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Abstract

Background: Political instability, economic sanctions and substandard quality of health care negatively affect tuberculosis (TB) control in the Middle East and North Africa (MENA) region.

Aims: We aimed to elucidate factors contributing to delays in TB diagnosis and treatment in MENA countries.

Methods: Two reviewers independently appraised eligible articles identified through comprehensive searching and extracted data which were subjected to meta-analysis.

Results: Delays in TB diagnosis were associated with older age and low income [(OR = 1.49; 95% CI: 1.31–1.70) and (OR = 1.26; 95% CI: 1.09–1.45)] respectively (n = 17 studies). Being female was associated with patient delay and health system delay [(OR = 1.24; 95% CI: 1.02–1.50) and (OR = 1.68; 95% CI: 1.18–2.38)] respectively. Knowledge and perception of TB, having employment and low levels of crowding were each protective against patient delay. The GRADE system rated the evidence as of low quality.

Conclusion: This review provides evidence for facilitators and barriers to TB diagnosis and health system delays. For successful TB control in the MENA region, TB awareness and interventions targeting the elderly and those from lower-income settings, particularly directed at gender differences, are essential.
Introduction

Tuberculosis (TB) remains a major global health problem (1). In 2015, an estimated 4.3 million cases were neither detected nor treated in national TB programmes globally (1).

A diagnostic delay of two months will result in transmission of TB to an average of 8 contacts (2) and within a year, this number will increase eight to 15 persons; the increase would be even higher in settings of overcrowding and higher social capital (3). Furthermore, delays between admission and initiation of treatment will result in the exposure to TB of an average of 23.9 health care workers (4). Therefore, to curb TB transmission and reduce poor disease outcomes and adverse social and economic consequences, timely diagnosis and prompt initiation of anti-TB treatment is vital (5).

Reasons for delayed TB diagnosis can be attributed to both patients and the health care system (6). Patients may delay in seeking help while the health care system may delay in suspecting TB and initiating relevant investigations. Delays, and ultimately TB control, are affected by patient factors such as sociodemographic characteristics, stigmatization effects of TB, fear of high individual expenses, symptoms on presentation and health care factors such as absence
The World Bank’s description of the Middle East and North Africa (MENA) region covers the 21 members of the Arab League, plus the Islamic Republic of Iran, Israel and Turkey (8). The MENA region is challenged with delayed detection of TB, which negatively affects treatment and control in the region (9). Factors in the region that have destabilized health care delivery are political instability and economic sanctions. Health care resources are thus stretched beyond control, and the quality of health care service delivery deteriorated to a level that can be described as “below standard” (9).

There is a scarcity of systematic reviews addressing TB diagnostic and treatment delays (10). Furthermore, these reviews included older studies, are applicable to high HIV prevalence settings, and specifically did not include diagnostic and treatment delays in MENA countries.

We conducted a systematic review to address this paucity of data. We wished to evaluate the evidence regarding factors associated with TB diagnostic and treatment delays in the MENA region. Successful identification of such factors may actually lead to interventions which may ultimately increase effective TB control.

**Methods**

**Protocol**

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

**Search methods for identification of studies**

This systematic review adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines 2009 (11). We searched MEDLINE using combinations of the following keywords: TB, tuberculosis, mycobacterium, patient delay, health seeking delay, care-seeking delay, health system delay, health facility delay, health provider delay, diagnosis delay, total delay and treatment delay. Key terms (factors or enablers and barriers) that did not provide new articles were excluded from the final search strategy. Search strategies incorporated both medical subject headings (MeSH) and free-text terms using controlled vocabularies applicable to databases. Published and unpublished articles, irrespective of language used, were interrogated up to June 2015.
Electronic searches were carried out on the following published databases: Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, PubMed, CINAHL, PsychInfo and Scopus. Grey literatures were searched using Index Medicus for the Eastern Mediterranean Region (IMEMR), (Africa-wide) allied health and Google scholar. In addition, we searched conference proceedings and reference lists of relevant articles.

Observational studies (case–control, cross-sectional and population-based) were considered for review. Studies which reported patient and health system delays in patients diagnosed with, or suspected of, pulmonary TB (PTB) were included. Andersen’s behavioural model of health care utilization was used to classify factors regarded as primary outcomes for the study (12). These factors were defined as predisposing factors (factors influencing the initial performance of behaviour); enabling factors (factors making it possible for individuals to enact their behaviour) and need factors (factors following behaviour enactment and influence continued behaviour). Secondary outcomes were: magnitude of patient delay (defined as time interval from onset of TB symptoms to first visit of any health provider), health system delay (defined as time interval from the first health provider visit to initiation of treatment) and total delay, which includes both patient and health system delays (defined as time interval from onset of TB symptoms to initiation of treatment).

Data collection and analysis

Selection of studies and data extraction

Two reviewers (DE and EP) independently screened titles and abstracts of all identified articles to select potential eligible studies; reviewed full texts of potentially eligible studies; nominated the final set of articles for inclusion into the review; extracted data using a standardized data extraction form and reviewed risk of bias. A third reviewer (ME or LA) facilitated disagreements regarding study selection and data extraction.

Assessment of risk of bias

We noticed a 2-study design, a descriptive phase and an analysis phase, in 12/20 studies. In these studies the descriptive phase, a cross-sectional design, was used to determine the extent of delay while during the analysis phase, a nested case–control design, patient delay was compared to the median time of delay. The quality of these studies was assessed based on results from the analysis phase. Two authors used the Newcastle–Ottawa Quality Assessment Scale for case–control studies (13) to assess the risk of bias in these 12 studies.

Cross-sectional and descriptive surveys were assessed according to an assessment tool by
Hoy et al. (14) as adapted by Werfalli et al. (15). This adapted assessment tool allows for allocation of a composite score to assist with relative comparison between studies.

Data analysis and synthesis

The results of each study were expressed as an odds ratio (OR) with the corresponding 95% confidence interval (CI) for dichotomous data. Studies that compared similar types of outcomes were grouped to get feasible results on an overall estimate of effect. Random effects meta-analysis was used due to heterogeneity in study results. Prevalence of TB delay from different studies was pooled in a meta-analysis using Review Manager, 5.3.

Assessment of heterogeneity and subgroup analysis

Statistical heterogeneity between the study results were examined using the $\chi^2$ test for homogeneity (with significance defined at the alpha-level of 10%) and quantified using the I-squared statistic. The $\chi^2$ test for subgroup differences was used to test for subgroup interactions.

Grading the quality of evidence

We used GRADEpro software to appraise limitations to validity in terms of the quality of evidence on the 12/20 observational studies pooled in the meta-analysis.

Results

Study flow and description of studies

Full-text evaluations were performed on 32 articles, of which 12 were deemed unsuitable for inclusion in the review (Figure 1 Flow diagram of studies selected for inclusion in the systematic review) (references available from corresponding author upon request). Reasons for exclusion were: in 2 studies participants did not meet the inclusion criteria; in 2 other studies participants were not from the MENA countries; and in the last 8 studies the outcomes measures did not address TB delay.

The 20 studies included in this systematic review were published between 2001 and 2015; 18 had a cross-sectional study design while 2 were nested case–control studies. Participants included in the studies ranged from TB suspects (1 study) (16), smear negative and smear positive PTB patients (2 studies) (17,18) and only new smear-positive patients (17 studies) (19–35). Almost all studies used a consecutive method of sampling and sample sizes ranged from 50 to 5702. Male sex was dominant in all of the studies and the majority were conducted in both urban and rural settings (detailed characteristic of studies included in the systematic review...
Sixteen studies assessed both sources of delay; 4 assessed only patient delay while 2 assessed total delay without any demarcation between patient and health system delay. Seventeen studies measured the duration of patient delay, of which only 10 analysed the factors attributed to this period (16,22,27,28,30–35). Out of 15 studies that measured the duration of health system delay, 6 analysed at least 1 factor associated with this period (22,23,26,32,34,35).

Assessment of risk of bias

We found 11 studies had a low risk of bias (16,19–25a–25d), 7 had a moderate risk of bias (17,26–31) and 5 had a high risk of bias (18,32–35) (Tables 1-2). We considered the WHO report as a single study with coverage of 4 countries that met our inclusion criteria (25).

Patient delay

Patient delay was measured in 17/20 studies. Measures of patient delay depended on patient recall of first symptoms for PTB. The majority of studies measured delay as a dichotomous variable based on a cut-off point, usually the median. The shortest (12.5 days) and longest (73 days) mean duration of patient delay was reported in the Islamic Republic of Iran (26,33). However, the quality of these studies should be considered before drawing any conclusion from this observation.

Factors associated with patient delay

At least one factor attributing to patient delay was analysed in 10 studies (16,18–25,35). Studies mostly assessed predisposing factors such as patient sociodemographic characteristics, TB knowledge and perception about TB. Enabling factors were less often assessed, while none of the studies assessed at least one needs factor.

Predisposing factors that were significantly associated with patient delay were older age (OR = 1.24; 95% CI: 1.02 to 1.50), female sex (OR = 1.42; 95% CI: 1.19 to 1.69), unemployment (OR = 0.83; 95% CI: 0.72 to 0.95), low patient income (OR = 1.95; 95% CI: 1.07 to 3.55) and low crowding index (OR = 0.75; 95% CI: 0.57 to 0.99) (Figure 2).

Factors found to be significantly associated with patient delay were: inadequate TB knowledge
(20,25a), although in 4 studies the summary OR was not significant for literacy (16,20,21,35); residing in rural areas (16); presence of chronic health problem (21,22); contact with a TB case (21) [yet protective against delay in another study (19)]; self-medication (25a) [although not significantly associated in another study (23)]; and high cost of medical services (20).

Factors found to be protective against patient delay were high TB perception (16,35); however, this predisposed to delay in 1 study (22); TB-related stigma was found to be protective from patient delay in 1 study (16) and predisposed to patient delay in another (25a). Marital status, smoking, a HIV positive status and travelling time were not associated with patient delay in any of the studies that interrogated these factors.

Health care provider (OR = 0.77; 95% CI: 0.70 to 0.85) (Figure 2) was the only enabling factor that had sufficient information to calculate summary OR. The type of provider at first consultation, i.e. consulting a non-health care provider, was associated with extended patient delay (19,20,21,23,25a). The high cost of medical services was significantly associated with patient delay in one study (20).

**Health system delay**

Duration of health system delay was measured in 15/20 studies. All 15 studies used the health facility’s record of first consultation as entry point to health care and 13/15 used start of treatment as the endpoint of time spent in the health system. Two studies used TB diagnosis as the endpoint. The majority of the studies measured delay versus non-delay as a dichotomous variable based on a cut-off point, usually the median. In patients who had health system delay, the shortest mean duration of health system delay (5 days) was reported in Iraq (25a) whereas the longest mean duration (129.25 days) was reported in the Islamic Republic of Iran (28).

**Factors associated with health system delay**

At least one factor associated with health system delay was analysed in 6/15 studies (19,23–25,29,34). Enabling factors such as type of facility, type of providers at first visit, number of visits, number of providers consulted before reaching a TB diagnosis and expenses plus travel time were assessed. These factors were related to the aspect of health system delay in which patient return for diagnosis and treatment were required.

Predisposing factors that assessed health system delay were female sex, older age and patient income. Being female was significantly associated with health system delay (OR = 2.12; 95% CI: 1.24 to 3.60) (Figure 3) in 3 studies that contributed to the summary OR (19,23,24). Older
age and patient income were not associated with health system delay in any of the studies that interrogated this factor. The enabling factors that were associated with health system delay were: high cost of medical services (25c); visiting a non-health care provider, i.e. a traditional healer and community or village healer at first visit (25c); more than 3 visits to a health care provider (24); and repeated visits to the same provider (23). Studies that reported lack of examination of sputum on the first visit (25b), obtaining a negative smear result for acid-fast bacilli (25b) and underutilization of chest X-ray and smear microscopy (Turkey and Sudan) (19,23), and a low suspicion index in 3 studies from Turkey (17,19,34) were not combinable to calculate the OR.

Visiting a public, compared with a private facility, at first consultation was the only enabling factor that we had sufficient information for to calculate summary OR. In 3 studies (21,24,25b), visiting a private facility was significantly associated with health system delay (OR = 1.41; 95% CI: 1.06 to 1.88) (Figure 3).

**Heterogeneity**
**Patient delay factors**

Heterogeneity was significant in terms of sex (P...