Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis

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Objective To assess the magnitude of loss to follow-up in smear- or culture-positive tuberculosis patients before treatment initiation and outcomes among patients who were traced.

Methods Ovid Medline and Global Health databases were searched for studies published between 1994 and January 2013 that described pre-treatment loss to follow-up in patients with smear- or culture-positive tuberculosis in routine national tuberculosis programmes (NTPs) in low- and lower-middle-income countries and in countries with a high burden of tuberculosis. Data on the proportion of patients who did not initiate treatment after their tuberculosis diagnosis were extracted from studies meeting inclusion criteria. Where available, data on causes and outcomes, including initiation of tuberculosis treatment at another facility, were investigated. Heterogeneity and publication bias were assessed and random-effects meta-analyses by subgroup (region) were performed.

Findings Twenty-three eligible studies were identified, with a total of 34 706 smear- or culture-positive tuberculosis patients from 14 countries (8 in Africa, 5 in Asia and 1 in the western Pacific). Most studies were retrospective and linked laboratory and treatment registers to identify pre-treatment loss to follow-up. Pre-treatment loss to follow-up varied from 4 to 38% and was common in studies from Africa (random-effects weighted proportion, WP: 18%; 95% confidence interval, CI: 13–22) and Asia (WP: 13%; 95% CI: 10–15).

Conclusion Pre-treatment loss to follow-up, common in most settings, can hinder tuberculosis control efforts. By not counting individuals who are lost to follow-up before treatment when reporting standard programme indicators, NTPs underestimate case detection rates and mortality and overestimate cure rates.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Since tuberculosis was declared a global emergency in 1993 by the World Health Organization (WHO), new cases of tuberculosis and deaths from the disease have dropped dramatically in several countries with a high burden of the disease.[1] All six WHO regions are on track to meet the Millennium Development Goal target of reducing tuberculosis incidence and deaths from tuberculosis by half between 1990 and 2015[1,2] and, with the sole exception of the African Region, all are on track to halve tuberculosis mortality rates.[2] Nevertheless, the situation remains precarious.[3] Twenty-two predominantly low- and middle-income countries were estimated to account for 82% of the 5.7 million tuberculosis cases notified in 2010[1] and high rates of death from tuberculosis among people living with human immunodeficiency virus (HIV) infection prevail in much of sub-Saharan Africa.[4,5]

Rapid case identification of individuals with sputum smear-positive tuberculosis and rapid initiation of anti-tuberculosis chemotherapy are key to controlling tuberculosis[6] and are promoted as part of the DOTS strategy model of passive case-finding that has been adopted by most national tuberculosis programmes (NTPs).[7] From the patient's perspective, the tuberculosis diagnostic and care pathway (Fig. 1) begins with a recognition of symptoms that prompt care seeking. Individuals may drop out of care during the diagnostic process ("loss to follow-up during diagnostic period"), before initiating treatment ("pre-treatment loss to follow-up", formerly known as "initial default") or after treatment has begun. Patients diagnosed with smear-positive tuberculosis who do not initiate treatment represent an important failing in the provision of care.[8,9] High rates of mortality are reported in this group.[10] Moreover, bringing these patients into care could reduce tuberculosis transmission to others.[11] Patients with a diagnosis of tuberculosis who are lost to follow-up before they receive treatment are not included in routine reporting by NTPs. Thus, programme effectiveness may be overestimated.[8]

Efforts to improve tuberculosis case detection rates have centred on ensuring rapid treatment for all individuals diagnosed with smear-positive tuberculosis.[12,13] With this goal in mind, WHO has recently changed its policy, which now calls for two sputum specimens instead of three and same-day collection.[13,14] However, assessing the impact of these changes on linkage to treatment has been hampered by a lack of understanding of the extent of pre-treatment loss to follow-up[8] and of the patient, provider and health system factors that contribute to it.[15]

Although nearly 50 years have passed since high rates of pre-treatment loss to follow-up were first identified as a potential major contributor to the failure of tuberculosis control programmes, researchers and policy-makers have paid little attention to the fate of patients who do not access treatment after receiving a diagnosis of tuberculosis.[16,17,18] Indeed, the "Piot model" used to describe loss to care at different stages for any disease was first developed for tuberculosis.[18]

This study had two main objectives: (i) to systematically quantify pre-treatment loss to follow-up in low- and lower-middle income countries and in countries with a high burden of tuberculosis; and (ii) to describe the reasons for drop-out and the outcomes seen in individuals with a tuberculosis diagnosis

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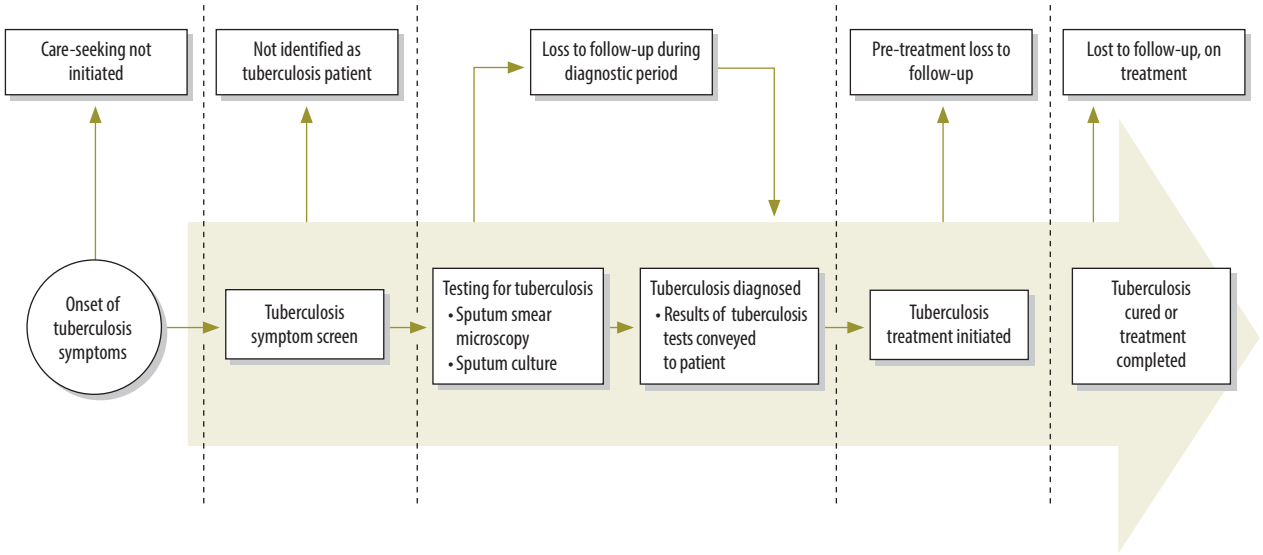
Fig. 1. **The diagnostic and care pathway for tuberculosis**



who do not initiate treatment. A secondary objective was to assess the quality of the studies reporting on pre-treatment loss to follow-up.

Methods

Definitions

We followed PRISMA reporting guidelines for systematic reviews.[19] To define the points at which tuberculosis patients drop out of care, we developed the tuberculosis diagnostic and care pathway described in Fig. 1 using terms recommended recently that replace previously used terms such as "initial default".[9]

For this study, patients in a national tuberculosis care programme who received a diagnosis of tuberculosis on the basis of at least one positive sputum smear or culture but did not start tuberculosis treatment were defined as having pre-treatment loss to follow-up. This included individuals who died before initiating treatment.

The recruitment period was defined as the time during which patients with a diagnosis of tuberculosis were recruited to studies or during which data from such patients were extracted from national programme registers. For studies with individual follow-up, the follow-up period was defined as the time between diagnosis and the most recent date of active follow-up. For studies in which tuberculosis treatment registers were checked retrospectively, we present the minimum and maximum follow-up periods available. Because studies had different follow-up periods and varying temporal definitions for pre-treatment loss to follow-up, we used the definition given in each study rather than a time-delineated definition. However, we did require a follow-up period of at least 4 weeks to allow enough time for patients to link to care and treatment.

Table 1. **Systematic strategy used to search for studies on pre-treatment loss to follow-up in tuberculosis patients**

Set	MEDLINE	Global Health
1	tuberculosis	tuberculosis
2	TB	patient refusal of treatment
3	TUBERCULOSIS	dropout
4	Sets 1–3 were combined with "OR"	dropouts
5	PATIENT DROPOUT	referral
6	DELAYED DIAGNOSIS	delayed
7	REFERRAL AND CONSULTATION	attrition
8	DIAGNOSTIC SERVICES	retain
9	TUBERCULOSIS, PULMONARY DIAGNOSIS	treatment programme
10	initial delay*	initial delay
11	initial default*	initial default
12	drop out	retention
13	attrition	diagnostic delay
14	retention	treatment delay
15	retain*	care seeking
16	diagnostic delay*	loss to follow-up
17	treatment delay*	lost to follow-up
18	treatment seek*	Sets 2–17 were combined with "OR"
19	care seek*	Sets 1 and 18 were combined with "AND"
20	loss to follow-up	Set 19 was limited to 1994–2013
21	lost to follow-up	
22	loss to follow-up	
23	lost to follow-up	
24	Sets 1–23 were combined with "OR"	
25	Sets 4 and 24 were combined with "AND"	
26	Set 25 was limited to 1994–2013	

Note: Words written in capital letters were used as MeSH headings; the others were used as free text. The asterisks are the truncation symbol in Medline (i.e. any possible ending after the preceding text).

Inclusion and exclusion criteria

Studies were included in the review if they reported on the proportion of patients having smear- or culture-positive tuberculosis who experienced pre-treatment loss to follow-up in NTPs in low- or lower-middle-income countries as defined by the World Bank on 1 July 2011,[20] or in any of the 22 countries with a high burden of tuberculosis as defined by the Stop TB department of WHO.[1] Studies that reported on clinical trials, including randomized and non-randomized active case-finding studies, were excluded because participants in these studies would be more likely to receive intensive follow-up and tracing and would not be representative of patients with tuberculosis diagnosed routinely. Studies that reported only on paediatric patients – i.e. children 15 years of age or younger – were excluded. Studies that recruited both adults and children were included even if the data were not disaggregated by age group.

Search strategy

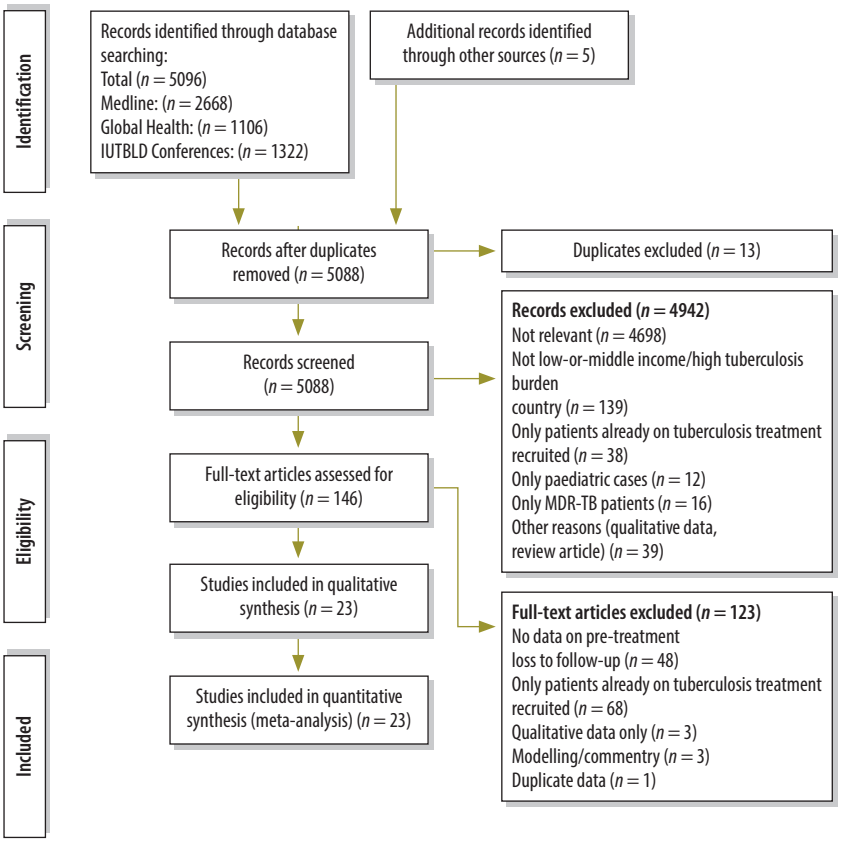
We systematically searched the Ovid, Medline and Global Health databases for studies published between 1 January 1994 and 31 January 2013. Our search strategy is outlined in Table 1. We also hand searched the abstracts of the Union World Conference on Lung Health from 2009 to 2012. We identified additional studies through reference lists and annotated bibliographies and by corresponding with researchers in the field. If the manuscript did not give the absolute number of individuals with pre-treatment loss to follow-up, we contacted the authors to obtain the data.

Three authors (KK, PM, RH) reviewed titles and abstracts to obtain the full texts of relevant articles. All three assessed the full texts to determine their suitability and based their final inclusion in the review on consensus as a team. PM and KK extracted data from included studies using a pre-designed table.

Quality of selected studies

One researcher (PM) used a modified version of the Newcastle-Ottawa scale to assess studies in terms of quality and of the risk of bias in the selection of participants and in the ascertainment of outcomes. Each study could score up to six points in each of these two categories, each having six items. The section for the selection of comparison groups was removed from the Newcastle-Ottawa scale because no study had a comparison group. The factors considered included: the representativeness of the patients recruited with respect to the underlying population of tuberculosis patients diagnosed in the routine health-care system; the test used to ascertain the diagnosis of tuberculosis; the method of identification of pre-treatment loss to follow-up; and the adequacy of follow-up (judged in terms of the proportion of participants whose outcomes were ascertained, with >85% being adequate). In studies in which laboratory and treatment registers were linked, we evaluated the process and variables used for linkage (including personal identifiers and dates).

Fig. 2. **Flowchart for the selection of studies on pre-treatment loss to follow-up in patients with a diagnosis of tuberculosis**



IUTBLD, International Union Against Tuberculosis and Lung Disease; MDR-TB, multidrug resistant-tuberculosis.

Data analysis and statistical methods

For each included study, we report on the number of patients who received a diagnosis of smear- or culture-positive tuberculosis and the proportion who initiated antituberculosis treatment. For patients identified as having experienced pre-treatment loss to follow-up, we report the duration of follow-up and, if available, the proportion who were successfully traced and their outcomes (alive but not on treatment; alive after starting treatment; deceased; or transferred to another facility but treatment and vital status unknown). To calculate summary estimates of pre-treatment loss to follow-up, we classified as treatment initiators those tuberculosis patients who were classified as having experienced pre-treatment loss to follow-up but who, on tracing, were found to have initiated treatment at an alternative site. We assessed heterogeneity using the I^2 statistic. On initial analysis, we found substantial heterogeneity between studies. Therefore, we estimated the pooled proportion of patients with a diagnosis of tuberculosis and pre-treatment loss to follow-up (and the corresponding 95% confidence intervals) using a random-effects model, weighting for the inverse of the variance and stratification by study region. Stata 12.1 (Statacorp, College Station, Texas, USA) was used to analyse the data.

Table 2. **Characteristics of studies included in the review and proportion of smear-positive tuberculosis patients who initiated treatment**

Study	Year(s) study conducted	Country	Setting	Diagnostic criterion	Recruitment period	No. with diagnosis of tuberculosis	Follow-up period	Temporal definition of pre-treatment loss to follow-up	Method used to confirm start of treatment	No. (%) of patients initiating treatment
Creek, 2000[27]	1997	Botswana	Gaborone, outpatient department of public hospital and 13 PHCs	≥ 1 positive smear	5 months	184	5–22 months	2 weeks	Retrospective linking of laboratory register and national electronic tuberculosis register	165 (90)
Dembele, 2006[28]	2001	Burkina Faso	6 districts (including the capital)	Any smear positive	1 year	31	NR	ND	Retrospective linking of laboratory and treatment registers	27 (87)
Afutu, 2012[21]	2009	Ghana	Regional hospital	Smear positive not further specified	1 year	84	9–27 months	ND	Retrospective linking of laboratory and treatment registers	52 (62)
Glynn, 1998[30]	1986–1994	Malawi	Rural PHCs, one district hospital	≥ 1 positive smear	90 months	682	Up to 110 months	ND	Prospective monthly follow-up as part of Demographic and Health Survey	642 (94)
Nyirenda, 1998[32]	1997	Malawi	National	Smear positive, not further specified	6 months	3482	2–8 months[a]	ND	Retrospective linking of laboratory and treatment registers	2980 (86)
Squire, 2005[10]	2000	Malawi	Rural, 31 PHCs, one district hospital	Smear positive, not further specified	6 months	157	0–6 months	ND	Retrospective linking of laboratory and treatment registers; home tracing of patients with missing treatment information	134 (85)
Uchenna, 2012[36]	2009	Nigeria	5 states in southern Nigeria	Smear positive, not further specified	3 months	323	Up to 3 months	2 days	Retrospective collation of total number of tuberculosis patients diagnosed in laboratory registers and treated in treatment registers (individual records not linked)	268 (83)
Botha, 2008[23]	2004–2005	South Africa	13 PHCs	≥ 2 positive smears	1 year	367	3–15 months	3 months	Retrospective linking of sputum collection register and treatment register	303 (83)
Botha, 2008[24]	2005	South Africa	11 PHCs in the Western Cape province (8 in Cape Town metropolitan area)	≥ 2 positive smears	3 months	227	4–16 months	2 months	Retrospective linking of laboratory and treatment registers	203 (89)
Claassens, 2010[37]	2009	South Africa	133 PHCs in 5 provinces	Smear positive, not further specified	5 months	3020	NR	1 month	Retrospective linking of laboratory and treatment registers	2268 (75)

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Study	Year(s) study conducted	Country	Setting	Diagnostic criterion	Recruitment period	No. with diagnosis of tuberculosis	Follow-up period	Temporal definition of pre-treatment loss to follow-up	Method used to confirm start of treatment	No. (%) of patients initiating treatment
Dunbar, 2011[29]	2007	South Africa	Two community clinics	Bacteriologically confirmed	1 year	306	Up to 24 months[b]	2 months	Retrospective linking of laboratory and treatment registers	243 (79)
Davis, 2011[41]	2009	Uganda	Five PHCs	≥ 1 positive smear	1 year	81	NR	ND	Prospective cohort follow-up, with additional retrospective linkage of laboratory and treatment registers for confirmation	62 (77)
Chadambuka, 2011[26]	2006	Zimbabwe	Gokwe district	Smear positive, not further specified	1 year	112	1 month	ND	Retrospective linking of laboratory and treatment registers/"stock cards"	82 (73)
Balasubramanian, 2004[22]	1998–2001	India	PHCs	≥ 2 positive smears	2 years	833	3 months	3 months	Retrospective linking of laboratory register and patient records	713 (86)
Gopi, 2005[31]	2001–2003	India	One PHC	Smear positive, not further specified	31 months	1049	2 months	2 months	Prospective reconciliation of laboratory and treatment registers	893 (85)
Sai Babu, 2008[34]	2006	India	20 districts in Andhra Pradesh state	≥ 2 positive smears	3 months	15 361	Cross-sectional: identification of all initial defaulters in one quarter of 2006	ND	Extraction of data from laboratory register; home tracing of patients with missing treatment information	14 676 (96)
Razia, 2011[39]	2009	Pakistan	One district, including 16 peripheral centres and five tertiary centres	Smear positive, not further specified	1 year	1698	Up to one year	ND	Retrospective linking of laboratory and treatment registers	1597 (94)
Rao, 2009[33]	2007–2008	Pakistan	Chest clinic, Karachi	Smear positive, not further specified	5 months	224	Patients prospectively recruited during a 5-month period; time before tracing undertaken not defined	ND	Telephone tracing of patients who did not return for treatment	162 (72)
Rao, 2011[40]	2010	Pakistan	Chest clinic, Karachi	Smear positive, not further specified	6-months	1121	Up to 6 months	ND	Telephone tracing of patients who did not return for treatment	947 (84)
Korobitsyn, 2010[38]	2008–2009	Tajikistan	Four districts	Smear positive, not further specified	1 year	254	Up to one year	ND	Retrospective linking of laboratory and treatment registers	209 (82)
Uthaivoravit, 2003[35]	1995	Thailand	Provincial referral hospital	≥ 1 positive smear	60 months	212	"Mid-1996" to "the end of 2000". Reported in yearly cohorts	ND	Prospective linking of laboratory, treatment register and medical records	168 (79)

(*continues. . .*)

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Study	Year(s) study conducted	Country	Setting	Diagnostic criterion	Recruitment period	No. with diagnosis of tuberculosis	Follow-up period	Temporal definition of pre-treatment loss to follow-up	Method used to confirm start of treatment	No. (%) of patients initiating treatment
Buu, 2003[25]	2000	Viet Nam	District tuberculosis units	≥ 1 positive smear	1 year	4208	1 month	1 month	Retrospective linking of laboratory and treatment registers	3859 (92)
Ram, 2012[42]	2001–2010	Fiji	4 laboratories and 2 DOTS sites	≥ 1 positive smear	9 years	690	NR	ND	Retrospective linking of laboratory and treatment registers	579 (84)

ND, not defined; NR, not reported; PHC, primary-health-care centre.

[a] The period during which tuberculosis laboratory registers were reconciled with tuberculosis treatment registers is not reported. The "data collection period" is given as ranging between 2 and 8 months.

[b] The treatment records of all individuals with bacteriologically confirmed tuberculosis during 2007 were identified by searching electronic treatment registers for 2007 and 2008.

Ethics statement

Ethical approval was not required for this study.

Results

Study characteristics

We identified 5096 potentially relevant studies, of which 23 were eligible for inclusion in the analysis (Fig. 2).[10,21–42] These reported on a total of 34 706 patients with smear- or culture-positive tuberculosis, 3474 of whom had experienced pre-treatment loss to follow-up. The characteristics of the included studies are summarized in Table 2. There were 13 studies from sub-Saharan Africa (8 countries), 9 from Asia (5 countries) and 1 from the western Pacific (1 country).

Most studies reported on pre-treatment loss to follow-up among smear-positive patients only. Two studies included patients who were either smear- or culture-positive.[29,30] In some studies smear positivity was defined as at least 1[25,27,28,30,35,41,42] or at least 2[22–24,34] positive smears, whereas others did not provide any definition.[10,21,26,31–33,36–40] A study from South Africa stratified rates of reported pre-treatment loss to follow-up by smear status (smear-positive or smear-negative but culture-positive),[23] whereas another study, also from South Africa, reported on pre-treatment loss to follow-up in tuberculosis patients whose diagnosis was established clinically and/or bacteriologically.[29]

Quality of included studies

The quality of the included studies varied (Table 3). Only a few studies ($n = 4$) showed a low risk of bias or scored full marks across all items assessing patient selection and ascertainment of outcomes. The methods for ascertaining pre-treatment loss to follow-up were suboptimal or poorly described in most studies; only seven studies adequately described the follow-up period allotted to each participant. The majority of studies ($n = 19$) identified patients diagnosed with tuberculosis by extracting data from laboratory or sputum collection registers (Table 2). Such extraction was performed retrospectively in 17 studies and prospectively in two. In the remaining 4 studies, patients with a diagnosis of tuberculosis were identified as part of ongoing epidemiological surveillance[30] or were prospectively recruited for follow-up from a chest clinic[33,40] or from primary-health-care centres.[41] The recruitment periods ranged from 3 months[24,34,36] to 90 months.[30] Only 9 studies[22–25,27,29,31,36,37] applied a cut-off for time since diagnosis – ranging from 1 month to 3 months – to define pre-treatment loss to follow-up.

Although most studies ($n = 16$) used retrospective linkage of laboratory and treatment registers to identify patients who initiated treatment for tuberculosis[10,21–29,32,37–39,41,42] – and so scored full marks for this item – the quality of the procedures used to ensure accurate linkage varied considerably. Only one study[27] described the variables used to link records and gave the proportion of records that were reliably matched.

Pre-treatment loss to follow-up

The proportion of patients with a diagnosis of tuberculosis who experienced pre-treatment loss to follow-up ranged from 4 to 38%.[21,34] In studies from Africa pre-treatment loss to follow-up ranged from 6 to 38%, whereas in studies from Asia it ranged from 4 to 28%. Studies that reported on data from a single clinical site[21,22,26,29,31,33,35,40] had higher rates of pre-treatment loss to follow-up (range: 14–38%) than studies reporting on national or regional data (range: 4–25%).[10,23–25,27,28,30,32,34,36–39,41,42]

In total, 10 studies[10,24,25,30–34,38,40] attempted to trace tuberculosis patients with pre-treatment loss to follow-up (Table 4). One of them did not detail the tracing method used.[38] Tracing rates were rather poor on average. The proportion of patients who could not be traced ranged from 0%[30] to 77%.[32] This limited our ability to draw inferences about the fate of tuberculosis patients with pre-treatment loss to follow-up.

Six studies – five of them from Asia – reported that patients who had initially been classified as being lost to follow-up before being treated had in fact initiated treatment for tuberculosis at another clinical facility.[25,31,32,33,34,40] In the Asian studies, transfer to a private clinic for tuberculosis treatment was the commonest reason for pre-treatment loss to follow-up; from 0 to 62% of patients were found to have been treated at private clinics, although only one such study successfully traced more than 80% of the patients.[33] In the only study from Africa that traced individuals and recorded if they initiated treatment elsewhere, 23% of tuberculosis patients who were initially classified as lost to follow-up before treat-

Table 3. **Modified Newcastle-Ottawa Scale for assessment of the quality of the studies included in the review of pre-treatment loss to follow-up in tuberculosis patients[a]**

Author	Country	Selection[b]	Outcome[c]
Creek[27]	Botswana	***	**
Dembele[28]	Burkina Faso	***	*
Afutu[21]	Ghana	***	**
Glynn[30]	Malawi	***	***
Nyirenda[32]	Malawi	***	*
Squire[10]	Malawi	***	**
Uchenna[36]	Nigeria	***	*
Botha[23]	South Africa	***	***
Botha[24]	South Africa	***	***
Claassens[37]	South Africa	***	*
Dunbar[29]	South Africa	***	***
Davis[41]	Uganda	***	*
Chadambuka[26]	Zimbabwe	**	
Balasubramanian[22]	India	**	
Gopi[31]	India	**	*
Sai Babu[34]	India	***	*
Razia[39]	Pakistan	***	*
Rao[33]	Pakistan		**
Rao[40]	Pakistan		
Korobitsyn[38]	Tajikistan	***	*
Uthaivoravit[35]	Thailand	***	*
Buu[25]	Viet Nam	***	**
Ram[42]	Fiji	***	*

[a] A study can be awarded a maximum of one star for each of three items within the "selection" and "outcome" categories.

[b] Assessment of patient selection comprised three items (those that score stars are shown): (i) representativeness of the cohort (truly representative,* somewhat representative,* selected group of users, no description of derivation); (ii) ascertainment of tuberculosis diagnosis (secure records/registers,* structured interviews,* written self-report, no description); (iii) demonstration that treatment for tuberculosis was not being taken at recruitment (secure records/registers,* structured interviews,* written self-report, no description).

[c] Assessment of outcome comprised three items (those that score stars are shown): (i) ascertainment of pre-treatment loss to follow-up (secure records/registers,* structured interviews,* written self-report, no description); (ii) sufficient follow-up time to allow outcome to occur (4 weeks) (yes,* no); (iii) adequacy of follow-up (complete*, follow-up > 80%*, follow-up < 80%, no description).

ment in Malawi had started treatment for tuberculosis in another district.[32]

When we counted traced individuals who had initiated treatment at an alternative site as tuberculosis treatment initiators, we noted substantial heterogeneity between studies in rates of pre-treatment loss to follow-up ($I^2 = 98.4\%$; $P < 0.001$). This remained after stratifying by study region (Africa: $I^2 = 96.1\%$; $P < 0.001$; Asia: $I^2 = 98.0\%$; $P < 0.001$; western Pacific: one study only). The funnel plot showed asymmetry, suggestive of publication bias (Egger's statistic: $P < 0.001$). Fig. 3 shows a forest plot for the included studies, stratified by region. In random-effects meta-analysis, the overall inverse-weighted proportion of patients with a diagnosis of tuberculosis who experienced pre-treatment loss to follow-up was 16% (95% confidence interval, CI: 13–18). Although this proportion was 18% in studies from Africa (95% CI: 13–22) and hence higher than in Asian studies, where it was 13% (95% CI: 10–15%), the CIs overlapped.

Case fatality

Among traced tuberculosis patients with pre-treatment loss to follow-up, the case fatality rate ranged from 0% (95% CI: 0–6)[40] to 82% (95% CI: 59–94).[10] The risk of death was highest in studies from Africa but varied widely and low rates of tracing rendered it unreliable. Only the study from Malawi described the time from diagnosis to death among 19 patients who were traced:[10] a median of 3.5 weeks (range: 2–12) in 14 deceased patients.

Reasons for loss to follow-up

Factors associated with an increased risk of pre-treatment loss to follow-up were male sex, older age,[31] living in an urban area,[25] diagnosis in a hospital or stationary clinic (rather than a mobile clinic),[23] geographical location of the tuberculosis laboratory (regional versus local),[42] and being diagnosed with smear-negative but culture-positive tuberculosis.[24] However, distance to treatment site was not associated with the risk of pre-treatment loss to follow-up in Ghana.[21]

Of the nine studies that traced patients with pre-treatment loss to follow-up, one undertook in-depth qualitative interviews to determine the reasons for drop-out,[10] and the other eight were based on structured patient interviews, either in person[24,25,30–32,34,40] or by telephone.[33,40] Health-system-related obstacles for not starting treatment for tuberculosis included dissatisfaction with long waiting times in health services, the need for repeated visits, and delays in receiving the results of sputum smears.[10,25,29,31] Some reasons for not starting treatment for tuberculosis were patient-related (e.g. difficulty getting time off from work or a lack of understanding of tuberculosis, its severity or the potential benefits of treatment).[10,24,31,33,40] Other reasons were disease-related (e.g. weakness and fatigue).[31,32]

Discussion

This review highlights the paucity of data on pre-treatment loss to follow-up among patients with a diagnosis of tuberculosis, despite high prevalence and mortality rates. Only 23 studies from 14 countries were identified over a period of 17 years, in sharp contrast with the 37 studies on HIV care programmes in low-resource settings that were published in a period of 5 years.[43] Yet pre-treatment loss to follow-up in patients with smear-positive tuberculosis is an important problem for tuberculosis programmes because these patients are highly infectious[44] and experience high morbidity and mortality.[45,46]

In the studies identified in this review, pre-treatment loss to follow-up was high – from 4 to 38% – and was higher in sub-Saharan Africa (18%) than in Asia (13%). Given the very high risk of death among tuberculosis patients who are not promptly treated, minimizing treatment delay and losses at all stages in the diagnostic and care pathway is critically important.[12] Although tracing was suboptimal in most

Table 4. **Outcomes observed in studies of pre-treatment loss to follow-up in tuberculosis patients**

Author	Country	No. lost to follow-up before treatment	Patients not traced		Patients traced							
			No.	% (95% CI)	No.	Deceased		No. treated elsewhere (private sector)	No. transferred, treatment status unknown	Alive, not on treatment		Lost[a]	
						No.	% (95% CI)			No.	% (95% CI)	No.	% 95% CI)
Glynn[30]	Malawi	40	0	0 (0.00–0.09)	40	25	0.63 (0.47–0.76)	0	0	0	0 (0.00–0.09)	15	0.38 (0.24–0.53)
Nyirenda[32]	Malawi	502	386	0.77 (0.73–0.80)	116[b]	40	0.34 (0.26–0.44)	27 (outside district)	23	2	0.02 (0.00–0.06)	20	0.17 (0.11–0.25)
Squire[10]	Malawi	20	3	0.15 (0.05–0.36)	17	14	0.82 (0.59–0.94)	0	1	2	0.12 (0.04–0.40)	0	0 (0.00–0.18)
Botha[24]	South Africa	58	26	0.45 (0.33–0.58)	32	14	0.44 (0.28–0.61)	0	0	18	0.56 (0.39–0.72)	0	0 (0.00–0.11)
Gopi[31]	India	156	79	0.51 (0.43–0.58)	77	23	0.30 (0.21–0.41)	13 (outside area)	0	33	0.39 (0.29–0.45)	8	0.09 (0.05–0.17)
Sai Babu[24]	India	685	402	0.59 (0.55–0.62)	278[c]	152	0.55 (0.49–0.60)	38 (private)	22	28	0.10 (0.07–0.14)	38	0.13 (0.10–0.18)
Rao[33]	Pakistan	62	7	0.11 (0.06–0.22)	55	0	0 (0.00–0.06)	6 (private)	0	25[d]	0.45 (0.33–0.58)	0	0 (0.00–0.06)
Rao[40]	Pakistan	173	82	0.47 (0.40–0.55)	91	1	0.01 (0.00–0.06)	15 (private)	0	0[e]	0 (0.00–0.04)	NS	NS
Korobitsyn[38]	Tajikistan	45	27	0.60 (0.45–0.73)	18	2	0.11 (0.03–0.33)	0	0	3	0.17 (0.06–0.39)	3	0.72 (0.49–0.88)
Buu[25]	Viet Nam	349	174	0.50 (0.45–0.55)	175[f]	NS	NS	108 (private)	NS	67	0.38 (0.31–0.46)	NS	NS

CI, confidence interval; NS, not stated.

[a] Patients with known addresses, but when the home visit was conducted they had moved away but were known to be alive.

[b] Four patients were discharged from hospital before smear result was reported.

[c] Nineteen patients were follow-up cases, not new diagnoses; 24 were chronic cases, not new diagnoses.

[d] Twenty-four patients were traced and put on tuberculosis treatment.

[e] Ninety patients were traced and put on tuberculosis treatment.

[f] Three patients did not want to participate in the study and five patients were judged not to have tuberculosis.

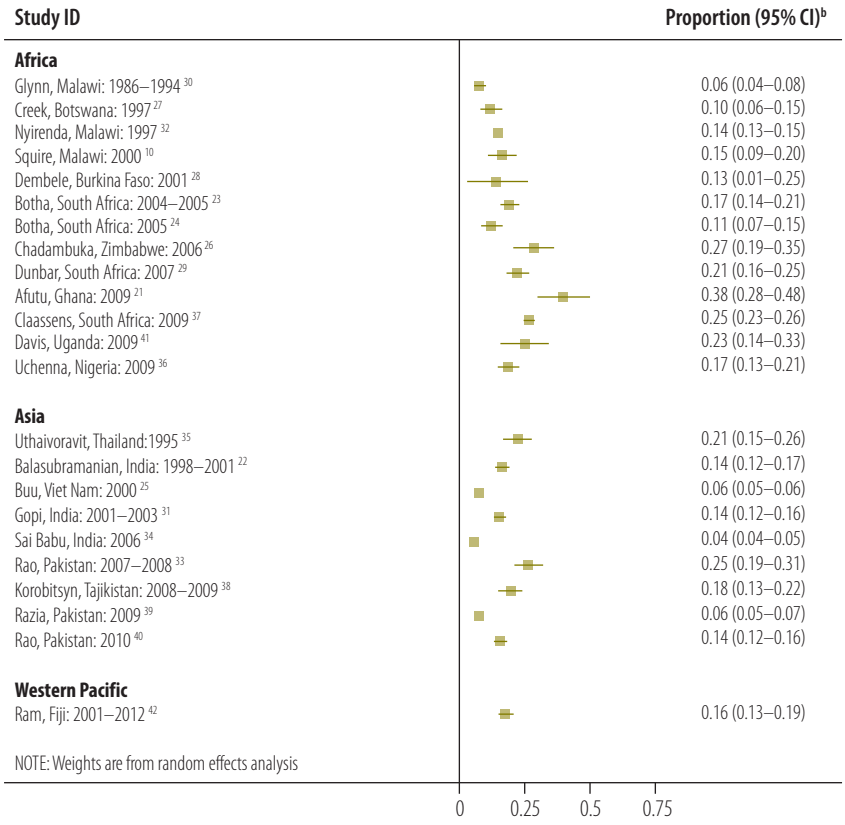
Note: The 95% CIs were calculated by authors using data in selected studies.

studies, the main reason for pre-treatment loss to follow-up was death, especially in countries in sub-Saharan Africa with generalized epidemics of HIV infection, perhaps because of the high mortality among patients having both tuberculosis and HIV infection.[47,48] It is difficult to ascertain whether these deaths are caused by or result from lack of treatment. Only one study reported the time between diagnosis and death in patients who did not start tuberculosis treatment; the median of 3.5 weeks found in the study suggests that patients were severely ill at the time of diagnosis.[10]

The diagnostic and care pathway is often costly and long, even in settings where health care and diagnostic tests are free at the point of delivery. Reducing costs and time for the patient might improve linkage to treatment. Thus, NTPs should consider the following measures: (i) reducing the number of sputum samples for initial diagnosis from three to two;[49] (ii) replacing "spot-morning-spot" sputum collection (requiring visits to the facility on two separate days) with collection of two spot sputum samples one hour apart;[14] (iii) preparing two smears from the same sputum specimen;[50] and (iv) introducing same-day light-emitting diode (LED) microscopy[51] or automated nucleic acid molecular diagnostics,[52] shown to be more sensitive and associated with reduced time to diagnosis and lower pre-treatment loss to follow-up. Further evaluation of the impact of these interventions on reducing pre-treatment loss to follow-up is required.

Health system factors, particularly relating to the recording and registration of suspected and confirmed tuberculosis cases, were found to be important contributors to pre-treatment loss to follow-up in several studies. Moreover, in many studies researchers were required to reconcile laboratory registers with treatment registers to determine the pre-treatment loss to follow-up rate, a task not easy to perform regularly under routine programmatic conditions. These issues could be addressed by using a single patient identifier for the entire diagnostic and care pathway for tuberculosis. Patients attending a facility with a positive screening for symptoms of tuberculosis would be recorded in a "cough register"[53] for subsequent monthly tracing of those whose smear results had not been received and of smear-positive patients who had not returned for treatment.

Fig. 3. **Proportion of patients with a diagnosis of tuberculosis who were lost to follow-up before treatment[a] in 23 studies from Africa, Asia and the western Pacific**



CI, confidence interval.

[a] All studies combined represent 34 706 patients with a diagnosis of tuberculosis; 3267 were lost to follow-up before treatment.

[b] The 95% CIs were calculated by authors from data provided in selected studies.

Note: In studies in which patients were traced, individuals with a diagnosis of tuberculosis who were lost to follow-up before treatment but who had started treatment for tuberculosis elsewhere are included as having initiated treatment.

By not including individuals lost to follow-up before treatment when reporting standard programme indicators, NTPs incorrectly report case detection, cure and case fatality rates. For example, with DOTS strategy targets of 70% case detection and 85% cure rate, including individuals who experience pre-treatment loss to follow-up (using 18% in Africa and 13% in Asia, for illustration), would result in the true case detection rate rising from 70% to 85% in African countries and 70% to 80% in Asian countries, as those diagnosed but not started on treatment are included (Table 5). The cure rate however would drop from 85% to 70% in Africa and from 85% to 74% in Asia, as those detected but not started on treatment are counted as "not cured". Moreover, in African countries, where the higher death rate in individuals with pre-treatment loss to follow-up could be attributable to HIV infection, the reported death rate would increase from 6 to 12%. In NTPs from Asia, the death rate would be unchanged at 3%. These numbers better reflect NTP's actual performance – they are finding more cases than thought, but are not performing so well at providing treatment.

In studies from Asia, where more private practitioners offer tuberculosis treatment services alongside NTPs,[54,55] a small number of patients lost to follow-up initiated treatment with private providers. Since they would not be included in NTP reports of outcomes, the success of the national programme would be underestimated. Interventions to improve links and data sharing between NTPs and private providers have proved effective in increasing case detection rates in studies from Asia[56,57] and are promoted by WHO.[58] Further expansion of such interventions will help to ensure that programme outcomes are accurately reported at the national level.

A limitation of this analysis is the poor quality of outcome ascertainment in several studies. The small number of traced individuals who had initiated treatment under a different provider underscores the need to tailor tuberculosis services to the individual patient and the difficulty of accurately estimating outcomes at the programme level. The varying length of follow-up of tuberculosis patients in cohort studies and the absence of time-delineated definitions for pre-treatment loss to follow-up make it difficult to draw firm conclusions. Following the framework set out in Fig. 1, NTPs should strive to adopt and routinely report retention in care throughout the diagnostic and care pathway.[16,59] A focus on retention could enhance the reporting of the pre-treatment loss to follow-up rate (e.g. the proportion of smear-positive patients not initiating treatment for tuberculosis within 3 months) as part of the regular quarterly reporting system, in addition to allowing comparison within and between NTPs.

A second limitation is that negative publication bias may have resulted in an under- or overestimation of pre-treatment loss to follow-up in this review. Although we undertook a systematic literature search, we may have missed some studies reporting on pre-treatment loss to follow-up if this was not the main focus of the study.

Because the studies identified were so heterogeneous, the summary estimates should be interpreted cautiously. Our ability to draw conclusions on the risk factors or reasons for pre-treatment loss to follow-up among people with tuberculosis is limited by the poor reporting of the baseline characteristics of study participants and low numbers of traced patients in several studies. We identified studies from 8 of the world's 22 countries with a high burden of tuberculosis. Although the data from these countries are helpful in showing the important contribution of pre-treatment loss to follow-up to suboptimal NTP performance, data from a broader range of countries and regions are urgently needed. In particular, no studies from Latin American countries or the Russian Federation were identified, perhaps because these countries have produced no studies or because we limited our search to English-language sources. To facilitate comparisons between studies and regions, all studies reporting outcomes in patients with a diagnosis of tuberculosis

Table 5. **Impact of including rates of pre-treatment loss to follow-up on national tuberculosis programme indicators in hypothetical programmes in Africa and Asia with 100 000 individuals and DOTS strategy targets (70% case detection, 85% cure) theoretically achieved, 2011**

Indicator	Africa		Asia	
	Outcomes reported under current WHO targets	After including tuberculosis patients lost to follow-up before treatment	Outcomes reported under current WHO targets	After including tuberculosis patients lost to follow-up before treatment
No. of cases	100 000	100 000	100 000	100 000
Cases detected, no. (%)	70 000 (70)	85 366[a] (85)	70 000 (70)	80 460[a] (80)
Tuberculosis patients lost to follow-up before treatment, no. (%)	Unknown	15 366 (18)	Unknown	10 460 (13)
Cases started on treatment, no. (%)	Unknown	70 000 (82)[b]	Unknown	70 000 (87)[b]
Patients cured, no. (%)	59 500 (85)	59 500 (70)[c]	59 500 (85)	59 500 (74)[c]
Deceased tuberculosis patients, no. (%)	4200[d] (6)	12 498[e] (12)	2100[d] (3)	3251[e] (3)

WHO, World Health Organization.
[a] Calculated as [1 ÷ (1 − fraction lost to follow-up before treatment)] × number of cases detected. For Africa: [1 ÷ 0.82] × 70 000; for Asia: [1 ÷ 0.87] × 70 000.
[b] Percentage calculated as number of cases initiating tuberculosis treatment divided by the number of cases detected. For Africa: 70 000 ÷ 85 366; for Asia: 70 000 ÷ 80 460.
[c] Percentage calculated as the number of patients who successfully completed treatment divided by the number of cases detected. For Africa: 59 500 ÷ 85 366; for Asia: 59 500 ÷ 80 460.
[d] Number obtained from WHO country database.
[e] Calculated as the number of deceased tuberculosis patients plus the product of the number of cases lost to follow-up before treatment and the median case fatality rate found in this review. For Africa: 4200 + (15 366 × 0.54); for Asia: 2100 + (10 460 × 0.11).
Note: Estimates for the western Pacific region not included, as only one study was identified.

should specify the proportion that is lost to follow-up before getting treated.

In conclusion, there is a paucity of evidence on the magnitude and clinical consequences of pre-treatment loss to follow-up in tuberculosis patients. The limited data available suggest that pre-treatment loss to follow-up is common and that it entails a high risk of death. There is an urgent need to improve the recording and reporting of pre-treatment loss to follow-up and to evaluate and scale up interventions to reduce this problem. ■

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ملخص

الفقدان في مرحلة ما قبل العلاج المقرر متابعته في مرضى السل في البلدان المنخفضة الدخل وبلدان الشريحة الدنيا من الدخل المتوسط والبلدان التي ترزح تحت عبء المرض الثقيل: استعراض منهجي وتحليل وصفي

الغرض تقييم حجم الفقدان المقرر متابعته في مرضى السل الذين ثبتت إيجابية نتائج اختبار اللطاخة أو المزرعة الخاص بهم قبل بدء العلاج والحصائل بين المرضى الذين تم تتبعهم.

الطريقة تم البحث في قواعد بيانات Ovid و Medline و Global Health عن الدراسات التي تم نشرها في الفترة من 1994 إلى يناير 2013 التي وصفت الفقدان في مرحلة ما قبل العلاج المقرر متابعته في مرضى السل الذين ثبتت إيجابية نتائج اختبار اللطاخة أو المزرعة الخاص بهم في البرامج الوطنية الروتينية لمكافحة السل في البلدان المنخفضة الدخل وبلدان الشريحة الدنيا من الدخل المتوسط والبلدان التي ترزح تحت العبء الثقيل للسل. وتم استخلاص البيانات بشأن نسبة المرضى الذين لم يبدؤا العلاج بعد تشخيصهم بالسل من الدراسات التي لبت معايير الإدراج. وتم تحري البيانات المعنية بالأسباب والحصائل، بما في ذلك بدء علاج السل في مرفق آخر، حيثما كان ذلك متاحا. وتم تقييم التغايرية والتحيز في النشر وإجراء التحليلات الوصفية للتأثيرات العشوائية حسب الفئة الفرعية (الإقليم).

النتائج تم تحديد ثلاث وعشرين دراسة مؤهلة اشتملت على إجمالي 34706 مريضاً من مرضى السل الذين ثبتت إيجابية نتائج اختبار اللطاخة أو المزرعة الخاصة بهم من 14 بلداً (8 في أفريقيا و5 في آسيا وواحدة في غرب المحيط الهادئ). وكانت معظم الدراسات استرجاعية وربطت بين المختبر وسجلات العلاج لتحديد الفقدان في مرحلة ما قبل العلاج المقرر متابعته. وتراوح الفقدان في مرحلة ما قبل العلاج المقرر متابعته من 4 ٪ إلى 38 ٪ وكان شائعاً في دراسات أفريقيا (النسبة المرجحة للتأثيرات العشوائية: 18 ٪؛

فاصل الثقة 95 ٪، من 13 إلى 22) وآسيا (النسبة المرجحة: 13 ٪؛ فاصل الثقة 95 ٪، من 10 إلى 15).
الاستنتاج من الممكن أن يعرقل الفقدان في مرحلة ما قبل العلاج المقرر متابعته، والذي يشيع في معظم البيئات، جهود مكافحة السل. وتقلل البرامج الوطنية لمكافحة السل من تقدير معدلات الكشف عن الحالات والوفيات وتزيد من تقدير معدلات الشفاء عند عدم عد الأشخاص الذين فقدت متابعتهم قبل العلاج عند الإبلاغ عن مؤشرات البرامج الموحدة.

摘要

中低收入国家和高负担国家的肺结核病治疗前失访情况：系统评价和元分析

目的 评估在治疗开始之前痰涂片或菌培阳性肺结核病人失访的量级和被追踪病人的结果。

方法 搜索奥维德（Ovid）、联机医学文献和检索系统（Medline）以及全球卫生（Global Health）数据库，寻找在 1994 年和 2013 年 1 月之间发表的描述中低收入国家和肺结核病高负担国家在常规国家结核病规划（NTP）中对痰涂片阳性或者菌培阳性肺结核病人治疗前失访情况的研究。从满足入选标准的研究中，提取肺结核诊断之后没有开始治疗的患者比例方面的数据。如果有的话，还调查原因和结果数据（包括在另一个医疗设施中开始肺结核治疗的情况）。评估异质性和发表偏倚，执行子群（地区）随机荟萃分析。

结果 确认了 23 个符合要求的研究，其中包括 14 个国家（非洲 8 个，亚洲 5 个，西太平洋 1 个）的总计 34706 名痰涂片阳性或者菌培阳性肺结核病人。大多数研究是回顾性研究，与实验室和治疗登记相关，用以识别治疗前失访情况。治疗前失访率为 4% 到 38% 不等，常见于非洲（随机加权比例 WP：18%；95% 置信区间，CI：13-22）和亚洲（WP：13%；95% CI：10-15）的研究中。

结论 常见于大多数环境中的治疗前失访会妨碍肺结核控制工作。在报告标准项目指标时，由于没有计算治疗之前失访的个人数量，NTP 低估了病例发现率和死亡率，高估了治愈率。

Résumé

Le manque de suivi avant le traitement chez les patients atteints de tuberculose dans les pays à revenu faible et à revenu moyen inférieur fortement touchés par la maladie: méta-analyse et analyse systématique

Objectif Évaluer l'ampleur du manque de suivi chez les patients atteints d'une tuberculose à frottis positif ou culture positive avant le début du traitement, ainsi que les résultats chez les patients qui ont été suivis.

Méthodes Des études publiées entre 1994 et janvier 2013, qui décrivaient le manque de suivi des patients atteints de tuberculose à frottis positif ou à culture positive dans des programmes nationaux courants de lutte contre la tuberculose (NTP) dans les pays à revenu faible et à revenu moyen inférieur fortement touchés par la tuberculose ont été recherchées dans les bases de données Ovid, Medline et Global Health. Des données concernant le taux de patients qui n'ont pas débuté le traitement après leur diagnostic de tuberculose ont été extraites des études satisfaisant les critères d'inclusion. Le cas échéant, les données portant sur les causes et les résultats, y compris le début d'un traitement contre la tuberculose dans un autre établissement, ont été examinées. L'hétérogénéité et le parti pris dans les publications ont été évalués, et des méta-analyses à effets aléatoires par sous-groupe (région) ont été réalisées.

Résultats Vingt-trois études éligibles ont été identifiées pour un total de 34 706 patients atteints de tuberculose à frottis positif ou à culture positive dans 14 pays (8 en Afrique, 5 en Asie et 1 dans le Pacifique occidental). La plupart des études étaient rétrospectives et associaient des registres de laboratoire et de traitement pour identifier le manque de suivi avant le traitement. Celui-ci variait de 4% à 38% et s'est révélé commun dans les études provenant d'Afrique (proportion pondérée à effets aléatoires, PP: 18%; intervalle de confiance à 95%, IC: 13–22) et d'Asie (PP: 13%; IC à 95%: 10–15).

Conclusion Le manque de suivi avant le traitement, commun dans la plupart des contextes, peut entraver les efforts fournis en matière de lutte contre la tuberculose. Comme les individus qui ne sont pas suivis avant le traitement ne sont pas pris en compte lors de l'élaboration des rapports sur les indicateurs de programme standard, les programmes nationaux de lutte contre la tuberculose sous-estiment les taux de dépistage des cas et la mortalité, mais surestiment les taux de guérison.

Резюме

Случаи отсутствия наблюдения до начала лечения больных туберкулезом в странах с низкими доходами и доходами ниже среднего уровня, а также в странах с высоким бременем туберкулеза: систематический обзор и мета-анализ

Цель Произвести количественную оценку числа случаев отсутствия наблюдения за мокрото- или культуропозитивными пациентами, страдающими туберкулезом легких, с момента диагностирования заболевания до начала лечения, а также обработать результаты по пациентам, которых удалось отследить.

Методы В базах данных Ovid, Medline и Global Health был произведен поиск исследований, проведенных в рамках стандартных национальных программ по борьбе с туберкулезом в странах с низкими доходами и доходами ниже среднего уровня, а также в странах с высоким бременем туберкулеза, опубликованных в период с 1994 года по январь 2013 года, и содержащих описания случаев отсутствия наблюдения до начала лечения за мокротопозитивными или культуропозитивными пациентами, страдающими туберкулезом легких. Данные по пропорциональному количеству пациентов, которые не начали лечение после диагностирования туберкулеза, были извлечены из исследований, соответствующих критериям включения в данный анализ. По мере возможности, также были исследованы данные по причинам и последствиям, включая прохождение лечения в другом медицинском учреждении. Также была проведена оценка разнородности и систематических ошибок, связанных с предпочтительной публикацией положительных результатов исследований, а также мета-анализ случайных эффектов по подгруппам (регионам).

Результаты Было выявлено 23 исследования, соответствующие критериям включения в данный анализ, которые охватывали в целом 34 706 мокротопозитивных или культуропозитивных пациентов, страдающих туберкулезом легких из 14 стран (8 в Африке, 5 в Азии и 1 в регионе Западной части Тихого океана). Большинство исследований были ретроспективными и включали анализ журналов регистраций результатов лабораторных анализов и прохождения лечения, что позволило выявить случаи непрохождения последующего наблюдения до начала лечения. Показатель непрохождения последующего наблюдения до начала лечения колебался от 4 до 38%, где наиболее высокие значения были отмечены в исследованиях, проводимых в Африке (взвешенная пропорция случайных эффектов, ВП: 18%; 95% доверительный интервал, ДИ: 13–22) и Азии (ВП: 13%; 95% ДИ: 10–15).
Вывод Непрохождение пациентами наблюдения от момента обнаружения заболевания до начала лечения, при схожих значениях остальных параметров, может снижать эффект от принимаемых мер по борьбе с туберкулезом. Неучет лиц, за которыми не велось наблюдение до начала лечения, и их невключение в отчеты со стандартными показателями программы приводит к тому, что национальные программы по борьбе с туберкулезом занижают показатели выявления случаев заболевания и смертности, одновременно завышая оценки показателей эффективности лечения.

Resumen

Pérdida de seguimiento antes del tratamiento de pacientes con tuberculosis en países de ingresos medios y bajos y en países con carga alta: una revisión sistemática y metanálisis

Objetivo Evaluar la magnitud de la pérdida de seguimiento de los pacientes con tuberculosis que dieron positivo en el análisis o el cultivo antes del inicio del tratamiento y los resultados entre los pacientes que se sometieron a un seguimiento.
Métodos Se realizó una búsqueda en las bases de datos Ovid, Medline y Global Health de estudios publicados entre 1994 y enero de 2013 que describían pérdidas de seguimiento antes del tratamiento en pacientes que dieron positivo en el análisis o el cultivo de tuberculosis en los programas nacionales contra la tuberculosis (PNT) ordinarios en países de ingresos medios y bajos y en países con carga alta de tuberculosis. Se extrajeron datos sobre la proporción de pacientes que no inició un tratamiento después del diagnóstico de la tuberculosis de estudios que cumplían los criterios de inclusión. Siempre que fue posible, se investigaron los datos sobre las causas y resultados, incluida la iniciación del tratamiento de la tuberculosis en otro centro. Se evaluó el sesgo de las publicaciones y la heterogeneidad, y se realizaron metanálisis de efectos aleatorios por subgrupos (región).
Resultados Se identificaron veintitrés estudios que cumplían los criterios, con un total de 34 706 pacientes que dieron positivo en el análisis o cultivo de tuberculosis de 14 países (8 de África, 5 de Asia y 1 del Pacífico occidental). La mayoría de los estudios eran retrospectivos y relacionaban los registros de laboratorio con los registros de tratamiento para identificar la pérdida de seguimiento antes del tratamiento, que osciló entre el 4 y 38 % y fue frecuente en los estudios de África (proporción ponderada de efectos aleatorios, WP: 18 %; intervalo de confianza del 95 %, IC: 13–22) y Asia (WP: 13 %; IC del 95 %: 10–15).
Conclusión La pérdida de seguimiento antes del tratamiento, común en la mayoría de los entornos, puede obstaculizar los esfuerzos de control de la tuberculosis. Sin contar los pacientes cuyo seguimiento se pierde antes del tratamiento, los programas nacionales contra la tuberculosis subestiman la mortalidad y las tasas de detección de casos, a la vez que sobrestiman las tasas de curación al informar sobre los indicadores del programa estándar.

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