Meta-analysis of factors related to health services that predict treatment default by tuberculosis patients

Metanálise de fatores relacionados aos serviços de saúde que predizem o abandono de tratamento por pacientes com tuberculose

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Abstract

The identification of factors that predict tuberculosis (TB) treatment default can help control this problem. The current study used a systematic review to investigate associations between TB treatment default and previously studied factors related to health services. Abstracts were searched in the MEDLINE and LILACS databases and in the bibliography of the full texts under evaluation. Studies were included if TB treatment default was evaluated by comparing two or more groups and data could be extracted. A total of 41 studies were included for combining data. It was possible to combine five exposures: "difficult access to health services"; "need for hospitalization"; "training or support for adherence"; "delay in initiating treatment"; "long wait before medical attendance". "Difficult access to health services", "training or support for adherence", and "need for hospitalization" were associated with TB treatment default. All exposures demonstrated heterogeneity, which was only explained in one. Publication bias was only detected for one exposure.

Tuberculosis; Patient Dropouts; Meta-Analysis

Introduction

Tuberculosis (TB) is a highly prevalent disease in the poorest regions of the world and a reemerging problem in the developed countries [1]. Tuberculosis was recognized as a major worldwide emergency in 1993 [2]. The main TB control strategy includes early diagnosis and treatment of individuals with the disease. This strategy allows for control of the sources of infection and blocking the disease [1,2]. The standard TB treatment regimen is effective but is not applied efficiently in most countries. Worldwide, TB treatment default has been estimated at between 1% and 20% [1], but the rate is as high as 60%, 70%, and even 80% in selected populations [3,4,5,6,7].

Considering this situation, since the 1990s the World Health Organization (WHO) has recommended the DOTS strategy (Directly Observed Treatment, Short Course) to be used by all countries as a means to control TB. Although WHO considers direct therapy observation the main key of treatment success, some authors also emphasize that other important features involving lack of patient care by the health team are also related to patient default [8,9].

Different strategies to improve compliance (or to reduce default) have been investigated, and different effects on treatment default have been estimated for TB [10,11] and other diseases [12,13]. Studies on the effects of incentives (cash, bus tokens, etc.) on TB treatment default have shown

the benefits of these approaches [10,14]. Some systematic reviews have demonstrated the benefits of these interventions (mainly incentives) in adherence to treatment regimens for different diseases [12,13,15]. Most of these interventions are considered to be outside the routine activities of health services, but the performance of routine surveillance and control measures appears to be a core feature that is crucial to improve TB patient compliance.

Analysis of causes of TB treatment default shows that patient-related factors are the most frequently evaluated. Health service characteristics have received insufficient attention. Causes of default are likely to be highly heterogeneous, considering different cultures, locations, and populations, disease severity, adverse effects of treatment, and health systems. Such sources of heterogeneity can even influence the results of clinical trials. A systematic review of BCG vaccine clinical trials showed that the latitude of the study location influenced the vaccine's effect [16]. The authors concluded that prevalence of TB infection in different locations could influence the effect of the vaccine.

We conducted a review to identify risk factors for TB treatment default as published in the international literature. The review showed that the most frequently investigated risk factors for TB treatment default could be grouped as: (1) individual patient profile; (2) clinical status or therapy; and (3) health services characteristics. For classification of these exposures, the number of studies arranged in decreasing order were: age, gender, alcoholism, HIV/AIDS, illicit drug use, foreign nationality, illiteracy (or low schooling), unemployment, homelessness, race, income, tobacco use, imprisonment, family support, trust in treatment effectiveness, diabetes, and profession in the patient-related group of exposures; TB clinical manifestations (pulmonary or extrapulmonary), retreatment, positive sputum smear (acid-fast bacillus), prior TB treatment default, short-course therapy, adverse effects of therapy, drug resistance, disease severity, use of steroid therapy, TB case contact, and positive culture in the group related to clinical status or therapy; directly observed treatment, difficult access to health services, incentives (financial or other), "need for hospitalization", "training or support for adherence", "delay in initiating treatment", and "long wait before medical attendance" in the group related to health services.

Given the lack of a summary of current knowledge, this paper specifically addresses the latter group of risk factors: health services characteristics. The evaluation of factors strongly associated with TB treatment default should allow the development of better TB control strategies or optimization of existing strategies.

This study thus aims to identify health services factors associated with TB treatment default and to evaluate the heterogeneity and publication bias of each exposure investigated.

Methods

Two remote databases were used to search for references: MEDLINE (PubMed) and LILACS. The search strategies were constructed according to recommendations found in the literature and based on characteristics such as sensitivity and precision [17]. In MEDLINE, references were collected from July 21, 2004, to July 30, 2004, with the following strategy: *(tuberculosis[Text] OR "tuberculosis" [MeSH Terms] OR "Antitubercular Agents/therapeutic use"[MeSH]) AND ("Patient Dropouts/statistics and numerical data"[MeSH] OR "Patient Compliance/statistics and numerical data"[MeSH] OR adherence[Text] OR Default*[Text])*. This strategy was adapted to the LILACS database in Portuguese and English and used as follows: *(([] (([] (((tubercul$)) or ([MH]"TUBERCULOSE") or ([MH]"ANTITUBERCULOSOS") or ([MH] ("antibióticos antituberculose")))) and ([] (([MH]"DESISTENCIA DO PACIENTE") or ([MH]"PARTICIPACAO DO PACIENTE") or ([MH]"RECUSA DO PACIENTE AO TRATAMENTO") or ([MH]"COOPERACAO DO PACIENTE") or ([] (adesao)) or ([] (aderencia)) or ([] (abandono)))))) or ([] (([] (((tuberculo$)) or ([MH]"TUBERCULOSIS") or ([MH] ("antibiotics, antitubercular")) or ([MH] ("antitubercular agents")))) and ([] (([MH] ("treatment refusal")) or ([MH] ("patient compliance")) or ([MH] ("patient dropouts")) or ([MH] ("patient participation")) or ([] (adherence)) or ([] (default$)) or ([] (compliance))))))) [Words]*.

The original articles found up to this point were used to obtain bibliographical citations for other research not listed in the electronic databases. No hand search was performed to find original articles, nor were authors contacted regarding incomplete data because these strategies were believed to require excessive labor in relation to the expected results. It was not possible to conduct the search strategy in EMBASE, and other databases were not consulted because they were not considered promising in terms of increasing relevant sources of data.

Two blinded reviewers evaluated the abstracts and full texts and performed data extraction. Abstracts were classified as eligible for full text evaluation if the specified objective was to: (i) identify possible associations between any

characteristic and TB treatment default (or compliance), (ii) predict TB treatment default by any factor, (iii) investigate relations between risk factors and TB treatment default, or (iv) calculate frequencies or measures of associations with TB treatment default (or compliance). Abstracts that partially met some of the above-mentioned criteria (objective not clear in the abstract) or were classified differently by the two reviewers were included. Articles that used mainly qualitative methods but also met the criteria were included for full text evaluation.

The full text articles were considered eligible for data extraction if they: (a) were based on original research; (b) included a quantitative analysis; (c) had group comparisons (or compared subgroups) and measures of association were calculated or could be calculated; and (d) had all data available. Also included were articles that studied factors related to TB prophylaxis. Articles that only presented summaries of meetings or congresses were excluded. During this process the reviewers convened to resolve disagreements on abstracts and full text evaluation and extracted data.

No restrictions due to different populations (e.g., children, HIV+ individuals, miners, indigenous peoples, prison inmates, etc.) were made in selecting the abstracts or full text articles. All study designs were initially included, but during the full text evaluation only four designs were selected: cohort, intervention, case-control, and survey.

Abstracts in English, Spanish, and Portuguese were evaluated. Full texts were searched in all languages if the abstracts were selected for full text evaluation. The reviewers read full texts in English, Spanish, and Portuguese, and texts in French and Japanese were translated into Portuguese for evaluation and data extraction.

The original texts that were evaluated presented different definitions of the outcome (TB treatment default) such as: (a) a patient that missed medical appointments or therapy for at least 60 days; (b) use of doses lower than prescribed (e.g., 85%); (c) incomplete number of tablets consumed by the end of treatment time; (d) incomplete duration of treatment (e.g., six months); and (e) no definition of treatment default. All definitions were included and fitted as a covariate in meta-regression to explain heterogeneity.

In the current article, we excluded the original studies that did not show the result of exposures that could be grouped as "related to health services". Exposures grouped here were: (a) difficult access to health care (time or distance to health units); (b) "need for hospitalization"; (c) training for adherence (peer training for adherence, reception groups, counseling by health professionals); (d) delay in initiating treatment (time between diagnosis and beginning of treatment); and (e) waiting time before medical attendance. DOTS and incentives (cash, bus tokens, etc.) as strategies to improve compliance had been studied in previous systematic reviews [10, 11] and were excluded.

Exposures were considered as defined by the authors of the original articles. Most of the original articles either did not define the exposure or the reviewers decided that different proxies were being used to express the same idea. The quality of this aspect of data collection may have been compromised because most of the studies used secondary data.

Specific forms were designed for data extraction. For each study design, a form was developed considering the data specificity. Four models were then tested until a final model could be used for each design: (1) cohort, before and later, quasi-experiments; (2) interventions; (3) case-control; and (4) surveys.

Data were keyed in twice by two independent processors using the free-domain software Epidata (Epidata Association, Odense, Denmark). The two data files were compared, and discrepancies were resolved by consulting the original forms. Data analysis used Stata version 9.1 (Stata Corp., College Station, USA), with user-written extensions specific for meta-analysis. Summary estimates were pooled using the random effects model [18], and the weight ascribed to each estimate was calculated using the Mantel-Haenszel method. We chose odds ratio (OR) as the measure of association, because most exposures were evaluated through case-control studies. For exposures not investigated by case-control studies, we chose risk ratio. Every pooled estimate for each exposure was stratified by study design.

Publication bias was explored in all exposures with the funnel graph (Begg) and Egger test [19,20].

Heterogeneity was explored with the I^2 test [21,22]. We considered I^2 values greater than 50% as indicating presence of heterogeneity. To evaluate possible explanations for heterogeneity, we fitted a linear meta-regression model with some characteristics from the original studies as covariates. The Restricted Maximum Likelihood method with the Knapp & Hartung test was used [23] to estimate p values for each covariate.

The covariates evaluated by meta-regression in all the exposures were: specificity of the concept of default (without definition; more than 60 days of treatment interruption or less than 85% of the prescribed doses); reduction of the exposure

concept (appropriate, less appropriate, not appropriate, or without information, by consensus among the reviewers); population default rates (continuous – calculated as the weighted arithmetic mean of the default rates for each exposure studied or informed for case-control); place of study (Latin America, North America, Europe, Africa, Asia or Australia, Middle East); number of factors studied in the original studies as possibly associated with default (continuous); considerations of adverse effects (appropriate, less appropriate, not appropriate, or without information, by consensus among the reviewers)l; submission to an IRB or institutional review board (yes, no, or not reported); year of publication (continuous); study design (cohort, intervention, case-control, and survey); and proportion of males in the sample (continuous).

Results

The abstract search resulted in 808 references. One hundred and twenty eight abstracts were found in LILACS and 680 in MEDLINE (PubMed). Of these, 298 were selected for full text retrieval (51 LILACS and PubMed 247), while eight abstracts were found in both databases. Full texts from 13 of 290 selected abstracts were not found, and four were not included because they were written in languages that we were not able to have translated (one article in Danish, one in Chinese, and two in Dutch). Among the abstracts found by electronic search, 273 were selected for full text evaluation. Another 88 abstracts retrieved by bibliographical citation were also selected. The reviewers finally evaluated 361 full texts of published articles (Figure 1).

After evaluation of these full texts, 169 were excluded from the meta-analysis for the following reasons: 12 were basically qualitative studies, 37 were considered reviews of TB treatment default, and 120 did not meet the data extraction criteria. In 192 original articles evaluated, approximately 100 factors investigated for association with TB treatment default were identified. The majority of these factors could be grouped in the individual patient profile group.

This paper does not address all the risk factors studied in our project, but focuses on health services characteristics. Thus, 131 articles were not considered in this analysis because they did not study any factor that could be grouped as "related to health services". Another 20 were excluded because they studied only DOTS or incentives, which were studied in previous systematic reviews [10,11]. The 41 remaining studies were included in this analysis.

Table 1 presents some characteristics of the studies included in this meta-analysis: author, year of publication, country where the research was conducted, study design, definition of TB treatment default (criteria), default rate in the sample or in the base population (in case-control design), number of individuals in the sample, and exposures extracted from original studies.

In Table 1, several cells have no information. The table's data include 22 cohort studies, nine interventions, eight case-controls, and two surveys. Considering the definition of default, the empty cells show that no information was available in 26% of the studies, and 43% of the papers did not describe the sample's gender distribution. Of these 41 studies, many documented different categories of age distributions, but only 12 (29%) documented the average (or median) age of the sample. Only one of the nine interventions and none of the 22 cohort studies recorded the mean follow-up time. Thirty-four of 41 studies failed to specify whether the study had been submitted to an IRB. Two of eight case-control studies failed to document the default rate in the base population.

Six of these studies were performed in United States, six in Brazil, four in Malaysia, three in Ethiopia, two each in Spain, Mexico, Nigeria, Pakistan, and Thailand, and one each in other countries.

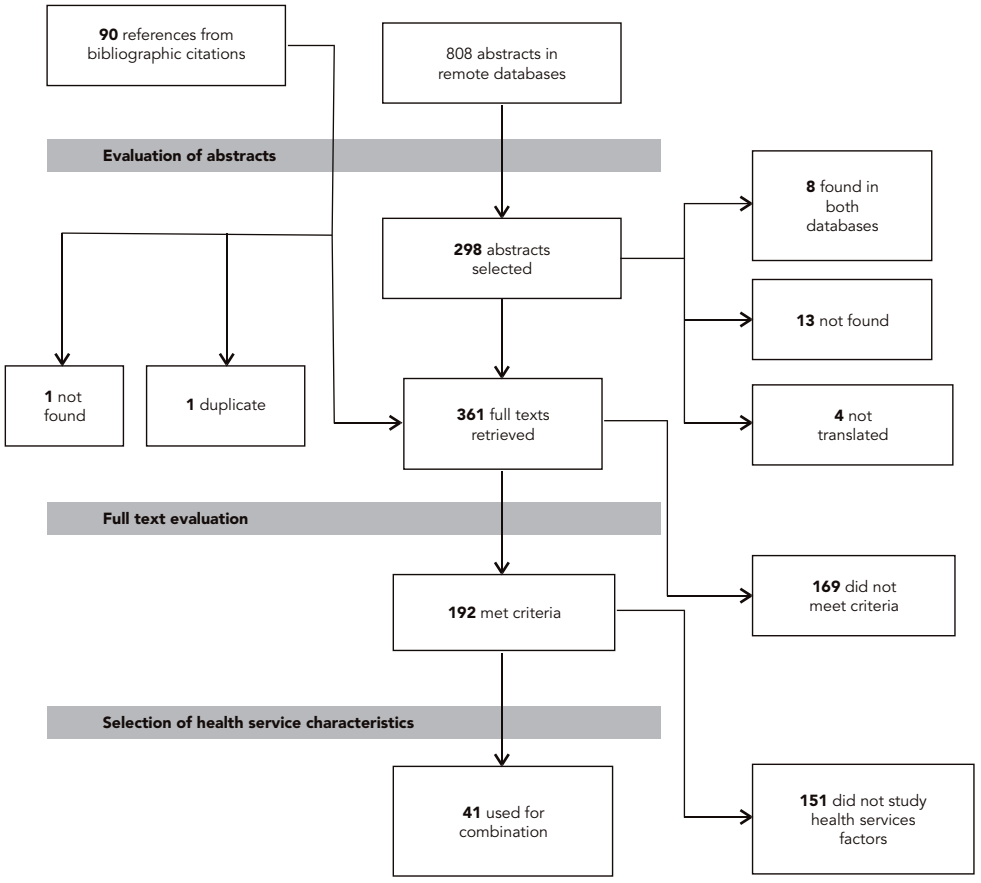
As noted earlier, 61 original studies evaluated exposures related to health services characteristics, therefore fewer than the 100 articles on factors related to individual patients. This group also showed many factors that were published in only one article, and it was thus impossible to extract and combine them, namely: cash deposit, strategies for retrieving missing patients (studied in a previous systematic review, but not only for TB treatment) [13], location of health care, blood pressure measurement (yes/no), weight measurement (yes/no), good physician-patient relationship, treatment by professionals trained in TB care, satisfaction with care, and incomplete answers to patients' questions, among many others.

Although this meta-analysis studied exposures using intervention designs, the exposures "need for hospitalization" and "delay in initiating treatment" were classified as observational studies, because these exposures were not experimental and allocation of groups was not random.

We detected an association with TB treatment default in two out of five factors (Table 2), namely "difficult access to health services" and "training or support for adherence". A third exposure, "need for hospitalization", showed an association after analysis of heterogeneity.

Figure 1

Stepwise demonstration of abstracts and full texts evaluation.



"Difficult access to health services" was studied with several different operational approaches, such as time from patient's residence to the health unit, number of buses taken to reach health unit, living in an area with more versus fewer health units (i.e., urban versus rural areas), and treatment at a local health unit versus in a referral hospital in a different area. A total of 19 studies evaluated this exposure (Table 2). Evaluation of this exposure resulted in OR = 1.71. The cohort design studies showed a pooled estimate with a positive association and the highest influence in the total pooled estimate (for all study designs). Estimates from the other designs gave inconclusive results.

One of the cohort studies had a sample of more than 20,000 subjects (Table 1) and showed a positive result (Table 2). Three studies showed associations in the opposite direction (one each, cohort, case-control, and survey), and six showed no evidence of association (four cohorts and two case-controls). The rest of the studies (seven cohorts, two case-controls, and one survey) showed a positive association. However, heterogeneity was high even among those showing a positive association (Table 2).

The exposure "training or support for adherence" was studied in 11 studies, nine of which were trials. Training for adherence mainly involved peer training, defined as an individual with a prior history of TB providing advice to patients currently under treatment. Peers were usually from the same culture, thus facilitating contacts and exchange of experience through communication with a social worker or other health professional who contacted patients reg-

Table 1

Study characteristics: lead author, year of publication, country, design, default criterion, default rate, proportion of males in sample, sample size, exposures.

Lead author	Year	Country	Design	Default criteria *			Default rate (%)	Males (%)	N	Risk factor
				a	b	c				
Cassels [32]	1982	Tibet	Cohort	60			51.54		247	Access to health unit; male gender
Armstrong [33]	1984	Zimbabwe	Cohort				41.38	75.00	290	Unemployment; extra-pulmonary TB; need for hospitalization
Buri [34]	1985	Thailand	Cohort	120			13.47		160	Alcoholism; access to health unit
van der Werf [35]	1990	Ghana	Cohort				49.41	65.07	569	Male gender; access to health unit
Irurzun [36]	1990	Argentina	Survey	61			66.16		195	Access to health unit; need for hospitalization; information about TB; delay in initiating treatment
Chuah [37]	1991	Malaysia	Cohort				45.85		219	Male gender; extra-pulmonary TB; delay in initiating treatment; need for hospitalization
Barnwell [38]	1992	USA	Intervention			100.00	60.00		40	Training for adherence
Oviawe [39]	1993	Nigeria	Cohort			100.00	47.95		146	Need for hospitalization
Moralez [40]	1993	Mexico	Cohort	45			41.19	53.00	174	Illiteracy; access to health unit
Demissie [4]	1994	Ethiopia	Case-control	90			81.50	62.20	1,196	Unemployment; male gender; illiteracy; adverse effects; access to health unit; information about TB; cash
Pilote [41]	1996	USA	Intervention				31.32	84.00	161	Incentives; training for adherence
Dick [42]	1997	South Africa	Intervention			75.00	14.55		110	Training for adherence
Comolet [43]	1998	Madagascar	Case-control					68.45	149	Alcoholism; male gender; illiteracy; adverse effects; access to health unit; information about TB
Nuwaha [44]	1999	Uganda	Cohort	60			36.34		1,495	Positive sputum smear; retreatment; male gender; treatment duration; location; need for hospitalization
Liefooghe [45]	1999	Pakistan	Intervention	60			48.95	41.85	1,019	Unemployment; male gender; training for adherence; need for hospitalization; information about TB; delay in initiating treatment
Morrone [46]	1999	Brazil	Cohort				10.67	61.17	1,226	Alcoholism; positive sputum smear; retreatment; male gender illiteracy; DOTS; race; delay in initiating treatment

(continues)

Table 1 (continued)

Lead author	Year	Country	Design	Default criteria *			Default rate (%)	Males (%)	N	Risk factor
				a	b	c				
Liam [47]	1999	Malaysia	Cohort	0			28.05	58.50	114	Foreign nationality; unemployment; male gender; illiteracy; treatment duration; need for hospitalization; positive culture
Natal [9]	1999	Brazil	Case-control	60					171	Previous default; alcoholism; positive sputum smear; unemployment; retreatment; illiteracy; access to health unit; need for hospitalization; information about TB; long wait before receiving care
Borgdorff [48]	2000	Netherlands	Cohort				0.55	59.83	7,529	Previous default; HIV; foreign nationality; male gender; extra-pulmonary TB; access to health unit; positive culture
Al-Hajjaj [49]	2000	Saudi Arabia	Cohort				44.05		628	Unemployment; smoking; retreatment; male gender; extra-pulmonary TB; access to health unit; treatment duration; disease severity
Ribeiro [50]	2000	Brazil	Case-control	60			20.00	58.00	100	Alcoholism; positive sputum smear; HIV; smoking; male gender; drug use; extra pulmonary TB; adverse effects; training for adherence
Piyaworawong [51]	2001	Thailand	Cohort	60			29.60	39.07	515	Male gender; access to health unit
Chaisson [52]	2001	USA	Intervention			80.00	19.50	73.33	199	DOTS; training for adherence
Escobar [53]	2001	Brazil	Cohort	60			12.33		294	Male gender; access to health unit; need for hospitalization; positive culture
Hoz [54]	2001	Spain	Cohort			100.00	53.71	96.00	64	Positive sputum smear; HIV; male gender; drug use; delay in initiating treatment; need for hospitalization

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Table 1 (continued)

Lead author	Year	Country	Design	Default criteria *			Default rate (%)	Males (%)	N	Risk factor
				a	b	c				
Liefhooghe [55]	2001	Pakistan	Cohort	90			11.30	56.00	563	Illiteracy; lack of family support; trust in treatment compliance; delay in initiating treatment
Morisky [56]	2001	USA	Intervention				20.41	51.00	377	Foreign nationality; lack of family support; training for adherence; race
Naing [57]	2001	Malaysia	Case-control			75.00	31.00		390	Alcoholism; positive sputum smear; HIV; smoking; retreatment; male gender; drug use; illiteracy; extra-pulmonary TB; DOTS; adverse effects; access to health unit; location; housewife; information about TB; income; long wait before receiving care; disease severity
White [58]	2002	USA	Intervention	30		100.00	51.56		62	Incentives; training for adherence
Rabahi [59]	2002	Brazil	Cohort	60			30.27	67.40	453	Alcoholism; positive sputum smear; unemployment; HIV; retreatment; male gender; adverse effects; need for hospitalization; race
Tekle [60]	2002	Ethiopia	Case-control	90			11.30	55.50	228	Unemployment; illiteracy; lack of family support; adverse effects; access to health unit; information about TB; income
O'Boyle [61]	2002	Malaysia	Case-control				10.00		86	Foreign nationality; unemployment; male gender; adverse effects; need for hospitalization
Hovell [62]	2003	USA + Mexico	Intervention		180	66.60	58.08	55.60	188	Training for adherence
Nyieirenda [63]	2003	Malawi	Cohort	60			13.34		3,298	Extra- pulmonary TB; access to health unit
Buu [64]	2003	Vietnam	Survey	60			8.29	70.50	4,208	Access to health unit
El-Sony [65]	2003	Sudan	Cohort	60			15.35	59.40	20,758	Access to health unit
Alvarez-Gordillo [66]	2003	Mexico	Intervention	60		75.00	3.45		87	Training for adherence
Demissie [67]	2003	Ethiopia	Cohort				32.75		128	Male gender; illiteracy; training for adherence; access to health unit; profession

(continues)

Table 1 (continued)

Lead author	Year	Country	Design	Default criteria * a	b	c	Default rate (%)	Males (%)	N	Risk factor
Salami [68]	2003	Nigeria	Cohort	90			50.21	52.00	1,530	Previous default; alcoholism; unemployment; HIV; smoking; male gender; illiteracy; access to health unit; need for hospitalization
Cayla [69]	2004	Spain	Cohort	60			4.69	64.50	1,291	Foreign nationality; HIV; male gender; drug use; DOTS; delay in initiating treatment; homelessness; need for hospitalization
Salles [30]	2004	Brazil	Case-control	60			20.20		163	Alcoholism; unemployment; HIV; male gender; race; income; long wait before receiving care

* Default criteria: (a) minimum number of days since last appointment; (b) minimum number of doses to complete treatment; and (c) minimum number of doses taken of total prescribed ratio to complete treatment).

ularly to encourage treatment compliance. Only instructions regarding compliance were included (but not teaching about the disease). Some studies also focused on concurrent interventions (e.g., different amounts of incentives) that could not be separated from this exposure evaluation. The pooled estimate from the trials, the estimate from the single cohort, and the single case-control showed similar OR values, which were similar to the overall estimate (OR = 0.48). Publication bias was not detected, but high, unexplained heterogeneity was present due primarily to the trials (Table 2). Even though the heterogeneity was not explained, almost all the studies showed results in the same direction (Figure 2), indicating that this exposure results in protection against TB treatment default.

The exposure "need for hospitalization" was investigated in 14 studies (Figure 3). Hospital admission for supervised treatment alone was not defined as hospitalization. The overall estimate did not show an association with TB treatment default. Among the study design groups, only the pooled OR from the cohorts did not show associations (OR = 1.29). The pooled estimate from case-controls (OR = 2.27) and the single survey (OR = 2.13) did show associations, and the single intervention showed a protective association (OR = 0.48). Publication bias (Egger p value of 0.013) and heterogeneity were detected (I^2 = 86.2%). However, this was the only exposure in which heterogeneity was partially explained.

Heterogeneity was not detected in the group of studies conducted in Latin America (OR = 2.46 [1.74-3.47]; I^2 = 0.0%) or those in Europe (OR = 1.46[0.45-4.76]; I^2 = 31.0%). In the other two categories (Africa and Asia & Australia), the heterogeneity remained (OR = 0.81[0.53-1.23], I^2 = 89.0%; OR = 1.26[0.48-3.29], I^2 = 80.5% respectively). Publication bias was not found in any category. In two of five categories there were not enough studies to calculate the publication bias statistics.

"Delay in initiating treatment" and "long wait before medical attendance" (investigated in four and three studies, respectively) were measured as differences in time between the various studies. The two exposures were considered indicators of how health units deal with the number of patients seeking treatment. Neither showed an association with TB treatment default. Heterogeneity was found in both exposures and publication bias only in the latter (Egger p value 0.005) (Table 2).

Publication bias was detected in only two of the five exposures. However, in these two, the number of publications included was low and heterogeneity limits the interpretation of this finding.

Table 2

Number of subjects, pooled estimates, heterogeneity statistic, and Egger test p value for each exposure and different designs.

Exposure	N	OR	95%CI	I² (%)	Egger p value	Design (N)	OR	95%CI	I² (%)
Difficult access to health service	19	1.71	1.17-2.49	95.7	0.305	Cohort (12)	1.67	1.11-2.50	94.7
						Case-control (5)	2.24	0.62-8.03	96.7
						Survey (2)	1.04	0.21-5.28	95.6
Need for hospitalization	14	1.31	0.91-1.89	86.2	0.013	Cohort (10)	1.29	0.85-1.97	83.8
						Intervention (1)	0.48	0.37-0.62	
						Case-control (2)	2.27	1.27-4.04	0.0
						Survey (1)	2.13	1.13-4.00	
Training or support for adherence	11	0.48	0.29-0.80	81.0	0.973	Cohort (1)	0.21	0.08-0.51	
						Intervention (9)	0.57	0.33-0.99	80.8
						Case-control (1)	0.23	0.13-0.69	
Delay in initiating treatment *	4	1.12	0.92-1.36	58.6	0.615	Cohort (2)	1.13	0.84-1.52	8.1
						Intervention (1)	0.97	0.84-1.12	
						Survey (1)	1.31	1.08-1.58	
Long wait before medical attendance	3	2.11	0.80-5.54	80.4	0.005	Case-control (3)	2.11	0.80-5.54	80.4

* Risk ratio.

Figure 2

Funnel plot (A) and Forest plot (B) of adherence training or support and TB treatment default.

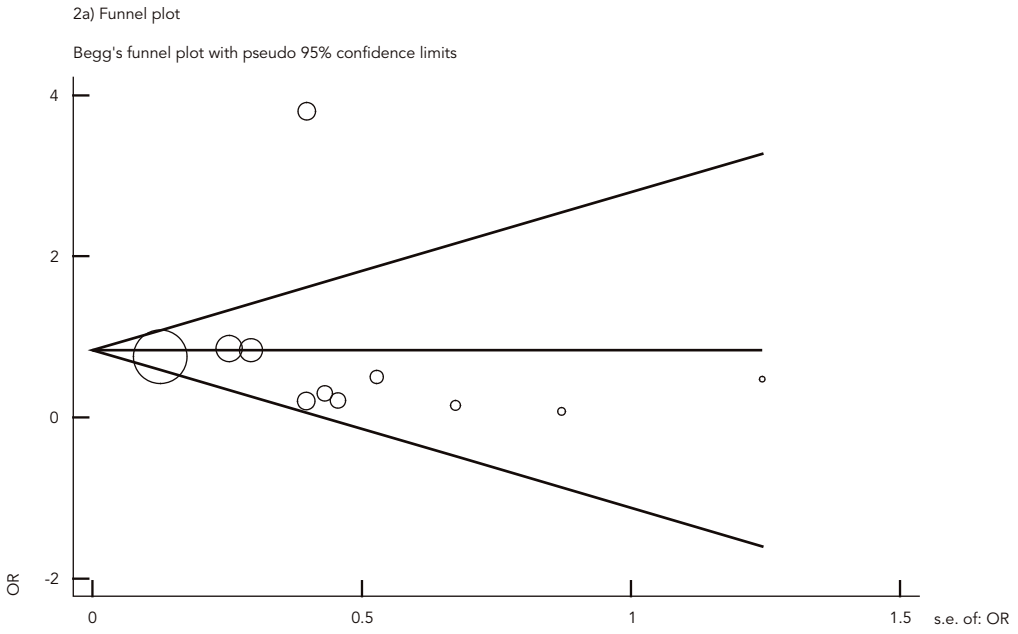

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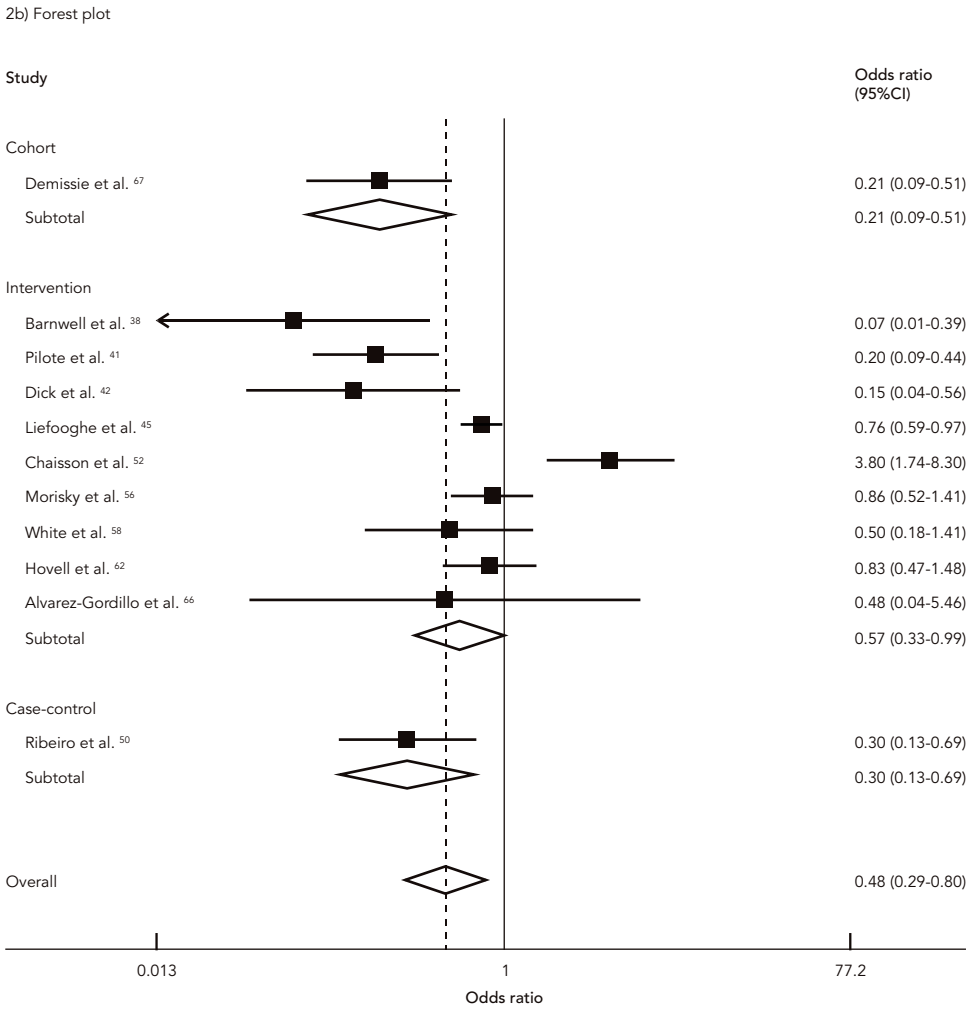
Figure 2 (continued)



Discussion and conclusion

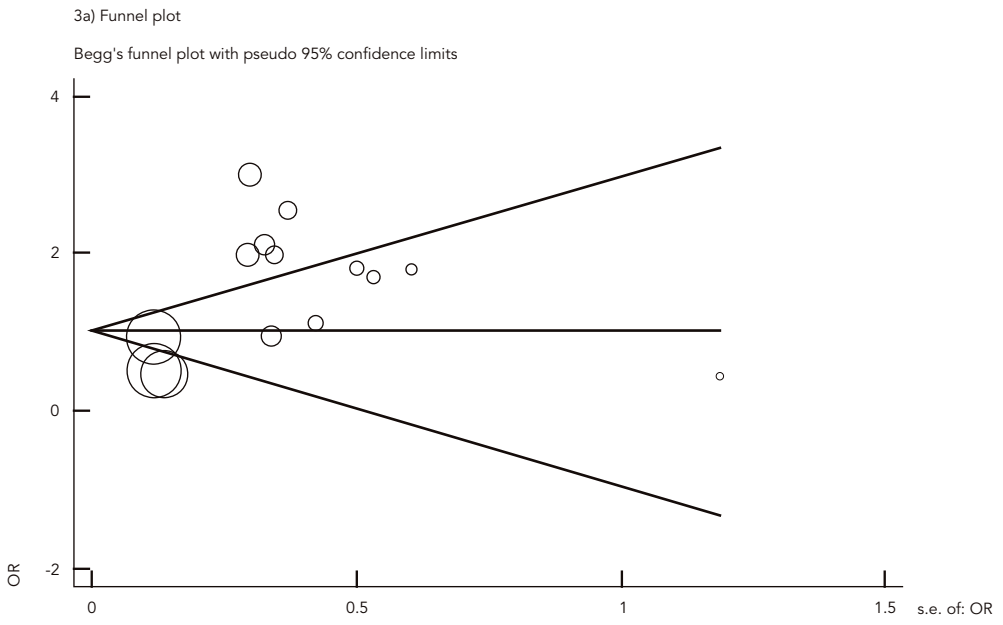
A difficult step in analyzing these exposures was deciding which of them could be grouped as health services characteristics. For example, hospitalization could be classified in the clinical status group instead. Patients could presumably be admitted to hospital because they have disseminated TB, i.e., more severe clinical status. However, we decided to include hospitalization in this group because hospitalized patients may have become more ill because the health system was unable either to detect and treat them early or to maintain them in appropriate treatment.

In the literature on meta-analysis methodology, some authors suggest that pooled measures should not be estimated because observational studies are more susceptible to bias [24]. According to other authors, systematic reviews of observational studies should explore heterogeneity and describe different characteristics instead. In fact, the quality of the original study directly interferes in the validity of the pooled estimate. However, there are several exposures that would never be tested as interventions, and therefore observational studies are the best evidence available. Finally, according to many researchers, systematic reviews and meta-analysis of observational studies should be performed, and they are performed as frequently as meta-analysis of clinical trials [24,25].

Two of five exposures ("training or support for adherence" and "difficult access to health services") have an overall pooled estimate showing as-

Figure 3

Funnel plot (A) and Forest plot (B) of hospitalization and TB treatment default.



(continues)

sociation with TB treatment default, while a third exposure ("need for hospitalization") showed an association in a particular scenario after exploring heterogeneity. All of the exposures we studied here demonstrated high heterogeneity.

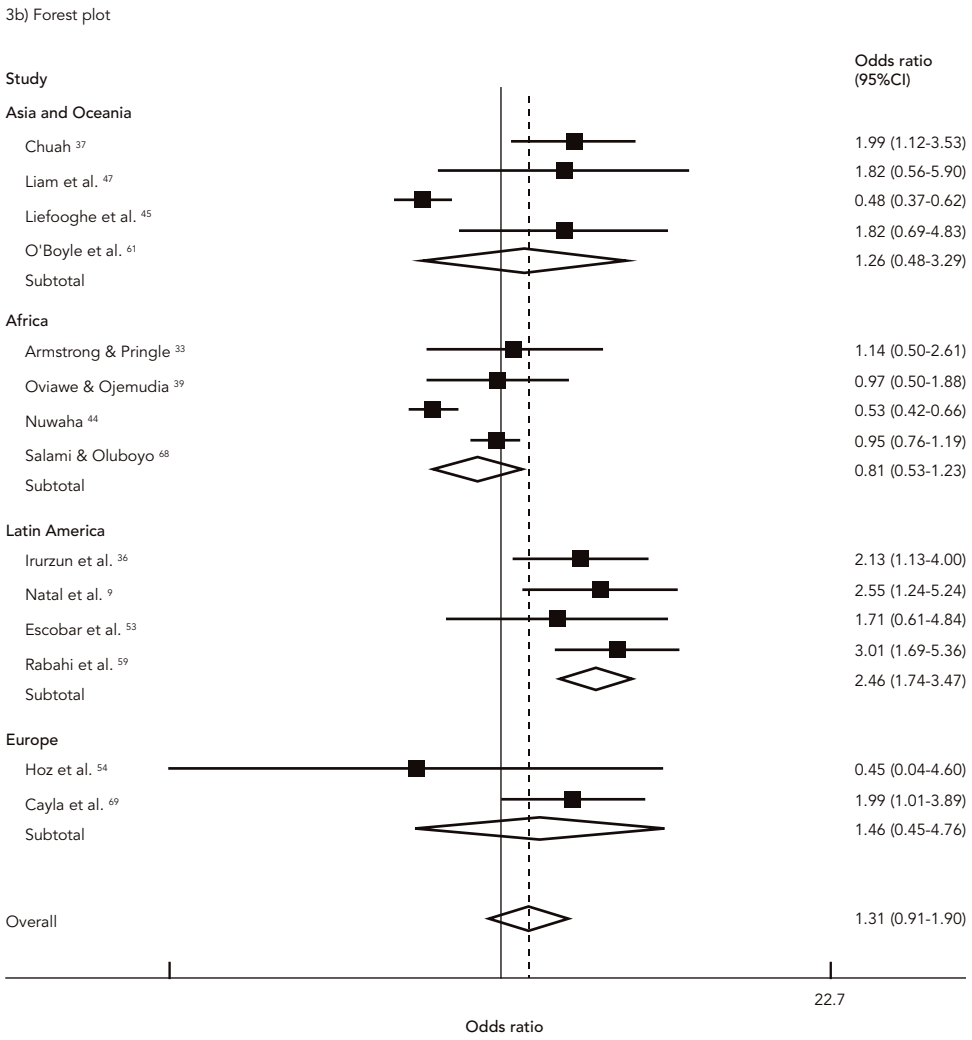
With only one exception, all the studies included as training for adherence showed results in the same direction. That is, even with concurrent interventions in some studies, adherence training could predict treatment compliance even when heterogeneity was detected. One can generally assume that treatment adherence training reduces default by about 50%.

The exposure "difficult access to health services" showed an association with TB treatment default with an overall OR of 1.71 (Table 2). This association indicates that individuals living far from the health units have about 1.71 times the odds of defaulting treatment as compared to those living nearby, but there are studies with results in both directions. In this case, three studies showed protection, six showed no evidence of association with treatment default, and 10 studies showed association with TB treatment default. One cohort study showing an association between difficult access and default had a sample of more 20 thousand subjects, which of course had a strong influence on the pooled estimate.

The exposure "need for hospitalization" was not associated with TB treatment default (Table 2). However, after heterogeneity analysis, the interpretation changed. The studies conducted in Latin America showed a positive association between hospitalization and treatment default, and no heterogeneity was found. In Latin America, TB patients admitted to hospital had a default rate nearly 2.5 times that of individuals not requiring hospitalization. Studies in Europe did not show this association with TB treatment default. Elsewhere, this association appears not to exist, but this cannot be determined categorically because of the observed heterogeneity.

The exposures "delay in initiating treatment" and "long wait before medical attendance" may indicate the same condition: the ability of the unit to meet local demand for TB care. Different health units may have different capacities to meet local demand, and these exposures may thus indicate how well organized and prepared they are to care for TB patients. Here, heterogeneity was not explained. Very few studies were included in these exposures (Table 2). Consid-

Figure 3 (continue)



ering "delay in initiating treatment", three of four studies (two cohorts and one intervention) showed no evidence of association, while one (a survey) showed evidence of association. The exposure "long wait before medical attendance" included only three studies. One (a case-control), with the highest influence, showed no evidence of association, while the other two (both case-controls) showed evidence of association. In the latter exposure, a tendency towards association was observed. However, the relative lack of studies and the fact that the largest study showed no evidence of relationship does not allow for detection of the association between these exposures and TB treatment default.

According to a systematic review published in 1997 [10] and including six trials, other strategies (mainly incentives) had a positive impact, i.e., increasing compliance. Importantly, the author discusses the conceptual and practical differences and in which situations theses strategies could be most beneficial. Most of the strategies could be applied together with those recommended by WHO [26]. However, some health services managers (even without scientific evidence) argue that incentives could create a culture of "professional" patients, who would fail to take the medicines and remain ill intentionally to keep receiving the cash incentives. Therefore, incentives could perpetuate the source of endemic TB behavior in some settings.

In this systematic review there were five exposures with three to 19 studies each, while the systematic reviews conducted by Volmink & Gar-

ner [10,11] included only six trials each. The main differences between this systematic review and those published previously were: (a) they included observational studies allowing the inclusion of factors that would be impossible to study in trials and (b) incentives were considered to be an extra effort by health units in most places, while the factors studied here are indicators of routine efforts to provide effective care to patients.

The high level of heterogeneity can be considered an important result and relevant limitation in summarizing information on risk factors for TB treatment default. Indeed, the heterogeneity should correspond in some way to clinical or epidemiological characteristics of different populations or even differences in investigative methods. Unfortunately, we were not able to show any evidence of these relationships. This may indicate that treatment default may not be equal in different locations, cultures, or even health units. If this is true, there is not just one single problem, but rather many problems to be solved regarding TB treatment default.

The heterogeneity frequently found in observational studies may also be explained by other features such as chance, bias (measurement, selection, and confounding), variation in the outcome rate among the unexposed, and effect modification [27]. Therefore, quality evaluation of methodology in observational studies included in meta-analysis is desired but controversial [28,29]. There is no way to assure that some, if not many, of the studies have biased results. Bias is a distortion of a truth that is impossible to know with certainty, although clues to these distortions may be perceived. Some of these clues have been discussed here, during analysis of the quality of some basic concepts.

Different theoretical models of treatment default in each investigation may also contribute to heterogeneity. Different factors may have different effects based on population characteristics, locations, clinical aspects, etc. Different locations may even have some population characteristics that would never be found in others, such as caste in India and Nepal. Factors related to health services with strong influence on TB treatment default may also vary in different populations and locations. The same arguments could be applied to health systems in different countries and even different health units in the same city.

Salles et al. [30], using a case-control design, investigated risk factors (related to individual patients and the health care team) for TB treatment default in outpatients at a tertiary teaching hospital (with a multidisciplinary health staff). No individual risk factors (such as HIV infection or alcoholism) were associated with default. However, some factors classified as proxies for health service activities and health staff-patient relations were associated with default.

It thus appears that even when patient characteristics such as smoking or alcoholism could be the most important factors for predicting TB treatment default, such patients might conceivably interrupt treatment because the health services fail to intervene in these problems. In most cases, these types of approaches (intervention other than provision of TB drugs per se) are not considered routine and may require extra effort to deal with such special needs by patients.

Perhaps due to this difficulty to deal with special needs, some countries (e.g., Israel, United Kingdom, and United States) have adopted legal actions (such as detention for treatment) to help control TB. Although controversial, this approach has been used since the 1980s. However, it is usually applied to patients with repeated hospital admissions for TB that have evaded at least once, contrary to medical orders. Some authors [31] argue that less restrictive measures are often more effective than these legal interventions.

As discussed earlier, most risk factors for TB treatment default studied in the literature have been related to individual patient characteristics. Health services characteristics could be more difficult to investigate, for both operational and ethical reasons.

In the current study, in addition to evaluating the magnitude and direction of associations, we have attempted to capture the diversity of approaches to the same problem by different authors in several different locations and times. An issue that merits increased attention by researchers is the choice of methods for data collection and analysis of secondary data and non-concurrent cohorts. Most of the cohorts included here were non-concurrent (using data from medical records or secondary data systematically collected for surveillance).

This type of design raises several concerns and suggests possible limitations, primarily due to information bias. Secondary data are often not valued because the data focus may not coincide with the research objectives. In addition, the researcher may not be aware of all problems in the selection and data collection, and control of important confounders may prove impossible in the analysis.

In studies using secondary data, it is common to see descriptions of surveillance system characteristics in the methods section, rather than in concepts and definitions, selection strategy, data collection strategy, and data analysis. In such cases, studies may present only crude data with no statistical tests. It is very rare to see discussions

about the limitations of the results, comments about unexpected results, or a more complex analysis such as survival or multivariate analysis.

Of all variables studied to explain heterogeneity with meta-regression in this review, seven are proxies of study quality, two are proxies of epidemiological characteristics, and one is a proxy of clinical characteristics.

The variables assumed to be proxies of study quality were not very good indicators. In the studies that addressed several exposures at the same time, some exposures were considered appropriate, while for others, no information was described. This created difficulty in determining whether exposures were properly defined or classified. As a variable, submission of the study protocol to an institutional review board was expected to have many missing data. Most of the cohorts were non-concurrent, with data collection from medical records or using secondary data. In the 1980s and 90s, submission of research projects involving human beings for IRB approval was not as common as today, nor was it considered as important. For example, even if only trials are considered, up to half did not mention submission to a research ethics committee. Consideration of adverse treatment effects by authors was missing in 77% of the studies included here. Although we expected some lack of data on adverse effects, this information proved to be missing in more than half of the trials.

As shown above, even the simplest variables commonly used to describe the study sample, such as age and gender, were lacking in most studies. Even though gender was previously assigned to the meta-regression, it was not possible to evaluate this variable because of missing data. Inclusion of gender as a covariate would exclude many studies using regression analysis.

The concept of default is key to this review. Even regarding this single aspect, quality of reporting in the original studies was poor. Two definitions of default were used: days without treatment (56%) and the proportion of pills taken throughout the prescribed duration of treatment (17%).

Indication of the year or time period when studies were conducted was also not available for all studies. Although there is a difference between the publication year and the time when the studies were conducted, we assume that the year of publication could explain some heterogeneity. In addition, it may be that over time, the quality of the research methods improved because of new theoretical and software analytical advances, and therefore the older studies could be more susceptible to bias and heterogeneity.

Interestingly, although heterogeneity was found in all exposures, publication bias was plausible in only two. The suspected publication bias in the exposure "need for hospitalization" did not remain when analyzing the presence of this bias for the categories of the factor that explained heterogeneity. For the exposure "long wait before medical attendance", there were too few studies and this finding could be spurious or influenced by the wide heterogeneity found in these studies. Explanations of publication bias for this exposure were not explored due to the small number of studies included.

We recommend that efforts to investigate reasons for TB treatment default focus on studies with prospective data collection, and that more attention be given to factors potentially related to health services. Data from retrospective studies could be used for theses purposes, but more attention should be given to methodological issues and statistical analysis in these studies.

Resumo

Acredita-se que a identificação dos fatores que são preditores do abandono de tratamento de tuberculose contribuiria para o seu controle. Este trabalho combinou, por meio de uma revisão sistemática, medidas de associação entre abandono do tratamento de tuberculose e de fatores relacionados com os serviços de saúde já estudados. Resumos foram procurados nas bases LILACS e MEDLINE e na bibliografia dos textos completos em avaliação. Foram incluídos estudos nos quais foi avaliado o abandono do tratamento através de comparações de dois ou mais grupos e nos quais foi possível a extração de dados. Ao final, 41 investigações foram incluídas para combinação de dados. Foi possível combinar cinco exposições: "difícil acesso aos serviços de saúde"; "necessidade de hospitalização"; "treinamento ou suporte para adesão"; "demora para o início do tratamento" e "espera longa antes da consulta". "Difícil acesso aos serviços de saúde", "treinamento para adesão" e "necessidade de hospitalização" demonstraram associação com o abandono de tratamento de tuberculose. Todas as exposições apresentaram heterogeneidade e em apenas uma esta foi explicada. Viés de publicação foi encontrado em apenas uma exposição.

Tuberculose; Pacientes Desistentes do Tratamento; Metanálise

Contributors

P. E. A. A. Brasil was responsible for the project development, review, data management, data analysis, and elaboration of the manuscript. J. U. Braga contributed to the project development, review, and elaboration of the manuscript.

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