns in the MENA region.

2. OBJECTIVES

2.1 Primary Objectives

- To study factors associated with patient and health system delay for diagnosis and initiation of treatment of pulmonary tuberculosis in Middle East and North Africa (MENA).

2.2 Secondary Objectives

- To determine the magnitudes and contributions of patient period in the total pre-treatment period.
- To determine the magnitudes and contributions of health system period in the total pre-treatment period.
- To determine the magnitudes of total delay.

3. METHODS

This review protocol has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42015023337

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

Observational studies: case control studies, cross sectional studies and population based studies.

In case of Randomized control trials (RCTs), cluster-randomized control trials (cRCTs), controlled before-and-after studies (CBAs) and cohort studies (prospective and retrospective) studies, we only used baseline population data.

3.1.2 Type of Participants

TB patients (or suspected TB patients) defined as:

1- All chest symptomatic individuals with cough ≥2 weeks and suspected for TB,
2- Pulmonary TB (PTB) patients (smear-negative, new smear positive or re-treatment patients),
3- Pulmonary and extra-pulmonary TB (EPTB) (if data were presented for PTB separately).

3.1.3 Types of outcome measures

3.1.3.1 Primary outcome

1- Factors associated with patient and health system delay.

3.1.3.2 Secondary outcome

The magnitude of:

1. Patient delay, defined as the time interval from onset of TB symptoms to first visit to any health provider.
2. Health system delay, defined as the time interval from the first health provider visit to initiation of treatment.

3. Total delay is the time interval from the appearance of major of TB symptoms to initiation of treatment.

3.2 Search methods for identification of studies

A comprehensive search to identify both published and unpublished articles with the relevant studies with no language and time limit has been performed. The electronic searches were conducted on publications dating up to June 2015. We developed our search strategy for MEDLINE using PubMed with a combination of the following keywords: TB, tuberculosis, mycobacterium, patient delay, health seeking delay, care-seeking delay, health system delay, doctor delay, health facility delay, health provider delay, diagnostic delay, diagnosis delay, total delay, detection delay, identification delay and treatment delay,

A search for factors using key terms (factors or enablers and barriers) did not add any new articles and was hence taken out of the final search strategy. The search strategies incorporated both medical subject headings (MeSH) and free-text terms and adapted to suit each individual database using applicable controlled vocabulary. In addition, we looked over the reference lists of identified studies for additional studies. The complete strategy is shown in Appendix 1.

3.3 Electronic searches

The electronic searches were carried out on the following databases; Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, CINAHL, Psychlnfo, Scopus. Grey literatures were searched in the Index Medicus for the Eastern Mediterranean Region (IMEMR), (Africa-wide) allied health and Google scholar.

3.4. DATA COLLECTION AND ANALYSIS

3.4.1 Selection of studies

Two authors screened all titles and abstracts of identified references from the searched databases to select potential eligible studies. Thereafter, the full texts of potentially eligible studies were obtained and the final selection for inclusion into the review was conducted by two independent authors (DE and EP). Any disagreements regarding inclusion of studies was resolved by discussion and any conflicts were resolved by a third reviewer (ME).

3.4.2 Data extraction and management

Data were extracted from selected studies independently by two authors using standardized data extraction forms (see Appendix 2). Disagreements on study selection and data extraction were resolved by consensus between the two review authors, failing of which a third author was arbitrated. The extracted data were entered into a spread sheet for final analysis. The following descriptive and outcome data were extracted from each study:

- Study identification details: authors, year of publication and relevance of cited references.
- Study characteristics: study design, study setting, study participants, method of obtaining the study sample, country and sample size.
- Details of our primary outcome measure: factors/variables assessed for association with patient‘ delay and health‘ system delay.
- Details of our secondary outcome measure: the magnitude of patient, health system and total delay. Also the definitions used for patient, health system and total delay.

3.4.3 Assessment of risk of bias in included studies

Risk of bias, was independently evaluated by two reviewers (DE & EP). Any disagreement was resolved by discussion, with arbitration by a third reviewer (ME) where necessary. At data extraction phase we noticed that the majority of our included studies (n-12) construct their study‘s design into two design phases. The beginning phase (descriptive phase) which is a cross-sectional design to determine the extent of the delay, and then the second phase (analysis phase) in which a nested case–control design were carried out comparing patients delaying above and below the median time. For

this reason we choose to assess the quality of these studies according to their second phase or analysis phase i.e. we treated these studies as case-control studies. Therefore, the Newcastle - Ottawa Quality Assessment Scale (NOS) for case-control studies has been used to assess the risk of bias in these studies [13]. NOS tool are star system based on three domains: 1) Selection of Study Groups, 2) Comparability of Groups and 3) Ascertainment of exposure. This system identifies ‗high' quality choices with a ‗star' in which a maximum of one ‗star' for each item within the ‗Selection' and ‗Exposure/Outcome' domains and maximum of two ‗stars' for ‗Comparability' domain. The thresholds score distinguishing between ‗good' and ‗poor' quality studies is 5 see table C1.

For the rest of our included studies which were cross-sectional and descriptive surveys, we employed the quality assessment tool by Hoy et al. 2012 [14] that were adapted by Werfalli and colleagues which allows for a composite score to assist with relative comparison between the studies [15]. Werfalli and colleagues added a quantitative scoring system to the Risk of Bias allocating four points for external validly scores and six points for internal validity see supplementary materials 2. The scoring system tool categorizes high risk studies as those with an overall score of 0-5 points moderate risk as 6-8 and low risk > 8 points [15] see table C2.

Table C1: Newcastle - Ottawa quality assessment scale for case control studies [13]

Selection	Comparability	Exposure
1) Is the case definition adequate? a) yes, with independent validation b) yes, e.g. record linkage or based on self-reports c) no description **2) Representativeness of the cases** a) consecutive or obviously representative series of cases b) potential for selection biases or not stated **3) Selection of Controls** a) community controls b) hospital controls c) no description **4) Definition of Controls** a) no history of disease (endpoint) b) no description of source	**1) Comparability of cases and controls on the basis of the design or analysis**. a) Study controls for _____ (Select the most important factor.) _ b) Study controls for any additional factor _ (This criteria could be modified to indicate specific control for a second important factor.)	1) **Ascertainment of exposure** a) secure record (e.g. surgical records) _ b) structured interview where blind to case/control status _ c) interview not blinded to case/control status d) written self-report or medical record only e) no description **2) Same method of ascertainment for cases and controls** a) yes _ b) no **3) Non-Response rate** a) same rate for both groups _ b) non respondents described c) rate different and no designation
Total of stars	**Total of stars**	**Total of stars**
Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.		

Table C: Quality assessment tool for cross-sectional studies [14] **modified by** [15]	
Items	**Quality Score**
External Validity	(4 points)
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
Internal Validity	(6 points)
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)

Overall score	**Quality**
0-5 points	**Low Risk:** Further research is very unlikely to change our confidence in the estimate
6-8 points	**Moderate Risk:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate
>8 points	**High Risk:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

3.4.4 Data analysis and synthesis:

We expressed the result of each study as an odd ratio with its corresponding 95% confidence interval for dichotomous data. We group studies that compare broadly similar types of outcome to get feasible results on an overall estimate of effect. Random effects meta-analysis was used due to anticipated heterogeneity in study results. Prevalence of TB delay from different studies was pooled in a meta-analysis using Review Manager 5.3.

3.4.5 Assessment of heterogeneity and subgroup analysis.

We examined statistical heterogeneity between study results using the Chi-squared test of homogeneity (with significance defined at the alpha-level of 10%), and quantify any statistical heterogeneity between study results using the I-squared statistic [16]. For subgroup analysis, we used the Chi2 test for subgroup differences to test for subgroup interactions.

3.5. Ethics

Systematic reviews draw on publicly available secondary data and, therefore do not require formal ethical review [17]. It is noted that ethical research, even if secondary research, relies on scientific validity. The study protocol was reviewed by supervisors with expertise in systematic review methods

and submitted to the University of Cape Town‘s Faculty of Health Sciences Human Research Ethics Committee for approval.

3.6. Funding

We did not receive any funding for this study.

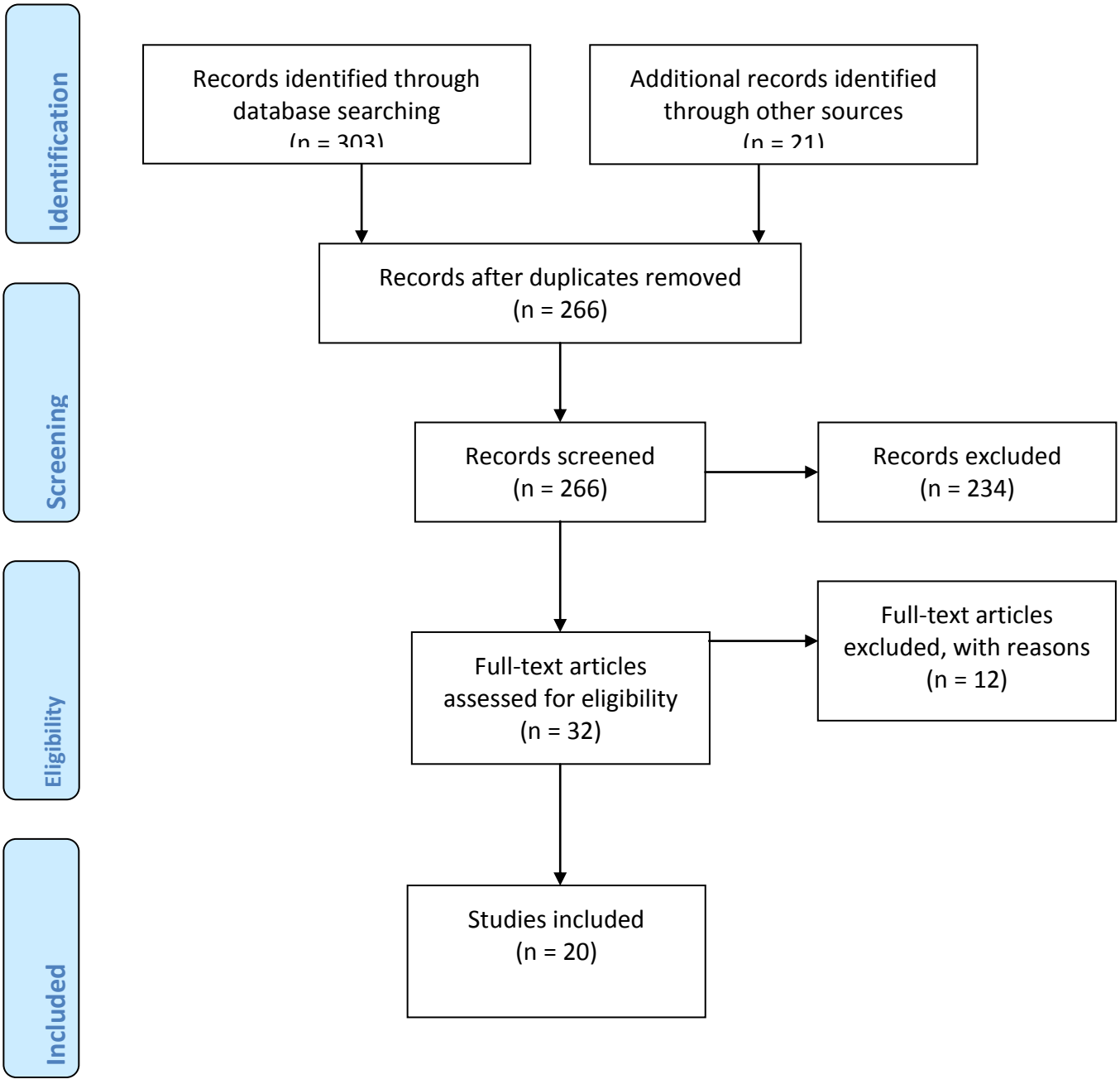
4. RESULTS

4.1. Study flow and description of studies

The literature search results are reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement [18].

We obtained 303 titles and abstracts from electronic databases and trial registries. We found 20 additional articles through a hand search of the reference lists and one article by contacting relevant authors in the field. In total, we considered 266 articles after removing 58 duplicates. From these, 234 articles were excluded after examining titles and abstracts leaving 32 articles requiring full-text evaluation. From these, 12 articles were deemed unsuitable for the following reasons: participants not meeting inclusion criteria [19,20], participants were not from the MENA region [21][22] and, the outcome measure was not TB delay [23-30]. A total of 20 articles met our inclusion criteria. Figure C2, shows a flow diagram of the search results.

Figure C2 PRISMA Flow Diagram



4.1.1 CHARACTERISTICS OF INCLUDED STUDIES

We included 20 observational studies. Six were conducted in Iran [31-36], five in Turkey [37-41], two in Yemen [42,43], two in Syria [44,45], two in Sudan [46,47], one in Jordon [48], one in Morocco [49] and one was a multicounty study conducted in seven countries in which Iran, Iraq, Egypt, Syria, Somalia and Yemen [50] were included. The majority of the studies (18/20) were cross-sectional in study design and two were nested case-control studies. The study participants were new smear positive PTB patients in 15 studies, TB suspects in one study [48] while four studies included both smear negative and smear positive PTB [39]. Fifteen assessed both sources of delay, four studies assessed patient delay only and two studies assessed total delay without demarcation between patient and health system delay. Almost all studies used a consecutive method of sampling with sample size ranging from 50-5,702 that looked at least on one of the outcomes. Publication dates were between 2001 and 2015. In all studies, male was the dominant gender and majority of the studies were conducted in both urban and rural settings. The characteristics and descriptions of the included studies are presented in Table C1.

Table C3: Methodological Characteristic of included studies

Study ID	Study aim	Study settings	Study population description	Data collection	Measurement of outcome(specifically PD)	Assessment of exposure
Al-Absi 2006 Yemen	Diagnostic and treatment delays of PTB	Health facilities with DOTS	598 new smear+ PTB > 15 years	Interview using questionnaire	Self-report	Summation score of education, Occupation and incomes to measure SES.
Alavi et al. 2015 Iran	Delay in TB diagnosis and treatment	Ahvaz Health Centre/ Khuzestan province in south-western Iran	181 new smear+ PTB	Information were extracted from the medical files	Unclear	Not defined
Akrim et al. 2014 Morocco	factors associated with patient and health system delay	(CDTMR) or (CSI)	250 new smear+ PTB	Interview using pretested and structured questionnaire	Self-report	Not defined
Bashour & Mamaree 2003 Syria	Sex differences in diagnosis and treatment of TB	all provincial TB centers (14 centers)	552 new smear+ PTB seen at all provincial TB centers Jan-July 2002	Interview using semi-structured questionnaire	Self-report	Summation scores for patients‘ knowledge, gender perceptions and satisfaction with care.
Date & Okita 2005 Yemen	How gender and literacy influence TB diagnosis and treatment	National Tuberculosis Institute	74 new smear+ PTB	Interview using questionnaire	Self-report	Patients who stated that they could not read were identified as illiterate
Ekinci et al. 2014 Turkey	Reasons for delays in smear+/- PTB	Sureyyapasa Center for Chest Diseases and Thoracic Surgery	136 newly diagnosed divided into smear+ and smear - groups.	Interview using questionnaire	Self-report	Not defined
Maamari 2008 Syria	Gaps in case-finding under DOTS	NTP centers implementing DOTS	800 new smear+ PTB >15 years	Interview using structured and pre-tested questionnaire.	Self-report	A summation score of education, occupation and incomes to measure SES.
Güneylioglu et al. 2004) Turkey	Factors affecting Diagnostic and treatment delays of inpatient PTB	Sureyyapasa Center for Chest Diseases and Thoracic Surgery	204 new smear+ PTB diagnosed inpatient	Interview using questionnaire	Self-report	Not defined
Masjidi et al. 2002 Iran	Reasons for TB delay	National Research Institute of TB and Lung Disease (NRITLD	50 PTB admitted for the first time to the NRITLD	Interview by single physician	Self-report	Not defined
Mirsaeidi et al. 2007 Iran	patient delay and physician delay	NRITLD	97 PTB admitted to the NRITLD with 2 smear +	Interview using questionnaire	Self-report	Not defined
Mohamed et al. 2013 Sudan	factors associated with, PTB patient delay in accessing care	All TB management units in Gezira State-Sudan	292 new smear+ PTB >15 years	Interview using a pre-coded, pre-tested questionnaire	Self-report	Not defined
Nasehi et al. 2012 Iran	Diagnosis delay in smear+/- PTB	General population	5702 smear+ PTB	NA	NA	Sputum smear positivity were graded as 1-9 bacilli, 1+, 2+ and 3+

Study ID	Study aim	Study settings	Study population description	Data collection	Measurement of outcome(specifically PD)	Assessment of exposure
Okur et al. 2006 Turkey	patterns and reasons for delays in smear+/- PTB	Heybeliada Center for Chest Disease and Thoracic Surgery	151 smear+ PTB	Questionnaire based on the patient‘s clinical files.	Self-report	Not defined
Okutan et al. 2005) Turkey	servicemen with tuberculosis	Camlica Chest Disease Hospital of Gulhane Military Medical Academy	97 PTB soldiers	questionnaire attempted to detect factors affecting delay in TB diagnosis	Self-report	Not defined
Rahim et al.2004 Sudan	Diagnosis delay in smear+ PTB	NTP management units in Khartoum State.	253 new smear+ PTB >15 years and being on treatment for less than 5 weeks	Interview using semi-structured questionnaire	Self-report	Not defined
Rumman et al. 2008 Jordan	Prevalence and healthcare-seeking behaviour of tuberculosis	House-hold	1544 TB suspect >15 years	Interview using a structured and pre-tested questionnaire	Self-report	stigma were recorded on a 5-point Likert scale
Shahriyar et al. 2012 Iran	Factors associated with patient and health system.	Zahedan TB center	98 smear+ PTB	Patient records, TB card and Interviews with patients	Self-report	Not defined
Shamaei 2009 Iran	Diagnosis delay and drug resistance pattern among drug addicts	Masih Davenshari hospital/ national referral centre for TB control	944 new PTB cases	The information were retrieved from the records	Self-report	Not defined
WHO 2008 Iran, Iraq, Egypt, Somalia, Syria and Yemen	Delay in the diagnosis and treatment of TB and its determinants.	In Iraq; the Respiratory and Chest Disease Institute in Baghdad. In Somalia, NTP with DOTS. In Egypt, Iran, Syria and Yemen, Nationwide	800 new smear+ PTB >15 years	Interview using structured and pre-tested questionnaire.	Self-report	Summation score of education, Occupation and incomes to measure SES.
Yilmaz et al. 2001 Turkey	Delay in the diagnosis and treatment of smear+ PTB	SSK SÏreyyapasa Centre for Chest Disease and Thoracic Surgery	134 smear+ PTB	A questionnaire created based on the patient‘s clinical files	Self-report	Not defined

PD; Patient Delay, (+); positive
CDTMR- Diagnosis of Tuberculosis and Respiratory Diseases Reference Centers, CSI or Integrated Health Centers

4.2 Assessment of risk of bias in included studies

The NOS criteria for case control study design and the quality assessment tool by Hoy et al. 2012 [14] that were adapted by Werfalli and colleagues [15] for cross-sectional study design that were adopted to assess the risk of bias in included studies is enclosed in the data extraction form in appendix 2. Eleven studies had a low risk of bias [37,42,45-50], while seven studies had a moderate risk of bias [32,33,36,38-40,44] and five studies had a high risk of bias [31,34,35,41,43]. Table C4 and C5 depicts a summary of the assessment of risk of bias of each study.

NOS criteria: The majority of our studies (n=8) had a full score of the ―selection of participants" criteria that composed of four subcomponents (A1 right case definition, A2 right controls definition, A3 the representativeness of the cases, A4 the representativeness of controls). In this criterion the right case definition means either confirmed PTB case or suspect PTB case not seeking healthcare for more than the cutoff value used by each study. Whereas the right controls definition refer to either confirmed PTB case or suspect PTB case not seeking healthcare for less than the cutoff value used by each study. The second criterion is the ―comparability of the groups" composed of two subcomponent (B1 control of main confounders, B2 control of any additional factor). Eight out of the twelfth studies had adjusted for the several confounders such as age, sex, income, employment status, education and others. The third criterion is ―ascertainment of the exposure" that composed of three subcomponent; (C1 appropriate method of exposure ascertainment, C2 same method of exposure ascertainment for cases and controls, C3 same non-response rate of case and control groups). The measures of patient delay in all included studies were dependent on patient recall of first symptoms for PTB, and then these studies might be exposed to recall bias. However, attempts had been taken to minimize problems of recall in Rahim 2004 by excluding any new smear-positive case with treatment duration of more than 5 weeks. All the studies scored full for C2 and C3 since both patients and controls treated similar in data collection.

Hoy criteria: This criterion has two domain external validity and internal validity. We found that majority of studies were not externally valid in spite of being internally valid. With regard to external validity, failure to have representative sample and/or minimal non-response bias were the main issues that hinder [32,34-36,38,40] from being externally valid. Whereas failure to collect the information directly from the participant in [36,34] and non-reliable and non-valid study' measures in [32,34-36,38,40] were the main issues that hinder these studies from being internally valid. Almost all the studies (n=8) succeeded to have acceptable case definition in which these studies was follow WHO definition for TB case. Eight out of ten studies collected data directly from the subject as opposed to a proxy by using same mode of data collection. Some studies such as [32,33,44,39] didn't provide substantial information with regards to various component of the criteria in which the response were unclear.

Table C4: Assessing risk of bias in case-control studies [13]

Study ID	A				B		C			Quality score	Risk of bias
	A1	A2	A3	A4	B1	B2	C1	C2	C3		
Al-Absi 2006 Yemen	1	1	0	0	1	1	0	1	1	6	Low
Alavi et al. 2015 Iran	1	1	0	0	0	0	0	1	1	4	High
Akrim et al.2014 Morocco	1	1	1	1	1	1	0	1	1	8	Low
Date & Okita 2005 Yemen	1	1	0	0	0	0	0	1	1	4	High
Maamari 2008 Syria	1	1	1	1	1	1	0	1	1	8	Low
Güneylioglu et al. 2004 Turkey	1	1	1	1	0	0	0	1	1	6	Low
Mohamed et al. 2013 Sudan	1	1	1	1	0	0	0	1	1	6	Low
Rahim et al.2004 Sudan	1	1	1	1	1	1	1	1	1	9	Low
Rumman et al. 2008 Jordan	1	1	1	1	1	1	0	1	1	8	Low
WHO 2008 Iraq	1	1	0	0	1	1	0	1	1	6	Low
WHO 2008 Egypt	1	1	1	1	1	1	0	1	1	8	Low
WHO 2008 Somalia	1	1	1	1	1	1	0	1	1	8	Low
WHO 2008 Iran	1	1	1	1	1	1	0	1	1	8	Low

A. selection of the study groups (A1 right case definition, A2 right controls definition, A3 the representativeness of the cases, A4 the representativeness of controls);
B. comparability of the groups (B1 control of main confounders, B2 control of any additional factor);
C. ascertainment of the exposure (C1 appropriate method of exposure ascertainment, C2 same method of exposure ascertainment for cases and controls, C3 same non-response rate of case and control groups).
1 indicates the study met the criteria; 0 indicates the study did not meet the criteria,
Quality score: <5 high risk of bias. > 5 Low risk of bias

Table C5: Assessing risk of bias in cross-sectional studies using the quality assessment tool (14) modified by (15)

Study ID	A1	A2	A3	A4	B1	B2	B3	B4	B5	B6	Quality score	Risk of bias
H.Bashour 2003	1	Unclear	1	0	1	1	Unclear	1	1	1	7	Moderate
Ekinci 2014	1	Unclear	Unclear	Unclear	1	1	Unclear	1	1	1	6	Moderate
Masjidi 2007	0	1	0	Unclear	1	1	Unclear	1	1	1	6	Moderate
Mirsaeidi 2007	1	0	0	Unclear	1	1	0	1	1	1	6	Moderate
Okur 2006	0	0	1	1	0	1	0	1	1	1	6	Moderate
Okutan 2005	0	1	1	1	1	1	0	1	0	1	7	Moderate
Shahriyar 2012	0	1	0	0	1	1	0	1	0	1	5	High
Shamaei 2009	1	1	1	0	0	1	0	1	1	1	7	Moderate
Nasehi 2012	1	1	1	0	0	0	0	0	0	1	4	High
Yilmaz et al. 2001Turkey	Unclear	unclear	unclear	Unclear	1	1	unclear	1	1	1	5	High

EXTERNAL VALIDITY:
A1, Representative of the target population; A2, Appropriate recruitment of the participants, A3 Appropriate sampling frame, A4 Minimal non-response bias)
INTERNAL VALIDITY (B1 Data collected directly from the subjects (as opposed to a proxy), B2 Acceptable case definition, B3 valid and reliable study instrument, B4 same mode of data collection used for all subjects, B5 Appropriate shortest prevalence period for the parameter of interest, B6 Appropriate numerator(s) and denominator(s) for the parameter of interest).
1 indicates the study met the criteria; 0 indicates the study did not meet the criteria, x indicate the response were unclear
Quality score: 0-5 high risk of bias; 6-8 moderate risk of bias; >8 Low risk of bias

4.3 QUANTITATIVE DATA SYNTHESIS.

Main results of included studies

4.3.1 Patient delay

From the 20 included studies, 17 studies measured the patient delay. Measures of patient delay depend on patient recall of first symptoms for PTB. In the entire studies first symptom was described as the onset of a persistent cough as the starting point and date of first consultation as endpoint. The majority of the studies measured delay as a dichotomous variable based on a cut-off point, usually the median. The shortest mean duration of patient delay (12.5 days) reported in Iran by Masjidi et al. 2002 [32], whereas, the longest mean duration (73 days) reported also in Iran by Shahriyar et al. 2012 [35]. The time period of the research was reported by all the studies. When we plotted the patient period according to the year of study not the year of publication (figure C2), the plot shows no reduction in patient delay over time. In fact in some countries such as in Iran, we observe that the delay increases dramatically overtime. However the quality of these studies should be considered before setting any conclusion about this observation.

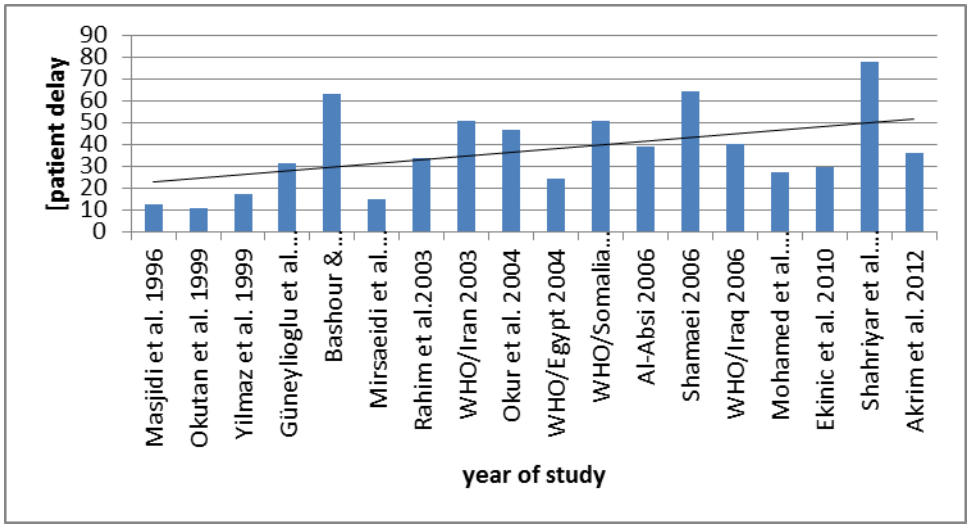


Figure C3: time trend of mean patient delay with studies ordered chronologically,

4.3.2 Analysis of patient delay by subgroup

A.1 Factors associated with patient delay

Out of 17 studies that measure the length of patient delay, only 10 studies analysed at least one factor attributed to this period [31,37,42,43,45-50a]. Each factor was classified as a predisposing, enabling or need factor as suggested by Andersen‘s behavioural model of health care utilization [51];

Predisposing factors are factors that influence the initial performance of the behaviour. Enabling factors are those factors that make it possible for individuals to enact the behaviour. Need factors are those factors that follow enactment of behaviour and influence continuation. Studies mostly assessed the predisposing factors such as patient socio-demographic characteristics, TB knowledge and perception about TB. The enabling factors were less assessed, while no studies found to be assessed at least one —need" factor. Table C2 and figure C2-10 give further details on the findings pertaining to factors associated with patient delay.

A1.1 Predisposing factors to patient delay

A1.1.1 Gender

Female gender was significantly associated with patient delay (OR, 1.24; 95% CI, 1.02 to 1.50), 10 studies contributed to summary odd ratio [31,37,42,43,45-50a]. Heterogeneity was significant (P <0.1; I^2 = 45%).

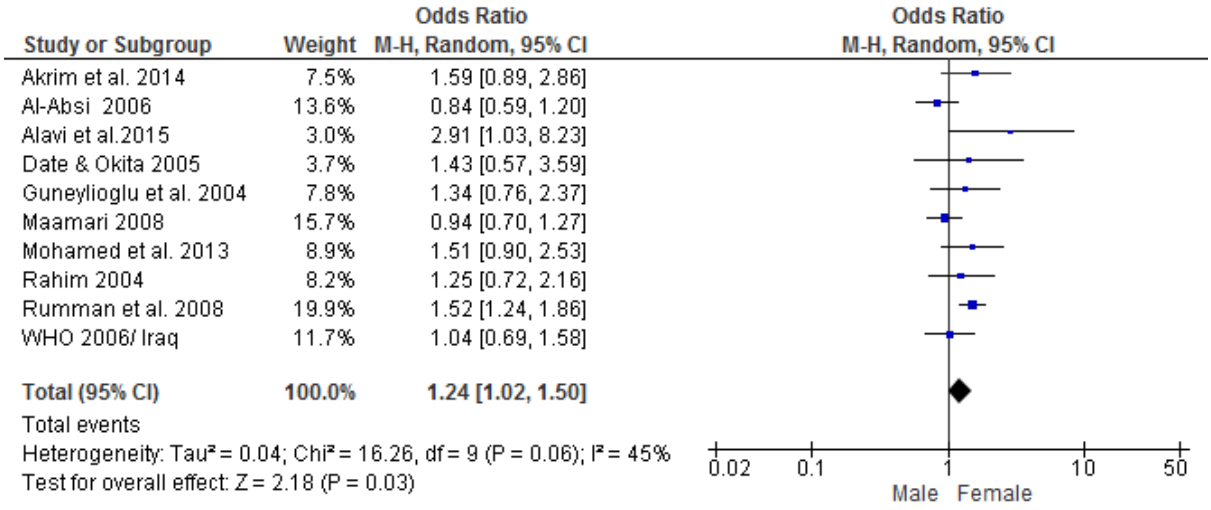


Figure C4: Forest plot, Gender vs. patient delay.

A1.1.2. Age

Older age was significantly associated with patient delay (OR, 1.42; 95% CI, 1.19 to 1.69), nine studies contributed to summary odd ratio [31,37,42,45-50a]. Heterogeneity was insignificant (P =0.18; I^2 = 31%).

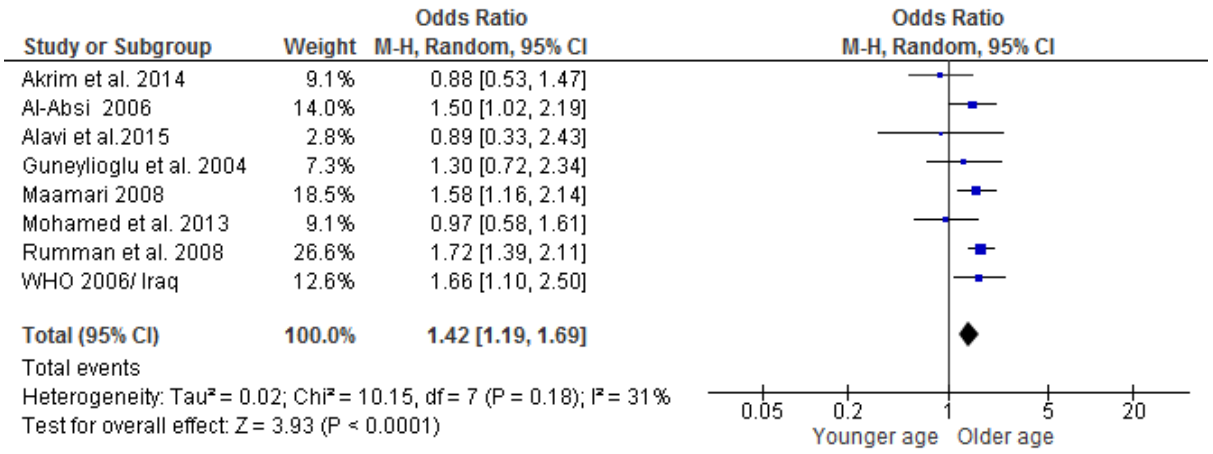


Figure C5: Forest plot, Age vs. patient delay.

A1.1.3. Employment

Employment was significantly inversely associated with patient delay (OR, 0.83; 95% CI, 0.72 to 0.95), five studies contributed to summary odd ratio [42,45,46,48,50a]. Heterogeneity was insignificant (H, p=0.65; I^2 = 0%)

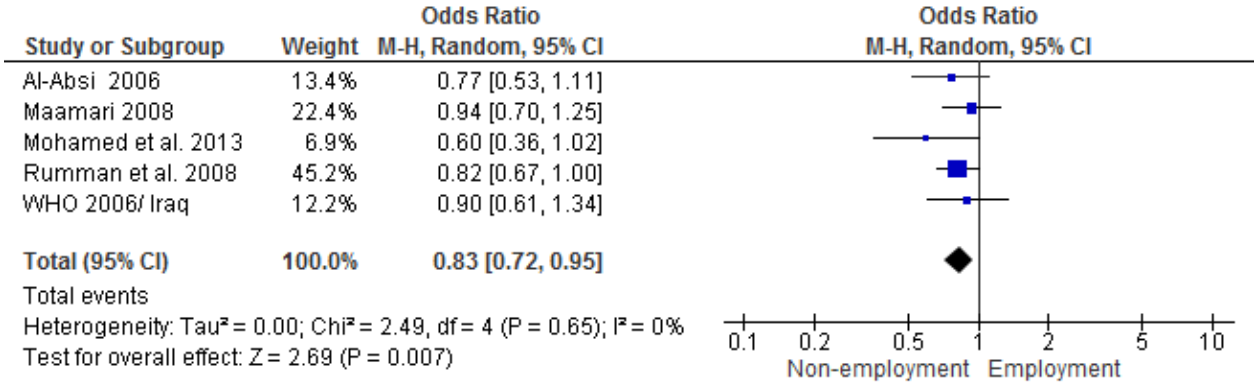


Figure C6: Forest plot, Employment vs. patient delay.

A1.1.4. Patient's income

Low patient's income was significantly associated with patient delay (OR, 1.95; 95% CI, 1.07 to 3.55), seven studies contributed to summary odd ratio [37,42,45-48,50a]. Heterogeneity was significant (P <0.00001; I^2 = 92%).

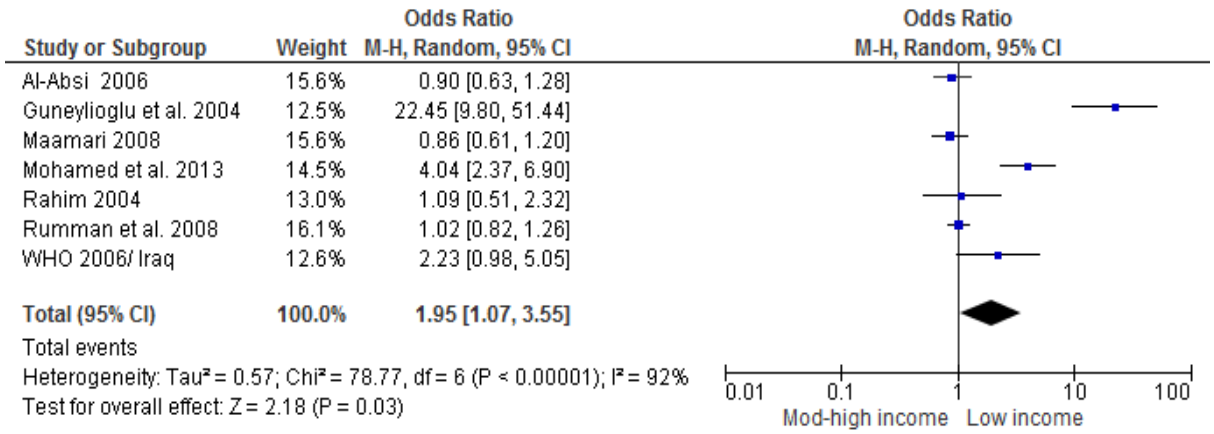


Figure C7: Forest plot, Patient's income vs. patient delay.

A1.1.5. Crowding

Low crowding was significantly inversely associated with patient delay (OR, 0.75; 95% CI, 0.57 to 0.99), three studies contributed to summary odd ratio [42,45,50a]. Heterogeneity was insignificant (P= 0.15; I^2 = 47%):

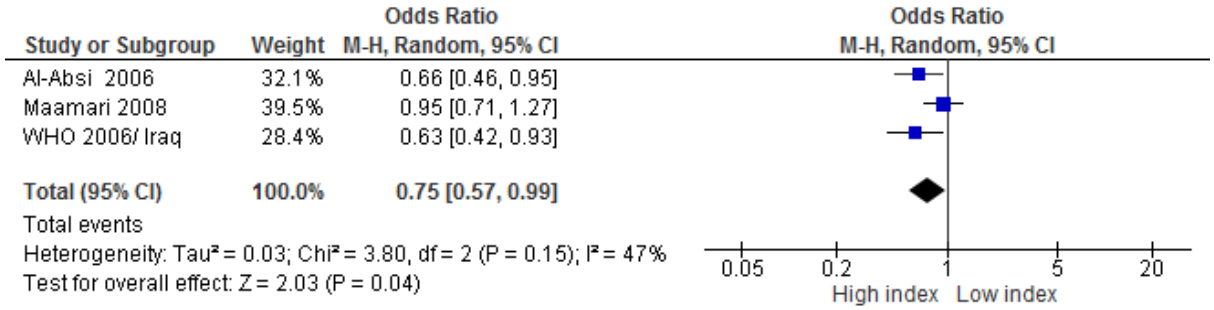


Figure C8; Forest plot, crowding index vs. patient delay.

A1.1.6. TB knowledge

Six studies assessed TB knowledge as predisposing factor to patient delay [42,45,47-50a]. In which, only two studies [42,50a] found the association between adequate TB knowledge to be significant with patient delay (OR, 0.28; 95% CI, 0.20 to 0.41) and (OR, 0.60; 95% CI, 0.39 to 0.93) respectively.

A1.1.7. TB perception

Four studies assessed TB perception as predisposing factor to patient delay [43,46-48]. While one study [47] found high TB perception to be significantly associated with patient delay (OR, 2.38; 95% CI, 1.25 to 4.54), other two studies [43,48] found high TB perception to be protective from delay (OR, 0.27; 95% CI, 0.10 to 0.74) and (OR, 0.46; 95% CI, 0.34 to 0.63) respectively. Study [46] found no association between TB perception and patient delay.

A1.1.8. Place of residence

Seven studies assessed the place of residence as a determinant of patient delay [31,37,42,45,46,48,50a]. Only one study [48], found that patient from rural residence being protected from the delay (OR, 0.75; 95% CI, 0.61 to 0.92).

A1.1.9. Marital status

Studies that assessed marital status for its association with patient delay found the association to be not significant [42,45,46,49,50a].

A1.1.10. Literacy

Four out of eight studies found significant association between literacy and patient delay [42,43,45,48], (OR, 1.97; 95% CI, 1.36 to 2.86), (OR, 3.83; 95% CI, 1.46 to 10.06), (OR, 0.50; 95% CI, 0.37 to 0.68) and (OR, 1.69; 95% CI, 1.29 to 2.20) respectively.

A1.1.11. Smoking

Four studies assessed smoking as predisposing factor to patient delay [31,46,48,50a]. The association was not significant among all the studies.

A1.1.12. Presence of chronic health problem

Four studies assessed this factor, in which one study [45] found presence of chronic health problem to be significantly associated with patient delay (OR, 1.16; 95% CI, 1.05 to 2.48). Another study [46], found the association to be imprecise i.e. wide CI (OR, 3.99; 95% CI, 1.10 to 14.54). One study found chronic illnesses to be protective from the delay [50a] (OR, 0.55; 95% CI, 0.33 to 0.94). And the left one found no significant association [31].

A1.1.13. HIV status

Surprisingly only one study had looked on HIV to be predisposing factor for patient delay, in which the association was not significant [31].

A1.1.14. TB related stigma

Four studies assessed stigma to be a predisposing factor for patient delay in which two studies [42,45] found non-significant association. One study [50a] found the TB related stigma to be significantly associated with delay (OR, 2.07; 95% CI, 1.05 to 4.08) and the other one found stigma to be protective from the delay [48] (OR, 0.74; 95% CI, 0.55 to 0.99).

A1.1.15. Contact with TB case

Two studies assessed this factor, while one study [46] found it to be significantly associated with patient delay (OR, 1.83; 95% CI, 1.01 to 3.30), the other one [37] found it to be protective from delay (OR, 0.50; 95% CI, 0.26 to 0.96).

A1.1.16. Self-medication

Two studies assessed this factor, while one study [47] found no significant association with patient delay, the other one [50a] found it to be significantly associated with delay (OR, 2.53; 95% CI, 1.20 to 5.62).

A1.2. Enabling factors for patient delay

The only enabling factors assessed among the included studies were travel time, expenses of care and place at first consultation.

A1.2.1 Provider at first consultation

Consulting health care provider vs. other provider (traditional healer, drugs seller and other) was protective from patient delay (OR, 0.77; 95% CI, 0.70 to 0.85). Five studies contributed to summary odd ratio [42,45,47,37,50a]. Heterogeneity was insignificant (P= 0.30; I^2 = 17%)

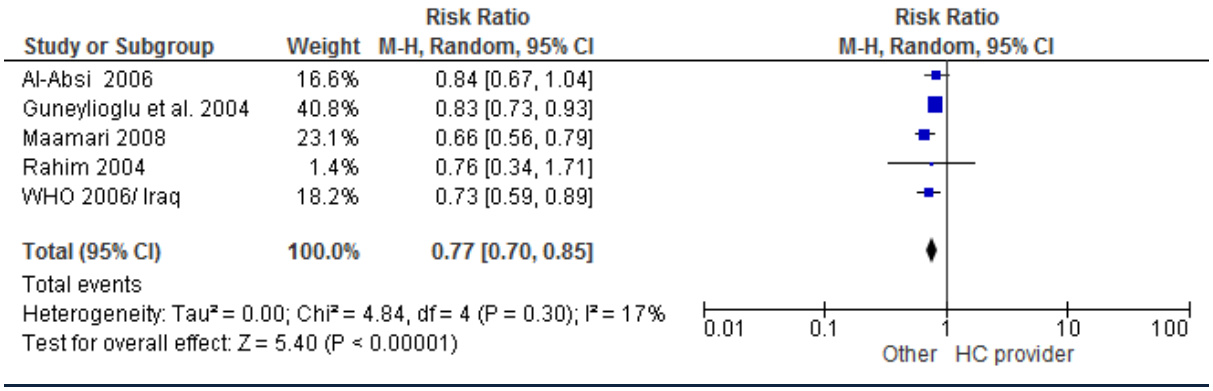


Figure C9; Forest plot, place at first consultation vs. patient delay.

A1.2.2 Travel time

Four studies assessed travel time/ distance to health facility for its association with patient delay found the association to be not significant [42,45,48,50a].

A1.2.3 Expenses

Only one study [42] assessed this factor in which the association was significant with patient delay (OR, 1.73; 95% CI, 1.20 to 2.51).

Table C6: Factors associated with patient delay

	Patient delay (in days)		Predisposing factors											Enabling factors			
Study ID	Mean SD	median	Older age	Female gender	Rural residence	literacy	Patient income	Unemployment	TB knowledge	TB perception	TB stigma	Crowding index	Others	Travel time	Expenses	NHCP at 1st visit	Others
Al-Absi 2006 Yemen	39± 50.3	28	▲	▲	▲	▲	**NS**	▲	▲	NA	▲	▲	Expenses **X**, Marital status **NS** Satisfaction with care **NS** Marital status **NS**	**NS**	▼	▲	**NA**
Akrim et al.2014 Morocco	36± 48.3	20 (8-47)															
Alavi et al. 2015 Iran	NR	NR	**NS**	▲	▼	NA	NA	NA	NA	NA	NA	NA	DM, Asthma, COPD, HIV, IVDU Imprisonment, Smoking and Immunosuppressive drugs **NS**	NA	**NA**	**NA**	**NA**
Bashour & Mamaree 2003 Syria	F:40 M:63	3 0	NA	▼	NA	NA	NA	NA	NC	NC	▲	NA	NA	NA	**NA**	**NA**	Public hospital at first consultation ▲
Date & Okita 2005 Yemen	NR	IL 30 L 15	NA	NA	NA	▲	NA	NA	NA	**NS**	NA	NA	NA	NA	**NA**	**NA**	
Ekinci et al. 2014 Turkey	S-= 29.4±49.4/ S-= 31.7±40.8	S-/S+ 10/14	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Neglect of symptoms ▲	NA	**NA**	**NA**	
Maamari 2008 Syria	52.7	31	▲	**NS**	**NS**	▼	▼	**NS**	▲	NA	▲	**NS**	Chronic diseases, Seeking care at non health provider and No of health provider encountered before final diagnosis ▲ Place at first consultation **NS**	**NS**	**NA**	▲	

	Patient delay (in days)		Predisposing factors											Enabling factors			
Study ID	Mean SD	median	Older age	Female gender	Rural residence	literacy	Patient income	Unemployment	TB knowledge	TB perception	TB stigma	Crowding index	Others	Travel time	Expenses	NHCP at 1st visit	Others
Güneylioglu et al. 2004 Turkey	31.4±38.9	NR	**NS**	**NS**	**NS**	**NS**	▲	NA	NA	NA	NA	NA	Index case ▼ Absence of cough▲ Haemoptysis ▼	NA	**NA**	▲	
Masjidi et al. 2002 Iran	12.5±7.5	7	NA	▼	NC	NC	NA	NA	NA	NA	NA	NA	Underestimation of their symptoms	NA	**NA**	**NA**	
Mirsaeidi et al. 2007 Iran	15±13	13	**NS**	**NS**	**NS**	**NS**	NA	**NS**	NA	NA	NA	NA	NA	NA	**NA**	**NA**	
Mohamed et al. 2013 Sudan	27.2± NR	4	**NS**	**NS**	▲	**NS**	▲	▲	NA	▲	NA	NA	Smoking NS, COPD ▲ Index case ▲ Marital status **NS**	NA	**NA**	**NA**	
Nasehi et al. 2012 Iran	NR	NR	▲	▲	▼	NA	NA	NA	NA	NA	NA	NA	HIV NS Prison history NS ▼ Nationality ▲	NA	**NA**	**NA**	
Okur et al. 2006 Turkey	46.4±54.6	30	**NS**	**NS**	NA	NS	NS	NA	NA	NA	NA	NA	Comorbidity **NS** Index case **NS** Neglect of symptoms ▲	NA	**NA**	**NA**	
Okutan et al. 2005) Turkey	10.6± NR	4.5	NA	NA	NA	▼	NA	NA	NA	NA	NA	NA	Night sweat ▲ Haemoptysis ▼	**NS**	**NA**	**NA**	
Rahim et al.2004 Sudan	33.85± 34.24	21	**NS**	**NS**	**NS**	**NS**	**NS**	▲	▲	**NS**	**NS**	**NS**	Not specific symptoms ▲ Self treatment **NS** Understimation of symptoms **NS**	NA	**NA**	▲	
Rumman et al. 2008 Jordan	NR	NR	▲	▲	▲	▲	▲	▲	**NS**	▲	▲	**NA**	Distance to facility ▲ Psychological burden of TB ▲ Smoking, Mean of transport ▲, Chest pain ▲, Haemoptysis ▲, Nationality▲ Fever ▼, Weight loss NS	NS	**NA**	**NA**	

Study ID		Patient delay (in days)		Predisposing factors										Enabling factors			
		Mean SD	median	Older age	Female gender	Rural residence	literacy	Patient income	Unemployment	TB knowledge	TB perception	TB stigma	Crowding index	Others	Travel time	Expenses	NHCP at 1st visit	Others
Shahriyar et al. 2012 Iran		78±52.8	NR	NC	**NS**	NA	▲	**NA**	**NC**	**NA**	**NA**	**NA**	**NA**	Previous infection with TB ▲ Index case **NS** Pulmonary diseases NS	NA	NA	NA	
Shamaei 2009 Iran		DU 64±58.28 NDU 8.69 ±46.38	NR	NA	NA	NA	NA	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	In drug users; homelessness. Poverty, Poor access to health services, Not admitting and not caring properly for disease manifestation in these patients, Clinical symptoms suppression due to opium use	NA	NA	NA	
WHO 2008	Somalia	69 ± 76.98	24	NA	NA	▲	NA	NA	NA	NA	NA	▼	NA	NA	NA	NR	NR	
	Iraq	39.96± 20.6	31	▲	**NS**	**NS**	**NS**	**NS**	**NS**	▼	**NA**	▲	▼	Self-treatment▲ Satisfaction with care ▲ Marital status **NS**	▲	**NS**	▲	
	Egypt	24.3 ± 37.2	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
	Iran	51± 74.4	24	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Yilmaz et al. 2001 Turkey		17.5	NR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	

NASEHI, RUMMAN AND ALAVI doesn't report the length of patient delay.
WHO 2008; ddelay was attributed to the patient in Iraq, Somalia, Syrian Arab Republic and Yemen, So only present the data for those countries.
NA: Not Assessed, NC: Not Correlated, NR: Not Reported ▲: positively associated with delay, ▼: negatively associated with delay, NS: Assessed but were not significant (p>0.05)
DU: drug users, NDU: non drug users, IL: Illiterate, L: Literate, S+; Smear positive, S-; Smear negative, F: female, M: male, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus, HIV: human immunodeficiency virus, IVDU: intravenous drug use

4.3.3 Health system delay

From the 20 included studies, 15 studies measured the length of health system delay. All the studies used the health facility‘s record of first consultation as the starting point and all except two used start of treatment as the endpoint (two used diagnosis). The majority of the studies measured delay as a dichotomous variable based on a cut-off point, usually the median. The shortest mean duration of health system delay (5 days) was reported in Iraq by [50a], whereas, the longest mean duration (129.25 days) was reported in Iran by [36].

4.3.4 Analysis of health system delay by subgroup

B.1 Factors associated with health system delay

Out of 15 studies that measure the length of health system delay, only six studies analysed at least one factor associated with this period [41,37,38,47,49,50a]. The studies frequently assessed the enabling factors such as type of facility and type of providers at first visit, number of visits and number of providers consulted before reaching TB diagnosis, expenses and travel time. These factors are related to the aspect of health system delay in which patient return for diagnosis and treatment is required. They also may indicate health provider‘s perceptions of patients that may cause them to be less/more likely to test for TB. The only predisposing factors assessed in those six studies were the age, sex and patient income.

B1.1 Predisposing factors to health system delay

B1.1.1 Age

Three studies assessed Older age as predisposing factor for health system delay in which no significant association was reported in [49,37]. The third study from Iran [50b] found the older age to be weakly significantly associated with delay (OR, 1.001; 95% CI, 1.003 to 1.007).

B1.1.2. Gender

Female gender was significantly associated with health system delay (OR, 2.12; 95% CI, 1.24 to 3.60) in three studies that contributed to the summary odd ratio [49,37,47]. Heterogeneity was significant (P = 0.14; I^2 = 49%).

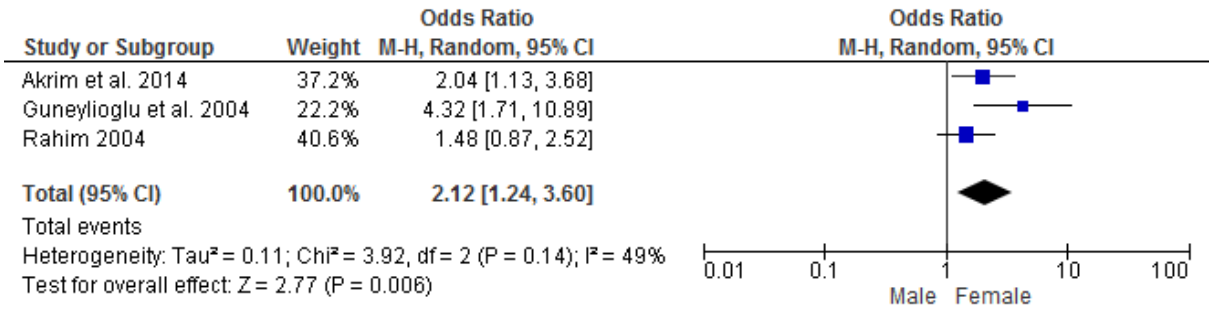


Figure C10; Forest plot, Gender vs. health system delay.

B1.1.3 patient's income

The two studies that assessed patient's income for its association with health system delay found the association to be not significant [37,47].

B1.2. Enabling factors to health system delay

B1.2.1 Expenses

Only one study looked for the association between expenses and health system delay in which, high cost of medical services was found to be weakly significantly associated with health system delay (OR, 1.01; 95% CI, 1.00 to 1.10) per pound) in Egypt [50c].

B1.2.2 Type of health facility at first visit

Three studies assessed whether public or private facility as sources for health system delay [49,45,50b]. These studies found the private facilities to be significantly associated with health system delay (OR, 1.41; 95% CI, 1.06 to 1.88). Heterogeneity was insignificant (P = 0.53; I² = 0%).

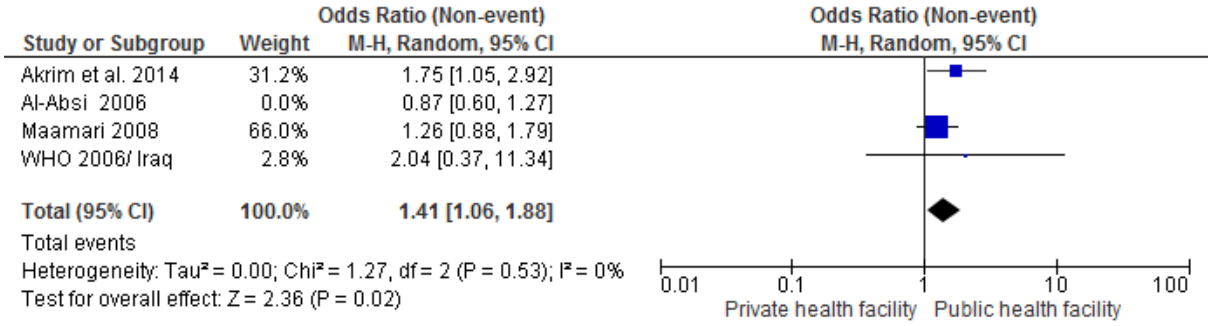


Figure C11; Forest plot, type of health facility at 1st visit vs. health system delay.

B1.2.3 Type of provider at first visit

Three studies had looked on the association between type of provider at first visit and health system delay [47,37,50c]. However, there were not combinable to calculate an effect size. Visiting non health care provider was significantly associated with health system delay (OR, 1.89; 95% CI, 1.20 to 2.90) in Egypt [50c]. Güneylioglu et al. 2004 [37] looked specifically on the specialization of the provider .i.e. chest specialist or general practitioner. He found that, patients referred by a chest specialist had a significantly shorter referral interval than those referred by the other physicians. No significant association reported by Rahim et al.2004 [47].

B1.2.4 Number of visit before diagnosis

Two studies looked on this factor as a source of delay [49,47]. However, there were not combinable to calculate an effect size. Akrim et al. 2014 found the association between more than three visit to HCP and health system delay to be imprecise (OR, 4.66; 95% CI, 2.09 to 10.62). While [47] found the number of visit to the same provider was significantly strongly associated with health system delay (r= 0.674).

B1.2.5. Number of providers encountered before diagnosis

More than one provider encountered before diagnosis was significantly associated with health system delay (r= 0.605; p<0.01) (OR, 6.87; 95% CI, 4.80 to 9.90) in Sudan [47] and Iran [50b] respectively. While not significant in Morocco [49],

B1.2.6 Type of investigation requested at first visit

Taking sputum smear at 1st attendance at a health facility was significantly inversely associated with health system delay (OR, 0.25; 95% CI, 0.22 to 0.28) while obtaining a negative smear result for acid-fast bacilli was significantly associated with health system delay (OR, 3.3; 95%CI, 2.94 to 3.66) in Iran [50b]. On the other hand, not performing TB investigation specifically chest x ray and sputum smear on the first visit was significantly associated with health system delay in Sudan [47]. Furthermore, [47] found that sputum smear was performed for only 48.8% of the patients who consulted private providers. Same way, Chest X-ray and sputum smear examinations were underutilized by physicians in Turkey [37].

B1.2.7 Provider suspicion index

Three Studies from Turkey found that on average; only 50% of patients were suspected for TB by HCP [37,38,41].

Table C7: Factors associated with health system delay

	Health system delay		Predisposing factors					Enabling factors					
Study ID	Mean ±SD	Median	Older age	Female gender	Patient's income	Expenses	Type of HCF at 1st visit	Type of HCP at 1st visit	No of visits before diagnosis	No of providers encountered	Type of investigation performed	Provider's suspicion index	Other
Al-Absi 2006 Yemen	19.98±37.2	4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
Akrim et al.2014 Morocco	30.3±44.6	15	NS	NS	NS	NA	▲	NA	▲	NS	NA	NA	NR
Date & Okita 2005 Yemen	S-= 64.5±85.8 S+=33.0±47.1	S-=41 S+=16	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
Ekinci et al. 2014 Turkey	NA	IL= 7 L= 2.5	NS	NS	NA	NA	NA	NA	NA	NA	NA	NA	NR
Maamari 2008 Syria	27.6±39.6	15	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
Güneylioglu et al. 2004) Turkey	26.7±NR	15	NS	▲	NC	NA	NA	Chest special ist ▲	NA	NA	underutilization of chest x-ray	▲	NR
Masjidi et al. 2002 Iran	93±80	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
Mirsaeidi et al. 2007 Iran	93±72	75	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR

		Health system delay		Predisposing factors					Enabling factors					
Study ID		Mean ±SD	Median	Older age	Female gender	Patient's income	Expenses	Type of HCF at 1st visit	Type of HCP at 1st visit	No of visits before diagnosis	No of providers encountered	Type of investigation performed	Provider's suspicion index	Others
Okur et al. 2006 Turkey		31±NR	19	NA	NA	NR	NR	NA	NA	NA	NA	NA	▲	NR
Okutan et al. 2005) Turkey		16.3±NR	7	NA	NA	NA	NA	NR	NR	NA	NA	NA	NA	NR
Rahim et al.2004 Sudan		32.88±30.74	21	NA	NS	NC	NA	NA	NS	▲	▲	No x-ray on the 1st visit ▲	NA	NR
Shahriyar et al. 2012 Iran		6±4.27	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
Shamaei 2009 Iran		DU=100±116.54 NDU=129.25±40.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NR
WHO 2008	Iran	75±7.05	42	▼	NS	NS	NS	▲	Private HCP ▲	NA	▲	No sputum smear at 1st visit ▲	NA	NR
	Iraq	5±7.05	2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NR
	Somalia	19.5±41.6	7	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NR

Study ID	Health system delay		Predisposing factors					Enabling factors					Others
	Mean ±SD	Median	Older age	Female gender	Patient's income	Expenses	Type of HCF at 1st visit	Type of HCP at 1st visit	No of visits before diagnosis	No of providers encountered	Type of investigation performed	Provider's suspicion index	
Egypt	33.6±44.5	18	NS	NS	NS	▲	NS	▲	NS	NS	NS	NS	Travel time ▲
Yilmaz et al. 2001 Turkey	14.4±18.7	3.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	▲	NR

Alavi 2015 and Nasehi 2012 didn't report the length of health system delay.
Bashour & Mamaree 2003, Mohamed et al.2013, and Rumman 2008 didn't assess the health system period.
WHO 2008; delay was attributed to the patient in Iran and Egypt, So only present the data for those countries.
NA: Not Assessed, NC: Not Correlated, NR: Not Reported ▲: positively associated with delay, ▼: negatively associated with delay, NS: Assessed but were not significant (p>0.05)
HCF; Health Care Facility
HCP; Health Care Provider
DU: drug users, NDU: non drug users, IL: Illiterate, L: Literate, S+; Smear positive, S-; Smear negative, F: female, M: male

4.3.5 Contribution of patient and health system delay in total delay

Out of our 20 included studies, fourteen studies assessed both patient and health system delays. These studies also took into account the total delay, which measures the patient‘s and the system‘s contribution to delay from the time of first symptoms to the start of treatment. Out of these 14 studies, nine studies [35,38,41,42,45,47,49,50a,50d] found the delay to be attributed to the patients. Whereas in the other five studies [32,33,40,50b,50c] the delay was mainly due to the health system. This can be translated into that; six countries in the region (Yemen, Morocco, Syria, Sudan, Iraq and Somalia) should mark an intervention aim to reduce the patient delay such as increasing the public awareness about TB. While in Egypt the efforts should pay to the health system strengthening and building good referral system and engaging the private and non-formal health providers in TB control. Turkey and Iran should work on both components to reduce the delay.

4.3.6 HETEROGENEITY IN INCLUDED STUDIES

Patient delay factors

Heterogeneity was significant for these factors; gender, patient's income, and crowding (P <0.1; I^2 = 45%), (P <0.00001; I^2 = 92%) and (P= 0.15; I^2 = 47%) respectively. Further investigation revealed that:

- For factor **gender,** Rumman et al. 2008 was the source of this heterogeneity. The participants in [48] were TB suspect rather than confirmed TB cases as in the other studies. Removal of this study from the meta-analysis for subgroup rendered the heterogeneity insignificant (H, p=0.47; I^2 = 0%).

- For the **Patient's income**, the measurement of patient income used in Mohamed et al. 2013 and Guneylioglu et al. 2004 was different from the rest of the studies [37,46]. Removal of these studies from the meta-analysis, rendered the heterogeneity insignificant (H, p=0.30; I^2 = 18%).

- For the **Crowding,** the cut-off point for crowding index was higher in Maamari 2008 than in the other studies [45]. Removal of this study from the meta-analysis, rendered the heterogeneity insignificant (H, p=0.84; I^2 = 0%).

Health system factors

Gender

Heterogeneity was significant (P = 0.14; I^2 = 49%): further investigation revealed that the source of heterogeneity was Guneylioglu et al 2004 [37]. Removal of this study from the meta-analysis, rendered the heterogeneity insignificant (H, p=1.00; I^2 = 0%).

4.3.8 GRADING THE QUALITY OF EVIDENCE

We used GRADE approach to assess the quality of evidence pooled in meta-analysis that are related to each significant factors associated with patient and/or health system delay using GRADEpro software. The meta-analysis included 12 observational studies. These studies were appraised for limitations to validity wherein it was found that measurement of the outcome was dependant on patient‘ self-report, so this created a possibility of bias (recall bias). The effects of the exposure in the 12 studies were assessed for similarity and it was found that there was consistency and that a meta-analysis was appropriate. Driven by concern for the shortcomings of the observational studies and plausibility of bias as well as the small size estimates except for the relation between female gender and health system delay (other estimates are not with rule of >2 or <0.5) and implications for the repeatability and generalizability of the estimates application of the GRADE system has produced a low quality grading for the evidence in this review. In view of the low quality of evidence the implications of this grading are that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the strength of the estimate.

Table C8: Summary of finding table on the quality of evidence

Population: TB patients or suspected TB patients. Settings: MENA			
Patient delay			
Outcomes	Impacts	No of Participants (studies)	Quality of the evidence (GRADE)
Gender	Female gender had more patient delay (OR, 1.24; 95% CI, 1.02 to 1.50)	4414 participants (10 studies)	⊕◯◯◯ VERY LOW
Age	Older age had more patient delay (OR, 1.42; 95% CI, 1.19 to 1.69),	4083 participants (8 studies)	⊕⊕◯◯ LOW
Employment	Protective from delay (OR, 0.83; 95% CI, 0.72 to 0.95)	3492 participants (5 studies)	⊕⊕◯◯ LOW
Patient' income	Low income had more patient delay (OR, 1.95; 95% CI, 1.07 to 3.55)	3958 participants (7 studies)	⊕⊕◯◯ LOW
Crowding index	Low crowding index is protective from patient delay (OR, 0.75; 95% CI, 0.57 to 0.99)	1659 participants	⊕⊕◯◯ LOW

		(3 studies)	
Provider at 1st consultation	Consulting health care provider vs. other provider (traditional healer, drugs seller and other) was protective from patient delay (OR, 0.77; 95% CI, 0.70 to 0.85)	1982 participants (5 studies)	⊕⊕◯◯ LOW
Health system delay			
Gender	Female gender had twice the risk of health system delay compare to male (OR, 2.12; 95% CI, 1.24 to 3.60)	705 participants (3 studies)	⊕⊕⊕◯ MODERATE
Facility at 1st visit	Private facilities had more health system delay (OR, 1.41; 95% CI, 1.06 to 1.88).	1791participants (4 studies)	⊕⊕◯◯ LOW

**We rated down the quality of the evidence by two points, because of shortcomings of the observational studies and plausibility of bias in included studies.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

5. DISCUSSION

5.1 Summary of main results

From a comprehensive literature search we identified 303 records of which 20 full-text articles met our inclusion criteria of the review. Of the twenty included studies, sixteen assessed both sources of delay, 4 - studies assessed patient delay only and 2 studies assessed total delay without demarcation between patient and health system delay. Seventeen studies measured the length of patient delay in which only 10 studies analysed the factors attributed to this period [31,37,42,43,45-50a]. Out of 15 studies that measure the length of health system delay, only six studies analysed at least one factor associated with this period [37,38,41,47,49,50a]. In all the studies standard definition for patient delay was consistent, but not for health system delay. Female gender was the only factor that are associated with both patient and health system delay.

For the patient delay; the predisposing factors that were significantly associated with patient delay are; older age, female gender, unemployment, low patient income, and crowding. Inadequate TB knowledge was found to be significantly associated with patient delay in two studies [42,50a]. High TB perception was protective from delay in two studies [43, 48] and predisposes to delay in one study [46]. Literacy was found to be significantly associated with patient delay in four studies. Rural residence found to be significantly associated with patient delay in one study [48], and presence of chronic health problem in two studies [45,46]. TB-related stigma was protective from patient delay in one study [48] and predispose to patient delay in another study [52]. Contact with TB case was found it to be significantly associated with patient delay in one study [46] and to be protective from delay in another study [37]. Self-medication founded to be significantly associated with patient delay in one study [50a] and not significantly associated in another study [47]. Marital status, smoking, and HIV were not associated with patient delay in all studies that looked on these factors. Provider at first consultation was the only enabling factor that we had sufficient information to calculate summary odd ratio in which consulting with non-health care provider was associated with longer patient period. The high cost of medical services was significantly associated with patient delay in one study [42]. Travel time was not associated with patient delay in all the studies that looked on it.

Older age, female gender and patient income were the only predisposing factors that assessed for health system delay in our included studies. Older age was weakly associated with health system delay in one study and patient income was not associated with health system delay in all the studies that looked on it. The enabling factors for health system delay was high cost of medical services in one study [50a], private facilities at first visit in two studies [49,50b], non-health care provider i.e. traditional healer and community or village healer at first visit in one study [50c], more than three visit to health provider in one study [49] and repeated visit to same provider in one study [47], not performing sputum examination on the first visit in [50/Iran], obtaining negative result on sputum microscopy in [50b], underutilization of chest x-ray and smear microscopy in Sudan [47] and Turkey [37] and finally low suspicion index in three studies from Turkey [37,38,41].

Table C8: summary of findings for patient delay factors

Predisposing factors	Studies assessed this factor	Summary odd ratio
Female gender	[31,37,42,43,45-50a]	(OR, 1.24; 95% CI, 1.02 to 1.50)
Older age	[31,37,42,45-50a]	(OR, 1.42; 95% CI, 1.19 to 1.69),
unemployment	[42,45,46,48,50a]	(OR, 0.83; 95% CI, 0.72 to 0.95)
Low patient income	[37,42,45-48,50a]	(OR, 1.95; 95% CI, 1.07 to 3.55)
High crowding index	[42,45,50a]	(OR, 0.75; 95% CI, 0.57 to 0.99)
Residence	[31,37,42,45,46,48,50a]	NS
Marital status	[42,45,46,49,50a]	NS
TB knowledge	[42,45,47-50a]	NS
TB perception	[43,46-48].	NS
TB stigma	[31,46,48,50a]	NS
Literacy	[42,43,45,48]	NS
HIV	[31]	NA
Smoking	[42,45,48,50a]	NS
Chronic illnesses	[31,45,46,50a]	NS
Contact with TB case	[37,46]	NS
Self-medication	[47,50a]	NS
Provider at 1st consultation	[42,45,47,37,50a]	(OR, 0.77; 95% CI, 0.70 to 0.85)
Travel time	[42,45,48,50a]	NS
Expenses	[42]	NA

NS; not significant, NA; not applicable; OR; odd ratio, CI; confidence interval.

Table C9: summary of findings for health system delay factors

Predisposing factors	Studies assessed this factor	Summary odd ratio
Older age	[49,37,50b]	NS
Female gender	[49,37,47]	(OR, 2.12; 95% CI, 1.24 to 3.60)
Low patient income	[37,47]	NS
health facility at 1st visit	[49,45,50b]	(OR, 1.41; 95% CI, 1.06 to 1.88)
Expenses	[50c]	NA
Provider at 1st visit	[37,47,50c]	NA
visits before diagnosis	[49,47]	NA
providers before diagnosis	[47,49,50b]	NS
investigation requested at 1st visit	[37,47,50b]	NA
Provider's suspicion index	[37,38,41].	NA

NS; not significant, NA; not applicable; OR; odd ratio, CI; confidence interval.

5.2 LIMITATIONS

There are some limitations to this review. The included studies were limited by their designs; the included cross-sectional studies had poor comparability and were oppressed with numerous confounders. This might have introduced some degree of bias to the review. Also cross-sectional studies limited by the temporal bias and cannot reach the causality. Some studies had used different start point and end point for the definition of health system delay, this limit the comparability of these studies, and make it difficult to combine them in the meta-analysis. In the meta-analysis we choose to include those studies that adopted the WHO definition that presented under ―**p**erational definition" at the beginning of this document. Another limitation is the generalizability of our findings, most of the studies recruited patients from public health facilities and TB management units (TBMUs) near the center or the capital of the country and no recruitment from private health facilities and from the peripheries were done. Hence to obtain generalizability, future studies should recruit the patients from private health facilities and patients from marginalized and far areas. Also, two articles were translated into English [20,49] which might have led to information loss, thus reducing the quality of data extracted.

5.3 AUTHORS' CONCLUSIONS AND RECOMMENDATIONS

5.3.1 Implications for Practice

This review identified numerous factors contributing to patient and health system delay. These factors need careful attention from the TB control planners when detailing the future interventions in order to reduce the delay and contain the transmission of the disease in the region. The commentary in this thesis raises the dilemma, that the region could not find a way to the case detection rate unless the regions paid extensive attention to the following points. The review suggest the need of paying more attention to health system enabling factors in the region and clearly announces that there are multiple windows for opportunities existing to reduce delay. Efforts should be enhanced to increase public awareness and promoting health education about TB especially in outreach areas. Maintaining of high suspicion index for TB among the health care providers is mandatory; this can be achieved through effective periodic training, monitoring and evaluation. In addition, there is desperate need for engaging all type of providers (public, private and non-formal providers) in tuberculosis care and control and building good referral system. Furthermore, building interventions that understand the gender discrepancies and differences in the region is critical for TB control particularly this review found that the female gender have twice the chance of both delays. Lastly, this review suggests incorporating more active case-finding interventions into current TB control efforts, mainly among the high risk group.

5.3.2 Implications for Research

This review revealed several research gaps; first, the majority of our included studies were cross-sectional. Cross sectional study design are useful in measuring prevalence and identifying associations still could not reach the causality [6]. So, other designs such as cohort design studies are needed to establish the causality. Secondly, the data on delay of TB among HIV patient is deficient. According to UNAIDS the region have fastest growing of HIV epidemic but the data is not available [53]. Hence, more research on HIV-related factors that might influence the diagnosis and treatment for TB is needed especially to the programmes and interventions planner. Thirdly, the data on health system related factors is lacking, out of 15 studies that measure the length of health system delay only six studies assessed few factors related to this period. Therefore, we recommend that future studies should assess more health system-related factors. Fourthly, as majority of our included studies assessed passive case finding i.e. patient wait longer until she/he recognized the severity of her/his symptoms and feel the need to go to the

health facility: this might create an opportunity for recall bias when measuring the patient delay depending on self-reports thus, to overcome this problem more studies through active case finding are needed. Also, there is a need for a systematic review of the incidence rates based on which countries in the region determining a target 70% detection rate, as DOTS suggested.

Lastly, our review does not include the qualitative studies, the usefulness of these studies are their strength in identifying factors like stigma that are difficult to be measured by the quantitative studies. Therefore the need for qualitative studies to assess factors such as stigma and consulting traditional healers is warranted.

5.4 DIFFERENCE BETWEEN PROTOCOL AND REVIEW

We planned in the protocol to use mean differences to summarize results for continuous outcomes. However, all the continuous outcomes such as age, income, number of visit and crowding index were already categorized in the primary studies; hence we don‘t find continuous variables to apply mean differences to them.

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7. APPENDICES

Appendix 1: Search strategy:

Search strategy developed in MEDLINE

#1	Search **(TB or pulmonary tuberculosis or tuberculosis or mycobacterium tuberculosis)**
#2	Search **(patient delay or health-seeking delay or care-seeking delay)**
#3	Search **(health facility delay or health provider delay or doctor delay or diagnostic delay or diagnosis delay or total delay or detection delay or identification delay or treatment delay)**
#4	Search **((Algeria OR Bahrain OR Djibouti OR Egypt OR Iraq OR Jordan OR Kuwait OR Lebanon OR Libya OR Jamahiriya OR Mauritania OR Morocco OR Oman OR Palestine OR Qatar OR Saudi Arabia OR Somalia OR Sudan OR Syria OR Tunisia OR The United Arab Emirates OR Yemen OR Iran OR Islamic Republic OR Israel OR Turkey OR Armenia OR Azerbaijan OR Georgia)**
#6	Search **(((((TB or pulmonary tuberculosis or tuberculosis or mycobacterium tuberculosis))) AND ((health facility delay or health provider delay or doctor delay or diagnostic delay or diagnosis delay or total delay or detection delay or identification delay or treatment delay))) AND ((patient delay or health-seeking delay or care-seeking delay))) AND ((Algeria OR Bahrain OR Djibouti OR Egypt OR Iraq OR Jordan OR Kuwait OR Lebanon OR Libya OR Jamahiriya OR Mauritania OR Morocco OR Oman OR Palestine OR Qatar OR Saudi Arabia OR Somalia OR Sudan OR Syria OR Tunisia OR The United Arab Emirates OR Yemen OR Iran OR Islamic Republic OR Israel OR Turkey OR Armenia OR Azerbaijan OR Georgia))**

Appendix 2: Data extraction form

Title:

Study ID *(surname of first author and year first full report of study was published)*

STUDY ELIGIBILITY

General Information

Date form completed*(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
References (of potentially eligible studies from the reference list)	
Notes:	

STUDY CHARACTERISTICS

Study Characteristics	**Eligibility criteria** *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	
MENA country	YES ☐ specify…… No ☐	
Participants	Suspect TB ☐ Newly diagnosed ☐ smear positive PTB ☐ smear negative PTB ☐ retreatment ☐ Other ☐ specify……	
Sample size		
Study design	Quantitative ☐ Qualitative ☐	
INCLUDE ☐	**EXCLUDE** ☐	

Reason for exclusion	
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

CHARACTERISTICS OF INCLUDED STUDIES

Methods

	Descriptions as stated in article/report	**Location in text or source** *(pg&fig/table/other)*
Aim of study	*What was the study designed to assess?*	
Study Design	☐ **Randomised Controlled Trial** ☐ **Non-Randomised Trial** ☐ **Cohort Study** ☐ **Case-control study** ☐ **Cross-sectional study** ☐ **Other**	
Start date		
End date		
Duration of participation		
Ethical approval obtained	☐ Yes ☐ No ☐ Unclear	
Informed consent and assent obtained	☐ Yes ☐ No ☐ Unclear	
Notes:		

METHODS

Population and settings

	Description	**Location in text or source** *(pg& /fig/table/other)*
Population description *(from which study participants are drawn)*	.	

Health facility	*Public TB health facility* ☐ *Public non TB health facility* ☐ private facility ☐ Other ☐ specify ……	
Distance to health facility	Less than 1 hour ☐ more than 1 hour ☐ Not assessed ☐	
Lab resources related to TB diagnosis	Smear +chest x-ray ☐ point care ☐ centralized lab ☐ gene xpert ☐	
Setting *(including location and social context)*	*Eg. Community, home, primary health centre, extended care facility*	
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants		
Notes		

Participants

	Description as stated in paper	**Location in text**
Number (Total no. Enrolled)		
Age	Age range, mean (standard deviation)	
Gender	Number; % female male	
Other health problems		
Notes:		

FACTORS ASSESSED FOR ASSOCIATION WITH PATIENT' DELAY:

		Location in text or source *(pg& /fig/table/other)*
Time to First consultation visit (mean±SD)/(median and IQR)		

Cut-off point used to consider this delay					
	No of patients above the cut-off point		No of patients below the cut-off point		
	PROPORTIONS	Total	Delayed	Not-delayed	
Place at first consultation	Community				
	Clinic				
	Private doctor				
	Public hospital				
	TBMU				
	Pharmacy				
	other				
Residence	Urban				
	Rural				
Gender who had delay	Female				
	Male				
Age who had delay	<15 years				
	>15 years				
Marital status	Married				
	Unmarried				
HIV status	Positive				
	Negative				
	Unknown				
Smoking status	Smoker				
	Non smoker				
Alcohol consumption	Alcohol drinker				
	Non-alcohol				
	drinker				
Presenting symptoms	Cough				

	Loss of weight				
	Sputum				
	Production				
	Chest pain				
	Fever				
	Haemoptysis				
	Night sweat				
	Tiredness/ fatigue				
	Other symptoms (specify) …….				
Education	No education				
	Primary level				
	Secondary level and above				
Household size	<3 persons				
	3-7 persons				
	> 7persons				
Patient‘s income	Low				
	Middle				
	high				
Socioeconomic status	Poor				
	Middle				
	High				
Employment	Employed Not employed				
TB knowledge	Yes				
	No				
TB perceptions/ Suspicion of having	Yes				

TB by patient	No				
Travel time to health facility	< 15 min				
	15-60 mins				
	Hour -2 hours				
	>2 hours				
How they get to the health facility	Walk				
	Using vehicle				
Traditional healer consulted	Yes				
	No				
Self-medication	Yes				
	No				
Stigma reported by patient	Yes				
	No				
Other	Specify				

FACTORS ASSESSED FOR ASSOCIATION WITH HEALTH' SYSTEM DELAY:

	Present in numbers		**Location in text or source** *(pg& /fig/table/other)*
Time from First consultation visit to diagnosis (mean±SD)			
Cut-off point used to consider this delay			
	No of patients above the	No of patients below the cut-off point	

	cut-off point				
Number of visits to the provider					
Number of provider consulted before diagnosis achieved					
Health facility	Proportions	total	delayed	Not-delayed	
	Public health facility				
	TBMU				
	Other specify				
Type of provider	Public providers				
	Private providers				
	Both private and public providers				
	Other types of providers (NGO clinic or pharmacist).				
Type of provider who made the successful diagnosis	Public providers				
	Private providers				
	Both private and public providers				
	Other types of providers (NGO clinic or pharmacist).				
Type of referral if the diagnosis was not successful	No referral				
	Referral to TBMU				
	Referral to non TBMU				
Diagnosis made based on clinical picture only	Yes				
	No				
	If yes specify the reasons .e.g shortage of lab equipment or no chest x-ray machine				

	Proportions	Total	Delayed	Not	
Type investigation c x requested by provider	No investigation				
	Tuberculin skin test				
	Sputum microscopy				
	Chest x-ray				
	Culture				
	Gene xpert				
	Other				
Place at where these investigation performed	Private health facility				
	Public health facility				
	Both public and private				
	TBMU				
Time from investigation requested to the result					
	Proportions	Total	Delayed	Not	
Type of diagnosis offered by provider	Tuberculosis				
	Non tuberculosis				
Type of treatment offered by provider	TB treatment				
	Non TB treatment				
Time from the correct diagnosis to initiation of treatment					
Reasons for delayed treatment					
Stigma related to TBMU – BY WHOM?		Total	delayed	Not-delayed	
	YES				
	NO				
Other (specify)					

Other Outcomes

Outcome 1: Patient delay

	Description as stated in report/paper	**Location in text** *(pg&/fig/table)*

What is the name used in the study to describe patient delay		
Duration (mean+SD or median +IQR)		
Outcome definition		
Unit of measurement *Days, weeks or months*		
Method of assessing outcome measure 1	*Eg. Duration of symptoms by questionnaire, date of first provider visit in the doctor record/ day of result of diagnostic test in lab records*	
Notes:		

Outcome 2: Health system delay

	Description as stated in report/paper	**Location in text** *(pg&/fig/table)*
What is the name used in the study to describe health system delay		
Duration (mean+SD or median +IQR)		
Outcome definition		
Unit of measurement *Days, weeks or months*		
Method of assessing outcome measure 2	*Eg. Duration of symptoms by questionnaire, date of first provider visit/ start of diagnosis in records*	
Notes:		

Outcome 3: Total delay

	Description as stated in report/paper	**Location in text** *(pg&/fig/table)*
Duration (mean+SD or median +IQR)		
Outcome definition		

Unit of measurement *Days, weeks or months*		
Method of assessing outcome measure 3	*Eg. Duration of symptoms by questionnaire, date of first provider visit/ start of diagnosis in records*	
Notes:		

Risk of bias assessment

Hoy et al 2012 criteria for cross-sectional studies modified by Werfalli et al 2014

Was the study's target population a close representation of the national population in relation to relevant variables?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was the sampling frame a true or close representation of the target population?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was some form of random selection used to select the sample, OR was a census undertaken?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was the likelihood of nonresponse bias minimal?	**Yes** ☐ **No** ☐ **Unclear** ☐
Were data collected directly from the subjects (as opposed to a proxy)?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was an acceptable case definition used in the study?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was the same mode of data collection used for all subjects?	**Yes** ☐ **No** ☐ **Unclear** ☐
Was the length of the shortest prevalence period for the parameter of interest appropriate?	**Yes** ☐ **No** ☐ **Unclear** ☐
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	**Yes** ☐ **No** ☐ **Unclear** ☐
Authors' reported limitations of study's methods/results	**Yes** ☐ **No** ☐ **Unclear** ☐

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Criteria	Star	Comment
Selection		
1) Is the case definition adequate? a) Yes, with independent validation b) Yes, eg record linkage or based on self-reports c) No description		
2) Representativeness of the cases		
a) Consecutive or obviously representative series of cases b) Potential for selection biases or not stated		
3) Selection of Controls		
a) Community controls b) Hospital controls c) No description		
4) Definition of Controls		
a) No history of disease (endpoint) b) No description of source		
Comparability		
1) Comparability of cases and controls on the basis of the design or analysis		
a) Study controls for TB knowledge (Select the most important factor.) b) Study controls for any additional factor stigma, gender (This criteria could be modified to indicate specific Control		

for a second important factor.)		
Exposure		
1) Ascertainment of exposure a) Secure record (eg surgical records) b) structured interview where blind to case/control status c) Interview not blinded to case/control status d) Written self-report or medical record only e) No description		
2) Same method of ascertainment for cases and controls		
a) Yes b) No		
3) Non-Response rate		
a) Same rate for both groups b) Non respondents described c) Rate different and no designation		

Other information:

	Description as stated in report/paper	**Location in text** *(pg&/fig/table)*
Key conclusions of study authors		
References found to be eligible studies		
Correspondence required for further study information*(from whom, what and when)*	**Correspondence with authors** **Question to Author:** **Verification with study investigators:** ☐Yes ☐No	

SUPPLEMENTARY MATERIALS

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Submission Guidelines for PLOS ONE

Style and Format

File format:	Manuscript files can be in the following formats: DOC, DOCX, RTF, or PDF. Microsoft Word documents should not be locked or protected.
Length:	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information.
Font:	Use any standard font and a standard font size.
Headings	Limit the manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout:	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers:	Include page numbers and line numbers in the manuscript file.
Footnotes:	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language:	Manuscripts must be submitted in English.
Abbreviations:	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text.
Reference style:	PLOS uses ―Vancouver" style.

Manuscript Organization: Manuscripts should be organized as follows.

Beginning section: The following elements are required, in order:

- Title page: List title, authors, and affiliations as first page of manuscript
- Abstract
- Introduction

Middle section:The following elements can be renamed as needed and presented in any order:

- Materials and Methods
- Results
- Discussion
- Conclusions (optional)

Ending section: The following elements are required, in order:

- Acknowledgments
- References
- Supporting Information Captions (if applicable)

Other elements

- Figure captions are inserted immediately after the first paragraph in which the figure is cited.
- Tables are inserted immediately after the first paragraph in which they are cited.
- Supporting information files are uploaded separately.

Systematic reviews and meta-analyses

Authors must also state in their ―Methods" section whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as Supporting Information and provide the registry number in the abstract.

If your article is a systematic review or a meta-analysis you should:

- Include the PRISMA flow diagram as Fig 1
- Include the PRISMA checklist as Supporting Information.