

## Quality of tuberculosis guidelines: urgent need for improvement

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### SUMMARY

**SETTING:** Clinical practice guidelines have been developed for many disorders, but their quality varies greatly and does not always reach an acceptable standard. No evaluation of clinical practice guidelines on tuberculosis (TB) has been carried out to date.

**OBJECTIVE:** To identify and assess the quality of TB guidelines.

**DESIGN:** We systematically searched documents published from January 1998 to May 2008 in Medline and the Turning Research into Practice (TRIP) database and in clearing houses and on websites of scientific societies. Three appraisers evaluated each guideline using the AGREE (Appraisal of Guidelines, Research and Evaluation) instrument. A standardised score was calculated separately for each of the six domains.

**RESULTS:** A total of 36 guidelines for TB were identi-

fied, and after appraisal good overall agreement was observed among the three evaluators. Results revealed that quality was acceptable in two domains but had serious shortcomings in the other four. A slight improvement in quality was observed in documents published in 2005 or later. After global assessment, 18 documents were considered 'recommended with provisos' and only two documents 'strongly recommended' for use in clinical practice.

**CONCLUSION:** The methodological quality of TB guidelines was disappointingly low. All guideline developers should adhere to instruments such as AGREE to produce documents of optimal quality.

**KEY WORDS:** tuberculosis; AGREE instrument; guidelines

TUBERCULOSIS (TB) currently kills about 1.5 million people each year and remains a leading cause of death worldwide, although TB control is a model of evidence-based public health practice and despite the availability of effective and inexpensive treatment.<sup>1</sup> Although TB incidence has been steadily decreasing in the last 5 years, paradoxically, the global burden of TB has increased, mainly due to demographic growth. Disease control therefore remains a global challenge.<sup>1,2</sup> Numerous health organisations and scientific societies have produced clinical practice guidelines (CPGs) aimed at setting management standards for TB, both at the global and at the local levels. Despite such efforts, global TB control interventions are hindered by the enormous variability in the standards of care.

The United States Institute of Medicine (IOM) defines CPGs as 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances',

and their aim is to reduce variability in care. Moreover, a CPG should be based on the best available scientific evidence so as to facilitate consistent and effective medical practice. A CPG is therefore potentially an instrument to link research and clinical practice.<sup>3</sup>

The number of such documents has grown tremendously in recent years, raising concerns about possible duplication of efforts and the risk of inconsistent and low-quality recommendations.<sup>4–6</sup> Several recent studies have shown that the methodological quality of published CPGs for different medical topics is highly variable and that there is considerable room for improvement.<sup>7–12</sup>

An international group of researchers—the Appraisal of Guidelines, Research and Evaluation (AGREE) Collaboration—has developed a tool to standardise the development of CPGs. AGREE is a systematic framework for assessing the methodological quality of CPGs and includes the process of

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Article submitted 6 October 2009. Final version accepted 5 February 2010.

development as well as the quality of reporting. The AGREE instrument has been translated into many languages, endorsed by several organisations and is the only validated and reliable appraisal tool available for this kind of document. It uses a numerical scale that allows a quantitative comparison of CPGs.<sup>13–15</sup>

To our knowledge, the standard of CPGs for TB management has not yet been assessed. The present study was conducted to evaluate the quality of CPGs on this topic.

## METHODS

### Identification of CPGs

We performed a literature search in the Medline database combining the term ‘tuberculosis’ and a filter to identify guidance documents (Practice Guideline [pt] OR Guideline [pt] OR guideline\*[ti] OR consensus [ti]). We also searched the Turning Research into Practice (TRIP) database, clearinghouses, prominent CPG developer groups and scientific societies using a simple search strategy or by searching their websites. We also used the Google and Pubgle search engines. The search was limited to documents in English or Spanish published between 1 January 1998 and 30 May 2008. We entered the results from the literature search into a bibliographic database and eliminated duplicates.

### Selection of CPGs

We included documents that contained explicit recommendations on diagnosis, treatment, prevention or control of TB patients at any age. If several versions of the same document were available, only the latest version was selected. We excluded documents that focused on the management of TB exclusively in penitentiary centres, during aerial or marine trips, organisation of care at health centres or laboratory facilities, or migration control at customs points. We also excluded documents that contained recommendations reached through consensus, documents such as systematic reviews, clinical trials, editorials and letters, and documents that were not available in full text format.

### Evaluation of CPGs

We evaluated the selected CPGs with the AGREE instrument. This instrument contains 23 items categorised in six domains: 1) scope and purpose, 2) stakeholder involvement, 3) rigour of development, 4) clarity and presentation, 5) applicability and 6) editorial independence (Table 1). A Likert scale of four categories, ranging from ‘strongly agree’ (4 points) to ‘strongly disagree’ (1 point), was used to evaluate each item. Three investigators independently appraised all the documents. The overall assessment of each CPG was reached by consensus after resolving any disagreements between appraisers.

The standardised quality score for each domain is

**Table 1** AGREE instrument

Scope and purpose (items 1–3):	
1	The overall objective(s) of the guideline is (are) specifically described
2	The clinical question(s) covered by the guideline is (are) specifically described
3	The patients to whom the guideline is meant to apply are specifically described
Stakeholder involvement (items 4–7):	
4	The guideline development group includes individuals from all the relevant professional groups
5	Patient views and preferences have been sought
6	The target users of the guideline are clearly defined
7	The guideline has been piloted among target users
Rigour of development (items 8–14):	
8	Systematic methods were used to search for evidence
9	The criteria for selecting the evidence are clearly described
10	The methods used for formulating the recommendations are clearly described
11	The health benefits, side effects and risks have been considered in formulating the recommendations
12	There is an explicit link between the recommendations and the supporting evidence
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided
Clarity and presentation (items 15–18):	
15	The recommendations are specific and unambiguous
16	The different options for management of the condition are clearly presented
17	Key recommendations are easily identifiable
18	The guideline is supported by tools for application
Applicability (items 19–21):	
19	The potential organisational barriers in applying the recommendations have been discussed
20	The potential cost implications of applying the recommendations have been considered
21	The guideline presents key review criteria for monitoring and/or audit purposes
Editorial independence (items 22–23):	
22	The guideline is editorially independent from the funding body
23	Conflicts of interest of guideline development members have been recorded

AGREE = Appraisal of Guidelines, Research and Evaluation.

obtained by adding all the scores of the individual items within this domain using the following formula:

$$\frac{\text{Obtained score} - \text{minimum possible score}}{\text{Maximal possible score} - \text{minimum possible score}} \times 100.$$

The maximum score for each domain is the number of items multiplied by the number of appraisers and then by 4, whereas the minimum score is the number of items multiplied by the number of appraisers and then by 1. The standardised score for each domain ranges between 0 and 100%.

The AGREE instrument includes a final step that provides guidance about how to make an overall assessment concerning the usefulness of the CPG. Each CPG can then be classified as ‘strongly recommended’ (the majority of domain scores are above 60%), ‘recommended with provisos or alterations’ (most domain scores are between 30% and 60%) or ‘not recommended’ (most domain scores are below 30%).<sup>13</sup>

### Statistic analyses

Descriptive statistics (mean, median, maximum, minimum and 95% confidence intervals [CI]) were calculated for each domain score for each CPG. Categorical variables were calculated with number of cases and corresponding percentages. We calculated the intraclass correlation coefficient (ICC) with a 95% CI as measure of appraiser agreement. Data were analysed using SPSS (15.0) for Windows (Statistical Package for the Social Sciences, Chicago, IL, USA).

### Ethical issues

As this was a retrospective observational study, ethical approval was not required.

## RESULTS

### Literature search

Of an initial search that yielded a total of 491 citations, only 241 were considered related references. An additional 183 references were excluded after reading the titles and the summaries and excluding old versions of more recent documents. This left 58 documents. A further 22 documents were eliminated after reading the full text version. A final total of 36 CPGs were appraised for methodological quality and included in the analysis (Figure 1).

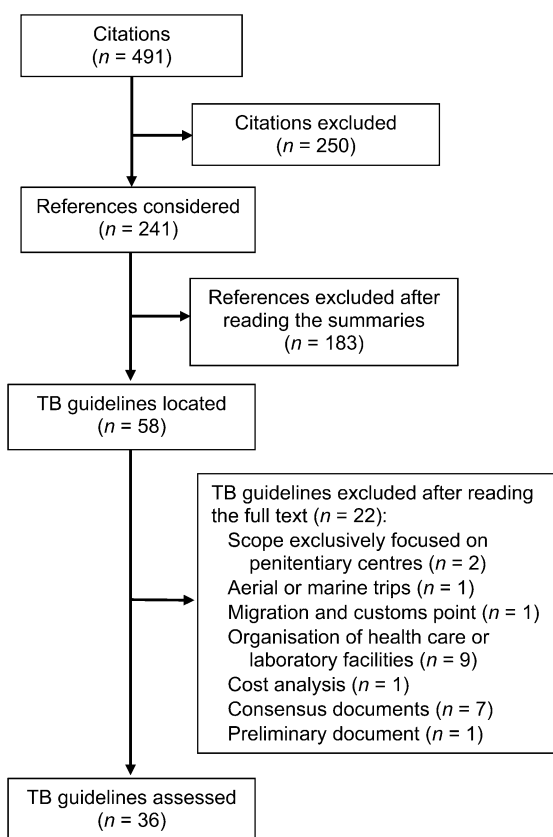


Figure 1 Flow chart. TB = tuberculosis.

Of the 36 CPGs included (Appendix),\* 14 were developed in the United States or United Kingdom. Other countries that developed at least one CPG were Spain, the Philippines, Australia, Canada, South Africa and New Zealand. The remaining documents were developed by international health organisations and agencies, such as the World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (The Union), the Pan-American Health Organization (PAHO), the Tuberculosis Coalition for Technical Assistance (TBCTA) and the International Council of Nurses (ICN). Most of the CPGs in TB management targeted both adults and children or adolescents. In 11 (30%) guidelines, the target population was exclusively adults, and three (8%) targeted only children (Table 2).

### Appraisal of guidelines

We obtained an overall ICC value of agreement between appraisers of 0.84 (95% CI 0.75–0.91), indicating high internal consistency. We did not therefore calculate ICC values for each domain. Table 3 shows the results for each CPG concerning the standardised mean of the quality score per domain and an overall descriptive assessment. Figure 2 gives the mean result for each domain for the total CPGs.

### Scope and purpose (Domain 1)

This domain contains the overall objective; it details the clinical questions and describes the target population. The mean score for this domain was 70% (range 22–100), with eight (22%) CPGs scoring below 50%.

### Stakeholder involvement (Domain 2)

This domain refers to the people involved in the development process. It states whether patient perspectives were considered, describes target users and defines whether or not the CPG was piloted among them. The mean score for this domain was 27% (range 3–86). Most documents (92%) scored below 50%, and all but one failed to show any evidence that patient perspectives were considered during the development process.

### Rigour of development (Domain 3)

This domain relates to the process used to gather and synthesise the evidence, the methods used to formulate the recommendations, and the methods followed to review and update these. The mean score in this domain was 24% (range 6–95). One third of the documents scored below 50%.

### Clarity of presentation (Domain 4)

This domain assesses whether recommendations were specific and unambiguous, easy to find, and covered

\* Appendix available in the online version of this article at <http://www.ingentaconnect.com/content/ijutld/ijutld/2010/00000014/00000008/art00020>

**Table 2** Characteristics of CPGs on tuberculosis management

Guideline*	Country	Organisation	Year of publication	Population
1	International	International Union Against Tuberculosis and Lung Disease	2007	Adults/children
2	United Kingdom	Department of Health/Health Protection Division/General Health Protection	2007	Adults
3	Canada	Public Health Agency of Canada and The Lung Association	2007	Adults/children
4	International	WHO	2007	Adults/adolescents
5	International	WHO	2007	Adults/adolescents
6	United Kingdom	Royal College of Physicians	2006	Adults/children
7	International	WHO	2006	Adults/children
8	Spain	Andalusian Society of Infectious Diseases	2006	Adults
9	The Philippines	Philippine Society of Microbiology and Infectious Diseases	2006	Adults
10	The Philippines	Philippine Rheumatology Association	2006	Adults
11	USA	American College of Chest Physicians	2006	Adults
12	International	WHO	2006	Children
13	International	Tuberculosis Coalition for Technical Assistance	2006	Adults/children
14	USA	National Tuberculosis Controllers Association and CDC	2005	Adults/children
15	United Kingdom	British Thoracic Society	2005	Adults
16	USA	American Thoracic Society, CDC and the Infectious Diseases Society of America	2005	Adults/children
17	USA	Department of Health and Human Services, CDC	2005	Adults
18	United Kingdom	British HIV Association	2005	Adults
19	European	European Association of Urology	2005	Adults/children
20	USA	Georgia Department of Human Resources	2005	Adults/children
21	International	WHO	2004	Adults/children
22	USA	Society for Healthcare Epidemiology of America	2004	Older Adults
23	South Africa	South African Department of Health	2004	Adults/children
24	International	International Council of Nurses	2004	Adults
25	USA	American Academy of Pediatrics	2004	Children
26	New Zealand	Ministry of Health	2003	Adults/children
27	USA	American Thoracic Society, CDC and Infectious Diseases Society of America	2003	Adults/children
28	USA	California Department of Health Service, California Tuberculosis Controllers Association	2003	Adults/children
29	International	Pan-American Health Organization	2003	Adults/children
30	International	WHO	2003	Adults/children
31	Spain	Fisterra	2003	Adults/children
32	Australia	Victorian Government Department of Human Service	2002	Adults/children
33	Australia	Australasian Society for Infectious Diseases and Paediatric Respiratory Group	2000	Children
34	International	WHO	1999	Adults
35	USA	US Department of Health and Human Services, CDC	1998	Adults/children
36	Spain	Spanish Society of Infectious Diseases and Clinical Microbiology	Unknown	Adults/children

\*References for the CPGs are available in the online version of this article at <http://www.ingentaconnect.com/content/iatld/ijtld/2010/00000014/00000008/art00020>

CPG = Clinical Practice Guidelines; WHO = World Health Organization; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus.

the corresponding options for disease management according to its scope, and also whether implementation or dissemination strategies were considered. The mean score was 56% (range 28–97) and 13 CPGs (36%) scored below 50%. Only two (6%) guidelines did not give specific or clear recommendations.

#### *Applicability (Domain 5)*

This domain refers to the potential implications in organisational aspects, the cost of implementing the recommendations, and measures of adherence. The mean score in this domain was 27% (range 0–93). Thirty CPGs (83%) scored below 50% and did not consider the potential costs in the implementation of the recommendations.

#### *Editorial independence (Domain 6)*

This domain refers to the sources of external funding and the possible conflicts of interest among the devel-

opment group. The mean score was 23% (range 0–100). Twenty-nine CPGs (81%) scored below 50% and seven (19%) did not include an explicit statement concerning conflict of interest.

#### *Overall assessment*

Only two CPGs (6%) were 'strongly recommended' for use in clinical practice, 18 (50%) were 'recommended with provisos or alterations' and the remaining 16 (44%) were deemed 'not recommended'.

#### *Subgroup analysis of CPGs published during 2005 or afterwards*

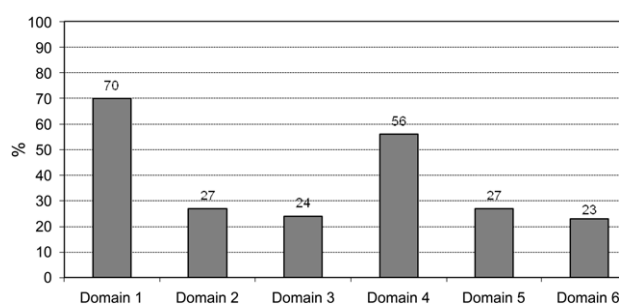
Of the 36 CPGs, 20 were published in 2005 or later (Appendix, 1–20). Although we did not attempt to statistically compare each domain score between groups, all domains performed slightly better after 2005. Furthermore, fewer CPGs scored below 50% in all of the domains after this date (Table 4).

**Table 3** Mean standardised score per domain and overall assessment results for each CPG

Guideline*	Mean standardised score, %						Overall recommendation
	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity and presentation	Applicability	Editorial independence	
1	63	28	19	42	56	22	Recommended with provisos
2	100	22	11	50	7	0	Not recommended
3	48	36	19	67	41	28	Recommended with provisos
4	63	14	8	69	22	11	Not recommended
5	85	47	48	75	52	33	Recommended with provisos
6	100	86	95	97	93	100	Strongly recommended
7	81	36	17	56	37	11	Recommended with provisos
8	41	17	27	44	11	6	Not recommended
9	93	50	51	72	30	6	Recommended with provisos
10	81	28	38	69	26	11	Recommended with provisos
11	59	3	21	56	7	6	Not recommended
12	81	19	14	50	11	11	Recommended with provisos
13	93	56	33	78	37	17	Recommended with provisos
14	74	25	13	58	56	83	Recommended with provisos
15	96	39	63	69	33	61	Strongly recommended
16	89	42	32	64	59	67	Recommended with provisos
17	81	28	19	47	26	72	Recommended with provisos
18	85	25	16	42	4	11	Not recommended
19	37	6	17	44	0	11	Not recommended
20	44	11	14	28	11	11	Not recommended
21	78	31	17	42	22	11	Recommended with provisos
22	63	44	24	72	4	11	Recommended with provisos
23	74	8	8	56	19	11	Not recommended
24	63	19	14	44	22	0	Not recommended
25	78	19	19	47	22	17	Recommended with provisos
26	52	14	32	58	52	11	Recommended with provisos
27	74	19	32	67	30	61	Recommended with provisos
28	48	6	19	47	15	17	Not recommended
29	41	14	6	31	30	11	Not recommended
30	89	33	21	50	41	22	Recommended with provisos
31	26	11	11	50	11	56	Not recommended
32	74	42	14	50	22	6	Not recommended
33	67	14	17	69	0	11	Not recommended
34	81	28	13	47	26	17	Not recommended
35	96	31	37	72	22	6	Recommended with provisos
36	22	6	13	39	0	0	Not recommended

\*References for the CPGs are available in the online version of this article at <http://www.ingentaconnect.com/content/iatid/ijtld/2010/00000014/00000008/art00020>

CPG = Clinical Practice Guideline.



**Figure 2** Mean quality score for each domain of the AGREE instrument for the total CPGs. Domain 1 = scope and purpose; Domain 2 = stakeholder involvement; Domain 3 = rigor of development; Domain 4 = clarity and presentation; Domain 5 = applicability; Domain 6 = editorial independence; AGREE = Appraisal of Guidelines, Research and Evaluation; CPGs = Clinical Practice Guidelines.

**Table 4** AGREE score analysis for all documents and the most recent documents

Domains	All CPGs		Recent CPGs*	
	Standardised score <sup>†</sup> %	Low quality <sup>‡</sup> n (%)	Standardised score <sup>†</sup> %	Low quality <sup>‡</sup> n (%)
Scope and purpose	70	8 (22)	74	4 (20)
Stakeholder involvement	27	33 (92)	31	17 (85)
Rigour of development	24	33 (92)	29	17 (85)
Clarity and presentation	56	13 (36)	59	6 (30)
Applicability	27	30 (83)	30	15 (75)
Editorial independence	23	29 (81)	29	15 (75)

\*Published in or after 2005.

<sup>†</sup>Mean standardised score value.

<sup>‡</sup>CPGs scoring below 50.

AGREE = Appraisal of Guidelines, Research and Evaluation; CPGs = Clinical Practice Guidelines.

## DISCUSSION

Our review of TB management CPGs showed that the overall methodological quality based on the AGREE instrument evaluation was disappointingly low. Four domains, 'stakeholder involvement', 'rigour of development', 'applicability' and 'editorial independence' had serious shortcomings. Domains concerning 'scope and purpose' and 'clarity of presentation' were more precisely reported.

'Rigour of development' may be considered the most important domain as it refers to methodological aspects concerning how the recommendations were developed. Most of the guidelines did not describe the literature search and selection methods, and they were ambiguous regarding how the evidence was appraised and whether or not the recommendations were truly evidence-based. Poor performance in this domain was partly due to poor performance in the external review and updating process items. As evidence may be interpreted in different ways by different CPG developers, guideline users need to know what evidence was used to support each recommendation. They also need to know what other factors were taken into account when grading recommendations. Rigorous and explicit systems for appraising the evidence and grading of recommendations, such as GRADE (Grading of Recommendations Assessment, Development and Evaluation), have recently been adopted by institutions such as the WHO and the Cochrane Collaboration, and they may help to gradually increase the quality of this key domain in guideline development.<sup>16</sup>

'Stakeholder involvement' reflects the extent to which CPGs include the views of their intended users, including patients. It is considered increasingly important that patient perspectives, expectations and preferences about health care are considered during the development process. Only one of the 36 CPGs studied provided reliable information about the involvement of patients or their representatives (Appendix, 6).

More surprising was the poor performance in the domain scores for 'editorial independence'. Information about potential conflicts of interest of authors was scarce and some guidelines did not even mention this, although 15 of the 36 CPGs were developed by independent international health organisations. Previously published studies have shown that many CPGs failed to provide information about conflicts of interest, although many authors had received economic support from pharmaceutical companies.<sup>17</sup> As conflicts of interest are the most frequent source of bias in CPGs, any economic tie with the industry or even funding from the public sector should be clearly stated. It has also been suggested that individuals who receive benefits from a company whose products are discussed should not participate in the decision-making process.<sup>6</sup> Low performance was also found in the 'applicability' domain. However, this could be explained by the fact that as international organisations target many different countries, they do

not state potential barriers to CPG implementation for each specific circumstance.

Only two CPGs were rated as 'strongly recommended'. Both were developed in the United Kingdom. These two documents had the highest scores in 'rigour of development'. One was published by the Royal College of Physicians (2006) and scored above 85% in all domains (Appendix, 6). The other document was published by the British Thoracic Society (2005) and had some flaws in 'stakeholder involvement' and 'applicability' (Appendix, 15).

We also analysed the quality of CPGs published during or after the year 2005. We chose this cut-off point as the AGREE Collaboration published their assessment tool in 2003.<sup>15</sup> Any CPG that was completed, for example, in 2005, could therefore have followed these standards. We detected a small, and at best moderate, improvement in the latter years.

There are several explanations for the generally poor performance observed in our results. The under-reporting in many CPGs could have minimised quality, but this seems unlikely, as many of these documents were over 100 pages long and therefore facilitated a full report of the developmental process. Another explanation could be that general principles of TB management have long been established and the scientific evidence has rarely been re-appraised. As a result, recommendations might be made on the basis of a less formal process than is currently required.

Our study has several limitations. As it was observational in design and thus essentially exploratory, we did not establish causal relationships between poor performance and CPG characteristics such as organisation, country or scientific society involvement. Another limitation may be related to the AGREE instrument, which has the drawback that it emphasises the extent of reporting rather than determining the potential impact of recommendations on patient outcome.<sup>15</sup> Finally, the low number of documents included in the analysis should also be considered. Despite these limitations, critical appraisal was reliable and the results obtained are consistent with previous publications.<sup>7-11</sup> Many CPGs on TB management were developed by reputable international health organisations, and it is widely accepted that adherence to these standards has produced global benefits in terms of disease control.

Our findings show that much remains to be done to reach excellence in the area of CPGs for TB. Adherence to instruments such as the AGREE tool during guideline development may improve the quality of these documents.

### Acknowledgement

CRG is a PhD candidate at the Paediatrics, Obstetrics and Gynaecology, and Preventive Medicine Department, Universidad Autónoma de Barcelona, Spain.

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## RÉSUMÉ

**CONTEXTE :** On a élaboré des directives de pratique clinique pour de nombreuses affections, mais leur qualité est très variable et n'atteint pas toujours des standards acceptables. Jusqu'à ce jour, on n'a mené aucune évaluation des directives de pratique clinique sur la tuberculose (TB).

**OBJECTIF :** Identifier et évaluer la qualité des directives en matière de TB.

**SCHEMA :** Nous avons recherché de manière systématique les documents publiés entre janvier 1998 et mai 2008 dans les bases de données Medline et TRIP ainsi que sur les sites web des institutions et sociétés scientifiques. Trois évaluateurs ont examiné chaque directive en utilisant comme instrument AGREE (Appraisal of Guidelines, Research and Evaluation). Un score standardisé a été calculé séparément dans chacun de six domaines.

**RÉSULTATS :** On a identifié au total 36 directives pour la TB, et après discussion on a observé un bon accord global entre les trois évaluateurs. Les résultats ont révélé que la qualité était acceptable dans deux domaines, mais avait des déficiences sérieuses dans les quatre autres. Une légère amélioration de la qualité a été observée dans les documents publiés en 2005 ou plus tard. Après évaluation globale, 18 documents ont été considérés comme « recommandés sous condition » et deux documents seulement considérés comme « fortement recommandés » pour utilisation en pratique clinique.

**CONCLUSION :** La qualité méthodologique des directives en matière de la TB est considérée comme faible et décevante. Tous les concepteurs de directives devraient respecter les instruments comme AGREE pour élaborer des documents d'une qualité optimale.

## RESUMEN

**MARCA DE REFERENCIA:** Aunque existen guías de práctica clínica para muchos trastornos de salud, su calidad es muy variable y no siempre alcanza un mínimo aceptable. Hasta la fecha no se ha realizado ninguna evaluación de guías de práctica clínica sobre tuberculosis (TB).

**OBJETIVO:** Identificar y evaluar la calidad de las guías de práctica clínica sobre TB.

**MÉTODO:** Se realizó una búsqueda sistemática de documentos publicados desde enero de 1998 hasta mayo de 2008 en los bases de datos Medline y TRIP, así como en páginas electrónicas de instituciones y sociedades científicas. Tres revisores evaluaron cada guía mediante el instrumento AGREE (Appraisal of Guidelines, Research and Evaluation). Se calculó la puntuación estandarizada para cada uno de seis dominios.

**RESULTADOS:** Se identificaron y leyeron críticamente un total de 36 guías sobre TB, con un buen acuerdo entre los tres evaluadores. Los resultados mostraron que la calidad de las guías fue aceptable en dos dominios, pero con graves deficiencias en los otros cuatro dominios. Se observó una ligera mejoría en la calidad de los documentos publicados durante y posterior al año 2005. Tras la evaluación de la calidad global, 18 documentos se consideraron como 'recomendados con modificaciones' y solo dos como 'muy recomendados' para su uso en la práctica clínica.

**CONCLUSIÓN:** La calidad metodológica de las guías evaluadas fue baja. Todos los grupos elaboradores de guías deberían incorporar en su proceso de elaboración herramientas como el instrumento AGREE para producir documentos de optima calidad.

## APPENDIX

## Clinical practice guidelines evaluated

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