What Is the Share of the Country’s Researches in Iran’s National Tuberculosis Guideline?

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Abstract

Background: Appraisal of clinical guideline, especially at the national level, has two potential benefits; one is the improvement of quality of care and the second is assessing the impact of researches on an applied setting. On the other hand, Tuberculosis (TB) is a major infectious disease which has national guideline in many countries. The present study was performed to assess sources of information and level of evidence in Iran’s national TB guideline. This could explore the impact of national researches on day by day practice in the health system.

Methods: A list of main “recommendations” of the guideline was explored. Then, in cases that the cited study for any decision was available, the type of study and its evidence level was specified using a standard tool. In addition, the source of information (national/international) was determined. In other cases that no any specific citation was found, the data source of the recommendation was determined by the senior experts in the Center for Communicable Disease Control.

Results: Fifteen (48.3%) recommendations of the national guideline, out of 31 reviewed, had clearly cited at least one study. There was just one single national study which was utilized as the basis for the recommendations. All other sources were international guidelines, mainly World Health Organization’s, and or international researches.

Conclusion: While, the methodology of the guideline development was not clear enough appropriately; the share of national researches in development of the national guideline was insignificant.

Keywords: Knowledge, Evidence-based practice, Utilization, Research, Tuberculosis

Introduction

Tuberculosis (TB) is one of the major problems threatening the health of communities and it is considered as one of the leading causes of death and as an obstacle in the health, especially in developing countries. Thus, the World Health Organization (WHO) has declared it as a public health emergency (1). Annually more than ten thousand TB cases are detected and treated in Iran. Neighboring Iran with Afghanistan and Pakistan, which have a very high incidence as well as the countries of the former Soviet Union which have a high proportion of multidrug-resistant TB, makes attention to this disease in the country necessary more than ever (2). Thus, appropriate planning for fighting against TB in the country is critical. Major interventions including case finding, treatment, prevention and vaccination of BCG should be planned based on scientific evidence for interventions. It is necessary that interventions plan in each country (or region with specific epi-
demographic conditions) be according to both global (international) and local (national) evidence (3). Clinical guidelines are sets of recommendations to assist decision making including diagnosis, treatment and management of health services. Unlike traditional approaches in which guidelines often did not have any clear manners of development and presentation, current clinical guidelines have specific methodology for development. They should be transparent enough to show how they take advantage of the best available evidence (4). Two approaches can be used in order to evaluate guidelines. The first one is appraising guidelines in a more common manner which includes methods used in their development, content of recommendations and their implement-ability. This appraisal can be done by specific tools such as appraisal instrument for ‘assessing the quality of clinical practice guidelines’ (AGREE)(5). The second approach shows the number of researches that utilized and the evidence level of recommendations (6). It illustrates the share of the researches on developing recommendations in the guideline. This can be considered the application of national researches in disease management settings. In addition, in case there is no appropriate evidence, i.e. information gap, the topic could be selected as a part of research priorities (7).

The first approach was used to the TB guidelines in previous publications. The example for this assessment is the appraisal of TB in Spain guideline (8). However, it is clear that so far there has been no particular study utilizing the second approach, with our best knowledge, in developing countries regarding the sources of information and evidence level of guidelines.

This study was designed and carried out to find utilization of the international and the country’s evidence in the Iran’s national TB guideline. The result of this study can show an overview on status of using research evidence in an applied setting for health research system policy makers. In a more specific setting, it can be used by research centers working on TB and the universities to assess the impact of their researches on the national health program. On the other hand, it can be a landmark for improving the quality of the national guidelines.

**Methods**

This study was carried out in four steps: A list of major recommendations of TB surveillance was extracted using national guideline (published in 2010) (9) in cooperation with the experts of disease surveillance at the district, as the first contact level in the TB control program. The experts consisted of those who coordinators of TB program at the district and provincial level for at least two years.

In case there was any study cited as the basis of recommendation in the guideline, type of the study and its evidence level was specified. The Oxford Centre for Evidence-based Medicine tool, which is available at http://www.cebm.net) for determining the levels of evidence; was used for this stage. According to this tool the evidence level is determined by the study type and the validity of each study. The strongest evidence level is ++++ that belongs to a perfect systematic review of clinical trials and the lowest is 4 which reflect an expert opinion and / or a manual without citing the source of information. This was done by two individuals who reviewed the papers and or reports, independently.

Then, for recommendations without any cited study in guideline, the senior experts of Center for Communicable Disease Control (CCDC) were interviewed. The recommendation basis was classified as national research, international research and / or upon the experts’ opinion in the national TB committee. Where the source was the later, their justification was determined.

Finally, extensive search was carried out to find systematic reviews (SR) for each recommendation to know the extent of being up-to-date, in the time of publication, and the best available evidence on the topic. To this end, scientific databases including Pub Med, Web of Science, Cochrane database, Trip database, Google Scholar and SID (Persian papers database) were searched in March 2011. The sample of the search strategy for the Pub Med is given in appendix 1.
Appendix 1: Search strategy in PubMed database for finding systematic review on the recommendations of the national Tuberculosis guideline

Medical Subject Headings (MeSH) term which were searched with combination of "systematic reviews":

|   |                                                                                                                   |
|---|------------------------------------------------------------------------------------------------------------------|
| 1 | tuberculosis vaccines/administration and dosage                                                                   |
| 2 | tuberculosis/calmetteguerin immunization in infants and children[All Fields]                                      |
| 3 | tuberculosis/drug therapy                                                                                        |
| 4 | tuberculosis/drug therapy                                                                                        |
| 5 | tuberculosis/AIDS[All Fields]                                                                                    |
| 6 | tuberculosis vaccines/contraindications                                                                          |
| 7 | tuberculosis/calmetteguerin immunization[All Fields]                                                            |
| 8 | tuberculosis/therapy                                                                                            |
| 9 | tuberculosis/transmission                                                                                       |
| 10| tuberculosis vaccines                                                                                             |
| 11| tuberculosis/prevention and control                                                                               |
| 12| tuberculosis/drug treatment                                                                                      |
| 13| pyridoxine/pharmacology                                                                                        |
| 14| pyridoxine/therapy                                                                                            |
| 15| pyridoxine/therapeutic use                                                                                       |
| 16| pyridoxine/administration and dosage                                                                             |
| 17| streptomycin/drug effects                                                                                       |
| 18| streptomycin/therapy                                                                                            |
| 19| streptomycin/therapeutic use                                                                                     |
| 20| streptomycin/administration and dosage                                                                            |
| 21| rifampin/therapy                                                                                                 |
| 22| rifampin/therapeutic use                                                                                         |
| 23| rifampin/administration and dosage                                                                                |
| 24| pyrazinamide/therapy                                                                                            |
| 25| pyrazinamide/therapeutic use                                                                                     |
| 26| pyrazinamide/administration and dosage                                                                            |
| 27| ethambutol/therapeutic use                                                                                       |
| 28| ethambutol/administration and dosage                                                                             |
| 29| isoniazid/therapy                                                                                                |
| 30| isoniazid/therapeutic use                                                                                        |
| 31| isoniazid/administration and dosage                                                                               |

Search strategy without MeSh terms, which combined with "systematic review":

|   |                                                                                                                   |
|---|------------------------------------------------------------------------------------------------------------------|
| 1 | tuberculosis[tiab]or mycobacter*(ti)or(tuberculosis/epidemiology/prevention and control)                         |
| 2 | BCG [tiab] or bacillus Chalmette Guerin*(ti) or (tuberculosis/epidemiology/ prevention and control)             |
| 3 | tuberculosis[tiab] or mycobacter*(ti) or (tuberculosis/treatment/ prevention and control)                       |
Results

There were 31 recommendations with particular importance at the district level. For 15 recommendations (48.3%), different studies have been cited in national guideline, and the source of information for another 16 (51.7%) was determined after interview with the senior experts. Table 1 illustrates the information sources and evidence level for those recommendations which had specified citations.

Table 1: Data sources and evidence level of recommendations with citation in the National Tuberculosis Guideline

| No | Recommendation Title                                                                 | Study cited in national guideline | Systematic review found in search | Evidence level of systematic review |
|----|--------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|------------------------------------|
|    |                                                                                      | Type of study | Location of study | Evidence level |                           |                      |
| 1  | DOTS strategy shall be used for treatment of patients                                | Systematic review | International   | ++1           | √                         | ++1                 |
| 2  | Sputum test shall be sued for diagnosis (first method of diagnosis)                  | Diagnostic tests | International   | ++3           |                           |                     |
| 3  | Sputum culture has more sensitivity compared to direct sputum test                    | Narrative review | International   | ++2           |                           |                     |
| 4  | Prophylaxis of in contact cases shall be done by Isoniazid                           | Systematic review | International   | ++1           | √                         | ++1                 |
| 5  | Treatment period of new cases shall be at least 6 months                             | RCT (10)       | International   | +1            | √ (11)                    | ++1                 |
| 6  | In the first treatment category, attack phase is 2 months and maintenance phase is 4 months | RCT (10)       | International   | +1            | √ (11)                    | ++1                 |
| 7  | Once vaccination of BCG is enough during life                                         | Case-control   | International   | +2            | √ (13)                    | ++1                 |
| 8  | Children undue 6 with 3 criteria out of 5 TB diagnostic criteria (history of contact, positive PPD, suspected pulmonary radiography, positive sputum or gastric juice, TB clinical symptoms) should receive TB perfect treatment | Narrative review | International   | ++2           |                           |                     |
| 9  | Prophylaxis of children under 6 in contact is required in case of TB rejection        | Narrative review | International   | ++2           |                           |                     |
| 10 | In individual with HIV-positive and PPD positive (stiffness diameter equal to 5 mg or greater) provided rejection of active TB, initiation of preventive treatment is necessary. | Systematic review | International   | ++++1         | √                         | ++++1               |
| 11 | 9 month Isoniazid for prophylaxis in HIV-positive patients treated with antiretroviral drugs | RCT (14)       | International   | +1            | √ (15)                    | ++++1               |
| 12 | Preventive therapy in HIV-positive patients who are treated with antiretroviral drugs is Isoniazid and Rifampin with usual dose for three months | Systematic review | International   | ++1           | √                         | ++1                 |
| 13 | In HIV-positive patients treated with anti-TB drugs because of the high prevalence of neuropathy in these patients, 50 mg of pyridoxine should be given daily with Isoniazid. | Narrative review | International   | ++2           |                           |                     |
| 14 | Rifampin interferes with the effects of contraceptives and may lead to unwanted pregnancy | Narrative review | International   | ++2           |                           |                     |
| 15 | Use of Streptomycin is contraindicated in pregnancy                                   | Narrative review | International   | ++2           |                           |                     |

† Definition of items in this column is given in table 3.
In addition, it shows the result of our search for SR and the evidence level, if existed. In the following paragraphs we reflected just those recommendations in which there was discrepancy between the citation of the guideline and our search. Regarding recommendations 5 and 6, i.e. 2-month (intensive) and subsequently 4-month (continuous) phases of treatment of pulmonary TB, in addition to cited clinical trial in the national guideline (10), we found one SR published in 2006 (11). Recommendation 7 advised a BCG vaccination to prevent TB and mentioned that once inoculation suffices for the entire life of a person. While the citation was a case-control study (12), an SR in Portuguese was found in our search (13). A clinical trial was mentioned in national guideline for the 11th recommendation, which stated a 9-month treatment period for prophylaxis in HIV patients (14). In this case, a related SR was found in independent search (13). International organizations and the US Center for Disease Control guideline (16) are in agreement with the recommendation in the national guideline.

Table 2 shows the result of phase 3 of the methods and consists of recommendations which did not have citation to any specific study.

Table 2: Data sources of the recommendations without citations in the National Tuberculosis Guideline

| No.† | Recommendation Title                                                                 | Data source stated in interviews |
|------|---------------------------------------------------------------------------------------|---------------------------------|
| 16   | The primary symptom in TB case finding is coughing for more than 2 weeks              | √ (17)                          |
| 17   | If two samples of sputum is positive, one is smear-positive                            |                                  |
| 18   | If 3 sputum samples are negative but radiologic symptom is positive, one with negative smear is treated (diagnosis of smear negative pulmonary tuberculosis) |                                  |
| 19   | Volume of sputum samples provided for review should be 3 to 5 ml.**                    |                                  |
| 20   | Diameter ≥ 10 mm in Mantoux test is positive                                           |                                  |
| 21   | Prohibition of use of Rifampin for TB prophylaxis in the Iran                          |                                  |
| 22   | 2 weeks after treatment of smear-positive patients, the risk of infection goes away   |                                  |
| 23   | In treatment category II, the attack phase is 3 months and maintenance phase 5 months.|                                  |
| 24   | Isoniazid and rifampin (base treatment) are used in the maintenance phase of category 1 of treatment |                                  |
| 25   | In CAT II, H,R,Z,E,S drugs are used for attack phase and H,R,E drugs are used for maintenance phase. |                                  |
| 26   | Following dosage are used for used drugs:                                            |                                  |
|      | H=4-6mg,R=8-12mg,Z=20-30mg,E=15-20mg,S=12-16mg                                        |                                  |
| 27   | Dosage of BCG vaccine in newborn infants is 0.05 and it is 0.1 ml in children above 1 year old |                                  |
| 28   | Newborns with pulmonary tuberculosis mothers with positive sputum smears should be prophylactic. |                                  |
| 29   | If the gastric juice smear is positive children, the patient is treated under name of pulmonary TB with sputum smear-positive. |                                  |
| 30   | Taking any anti-TB drugs except streptomycin during lactation is not prohibited        |                                  |
| 31   | Maintenance treatment in meningitis, miliary TB, TB of spine and nerve lesions must be is at least 7 months |                                  |

† the number devoted to the recommendations in this table is sequential of table 1. / A: national research, B: international research, C: recommendation of international organizations (WHO, etc), D: recommendation of national Tuberculosis committee / H: Isoniazid, R: Rifampin, E: Ethambutol, Z: Pyrazinamide, S: Streptomycin

The general finding is that we did not find relevant SR for these recommendations. Following
paragraphs reflect the controversies between national TB committee decisions and international guidelines, according to the CCDC senior experts. One reference that had not been reflected in the text of the guideline was added by the senior experts. This was the only national study which is referred to in the present study. According to this evidence, delay in diagnosis of patients is substantial (18). Along with this local finding, WHO advised changing duration of caught as the landmark for diagnosis of pulmonary TB from 3 to 2 weeks. It facilitated decision of the national TB committee to change the definition in order to increase sensitivity of diagnosis and subsequently the case finding. In recommendation number 17, classifying individual as smear-positive, WHO recommended that 2 sputum specimens should be taken from suspected cases and in case one of the samples is positive, the person must be considered as smear-positive patient. This recommendation is conditional on having a qualified laboratory. The national TB committee advised that due to the reservation on quality of TB laboratories, still cases should be considered as smear-positive if there are two positive sputum tests. Recommendation 21, keeping out the use of Rifampin for TB prophylaxis in Iran, was adopted to prevent multi-drug resistance in the country. In recommendation 29, using gastric lavage was advised for diagnosis of pulmonary TB in children. The national TB committee advised this due to inability of children to give appropriate sputum samples.

According to Table 3, the frequent source of evidence in the national TB guideline comes back to the experts’ opinion and or WHO guidelines. The level of these sources should be considered 4 (while there is reservation in this regard elaborated in the discussion). 25.8% of the cited studies had strong level of evidence, i.e. 1.

Table 4 indicates that all of the 15 studies cited in the national guideline were from international studies and there was not one single study from the country’s researches.

Table 3: Evidence level of recommendations in the National Tuberculosis Guideline of Iran

| Evidence level | Definition | Percent of recommendation evidence in total recommendations | Recommendation No. |
|---------------|------------|----------------------------------------------------------|-------------------|
| +++1          | Very good systematic review                           | 6.4             | 10-11             |
| ++1           | Medium systematic review and or good Randomized Controlled Trial (RCT) | 19.3           | 1-4-5-6-7-12      |
| ++2           | Systematic review on observational studies            | 19.3           | 3-8-9-13-14-15    |
| ++3           | Appropriate descriptive study                         | 3.2            | 2                 |
| +3            | Descriptive with bias probability                      | 3.2            | 16                |
| 4             | Opinion of experts (internal or International) including WHO recommendations | 48.4         | 17-18-19-20-21-22-23-24-25-26-27-28-29-30-31 |

Table 4: Source of the information according to the type of study and its location for recommendations of the National Tuberculosis Guideline of Iran

| Type of study       | Location of study | Percent of total recommendations in guideline with cited study |
|---------------------|-------------------|---------------------------------------------------------------|
|                     | Internal          | International                                                 |
| Narrative review    | 0                 | 6                 | 40.0                |
| Systematic review   | 0                 | 4                 | 26.6                |
| Clinical Trial      | 0                 | 3                 | 20.0                |
| Observational       | 0                 | 2                 | 13.3                |
However, the only exclusion is recommendation number 16 in Table 2, which was mentioned during interviews with the CCDC senior experts.

**Discussion**

The national guidelines are supposed to be the source of information for practitioners. Therefore, it should reflect the best available evidence. Also the researches of each country should trigger providing evidence for widely used guidelines.

The result of the present study showed that there is just one citation from the country’s researches in the national TB guideline. Despite the existence of references for half of the recommendation, they have not been cited in the guideline, and there were at least four recommendations whose SRs, with strong evidence level, were found in independent search of the literature. On the other hand, most citations were based on body of knowledge from SR and / or narrative reviews, if cited. In most recommendations that had not any cited specific study, the source of decision was internationally recognized guidelines and / or the modifications by panel of the experts, i.e. national TB committee.

Concerning the characteristics of the present study, it should be noted that selection of the recommendations, which Tables 1 and 2, were the most important decisions in taking care of TB patients. However, having quantitative approach is not correct, since there is a high chance that one of them has so many particulars which can be distinguished from the others. For instance, the 26th recommendation shows the combination of five drugs alongside their dosages. This recommendation has many alternatives not only on drugs types but also in their dosages. Therefore, it might not be fair to look at many recommendations as single decision in a quantitative form.

The weak point that can be accounted for this study is the selection of recommendations. Although, being very essential in management of TB patients, recommendations could be considered as very clear decisions that do not need further investigations to be considered as research priorities. In other words, the answer of such questions is clear enough for research institutions/ researchers. Despite the fact that many decisions have been made by the national TB committee, being considered as expert opinion, it seems these need to be quoted by national researches and answered by more strict evidence based manner.

There are several frameworks for impact assessment of researches (19). The main concern is that with the evolution which has been happening in the production and utilization of research knowledge, the framework for impact assessment of knowledge should be changed (20). The most widely used framework is the payback which introduced five areas to be assessed as the possible impact of research. Among them, the first is publication and citation. However, the other one is informing policy making with the exact example of using primary researches in the practice guidelines (21).

It is estimated that 25% of recommendations in 15 major guidelines in UK relied on researches which had been done in the UK. This is in contrast with the share of biomedical evidence that shows just 10% of biomedical citations were from the UK (22). The present study has followed the same approach as the later study. However, there is quite obvious bibliometric problem with this kind of assessment. It means that the development of the present national guideline was not in line with international initiatives (23). It is due to the fact that the country is still in the preliminary steps of evidence based decision making arena (24). There are several barriers on development and implementation of the guidelines and among them the lack of stewardship is remarkable (25). On the other hand, the new movements at the country are promising for development of necessary infrastructure for guideline development (26-28). The other issue which must be addressed is the evidence level of the WHO guidelines that was the main source of the information for the Iran’s national TB guideline. It is naïve to consider the lowest evidence level, i.e. 4, for these guidelines. However, this would be the result of weakness in presenting citation in these guidelines and also the standard tool which was used to assess the evidence levels.
The present study suggests three important suggestions. The first is that by finding only one recommendation which was based on the national researches we can conclude that there-defining research priority setting in TB is an urgent need. Just in this case the national researches can have responsiveness to the operational needs of the control program. This issue of priority setting was recognized as one of the main barriers of evidence-based decision making as a general concern in Iran (29). Another finding of the study was not having citation for almost half of the recommendations. This brings the second suggestion that the national program needs to follow the standard procedures for guideline development. Hopefully, some infrastructures are on the ground (30, 31) and can be used. The third suggestion is based on the fact that, even with the resources devoted to research and publication in Iran, still there a wide gap between research universe and the practice. The issue of knowledge translation needs to be more operationalized in the present situation of the country, especially with the rapid pace of scientific productivity in Iran.

Conclusion

The share of research knowledge in development of national TB guideline was significant. It gives two directions; to review the research priority setting in this field and need for strengthening the quality of guideline adaptation and/or development.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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