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Systematic reviews

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

Peter MacPherson, a Rein MGJ Houben, b Judith R Glynn, a Elizabeth L Corbett a & Katharina Kranzer a

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.

Abstract in العربية, 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 2,3 and, with the sole exception of the African Region, all are on track to halve tuberculosis mortality rates. 4 Nevertheless, the situation remains precarious. 5 Twenty-two predominantly low- and middle-income countries were estimated to account for 82% of the 5.7 million tuberculosis cases notified in 2010 6 and high rates of death from tuberculosis among people living with human immunodeficiency virus (HIV) infection prevail in much of sub-Saharan Africa. 7,8

Rapid case identification of individuals with sputum smear-positive tuberculosis and rapid initiation of anti-tuberculosis chemotherapy are key to controlling tuberculosis 9 and are promoted as part of the DOTS strategy model of passive case-finding that has been adopted by most national tuberculosis programmes (NTPs). 10 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. 10,11 High rates of mortality are reported in this group. 12,13 Moreover, bringing these patients into care could reduce tuberculosis transmission to others. 14 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. 15

Efforts to improve tuberculosis case detection rates have centred on ensuring rapid treatment for all individuals diagnosed with smear-positive tuberculosis. 16,17,18 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. 19,20 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 6 and of the patient, provider and health system factors that contribute to it. 21

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. 22,23,24 Indeed, the “Piot model” used to describe loss to care at different stages for any disease was first developed for tuberculosis. 25

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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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. 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”.

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.
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 2011,10 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).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year(s) study conducted</th>
<th>Country</th>
<th>Setting</th>
<th>Diagnostic criterion</th>
<th>Recruitment period</th>
<th>No. with diagnosis of tuberculosis</th>
<th>Follow-up period</th>
<th>Temporal definition of pre-treatment loss to follow-up</th>
<th>Method used to confirm start of treatment</th>
<th>No. (%) of patients initiating treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creek, 2000&lt;sup&gt;27&lt;/sup&gt;</td>
<td>1997</td>
<td>Botswana</td>
<td>Gaborone, outpatient department of public hospital and 13 PHCs</td>
<td>≥ 1 positive smear</td>
<td>5 months</td>
<td>184</td>
<td>5–22 months</td>
<td>2 weeks</td>
<td>Retrospective linking of laboratory register and national electronic tuberculosis register</td>
<td>165 (90)</td>
</tr>
<tr>
<td>Dembele, 2006&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2001</td>
<td>Burkina Faso</td>
<td>6 districts (including the capital)</td>
<td>Any smear positive, not further specified</td>
<td>1 year</td>
<td>31</td>
<td>NR</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>27 (87)</td>
</tr>
<tr>
<td>Afutu, 2012&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2009</td>
<td>Ghana</td>
<td>Regional hospital</td>
<td>Smear positive, not further specified</td>
<td>1 year</td>
<td>84</td>
<td>9–27 months</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>52 (62)</td>
</tr>
<tr>
<td>Glynn, 1998&lt;sup&gt;30&lt;/sup&gt;</td>
<td>1986–1994</td>
<td>Malawi</td>
<td>Rural PHCs, one district hospital</td>
<td>≥ 1 positive smear</td>
<td>90 months</td>
<td>682</td>
<td>Up to 110 months</td>
<td>ND</td>
<td>Prospective monthly follow-up as part of Demographic and Health Survey</td>
<td>642 (94)</td>
</tr>
<tr>
<td>Nyirenda, 1998&lt;sup&gt;32&lt;/sup&gt;</td>
<td>1997</td>
<td>Malawi</td>
<td>National</td>
<td>Smear positive, not further specified</td>
<td>6 months</td>
<td>3482</td>
<td>2–8 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>2980 (86)</td>
</tr>
<tr>
<td>Squire, 2005&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2000</td>
<td>Malawi</td>
<td>Rural, 31 PHCs, one district hospital</td>
<td>Smear positive, not further specified</td>
<td>6 months</td>
<td>157</td>
<td>0–6 months</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers, home tracing of patients with missing treatment information</td>
<td>134 (85)</td>
</tr>
<tr>
<td>Uchenna, 2012&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2009</td>
<td>Nigeria</td>
<td>5 states in southern Nigeria</td>
<td>Smear positive, not further specified</td>
<td>3 months</td>
<td>323</td>
<td>Up to 3 months</td>
<td>2 days</td>
<td>Retrospective collation of total number of tuberculosis patients diagnosed in laboratory registers and treated in treatment registers (individual records not linked)</td>
<td>268 (83)</td>
</tr>
<tr>
<td>Botha, 2008&lt;sup&gt;35&lt;/sup&gt;</td>
<td>2004–2005</td>
<td>South Africa</td>
<td>13 PHCs</td>
<td>≥ 2 positive smears</td>
<td>1 year</td>
<td>367</td>
<td>3–15 months</td>
<td>3 months</td>
<td>Retrospective linking of sputum collection register and treatment register</td>
<td>303 (83)</td>
</tr>
<tr>
<td>Botha, 2008&lt;sup&gt;35&lt;/sup&gt;</td>
<td>2005</td>
<td>South Africa</td>
<td>11 PHCs in the Western Cape province (8 in Cape Town metropolitan area)</td>
<td>≥ 2 positive smears</td>
<td>3 months</td>
<td>227</td>
<td>4–16 months</td>
<td>2 months</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>203 (89)</td>
</tr>
<tr>
<td>Claassens, 2010&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2009</td>
<td>South Africa</td>
<td>133 PHCs in 5 provinces</td>
<td>Smear positive, not further specified</td>
<td>5 months</td>
<td>3020</td>
<td>NR</td>
<td>1 month</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>2268 (75)</td>
</tr>
</tbody>
</table>

(continues...)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year(s) study conducted</th>
<th>Country</th>
<th>Setting</th>
<th>Diagnostic criterion</th>
<th>Recruitment period</th>
<th>No. with diagnosis of tuberculosis</th>
<th>Follow-up period</th>
<th>Temporal definition of pre-treatment loss to follow-up</th>
<th>Method used to confirm start of treatment</th>
<th>No. (%) of patients initiating treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunbar, 2011&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2007</td>
<td>South Africa</td>
<td>Two community clinics</td>
<td>Bacteriologically confirmed</td>
<td>1 year</td>
<td>306</td>
<td>Up to 24 months&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 months</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>243 (79)</td>
</tr>
<tr>
<td>Davis, 2011&lt;sup&gt;41&lt;/sup&gt;</td>
<td>2009</td>
<td>Uganda</td>
<td>Five PHCs</td>
<td>≥ 1 positive smear</td>
<td>1 year</td>
<td>81</td>
<td>NR</td>
<td>ND</td>
<td>Prospective cohort follow-up, with additional retrospective linkage of laboratory and treatment registers for confirmation</td>
<td>62 (77)</td>
</tr>
<tr>
<td>Chadambuka, 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2006</td>
<td>Zimbabwe</td>
<td>Gokwe district</td>
<td>Smear positive, not further specified</td>
<td>1 year</td>
<td>112</td>
<td>1 month</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>82 (73)</td>
</tr>
<tr>
<td>Balasubramanian, 2004&lt;sup&gt;12&lt;/sup&gt;</td>
<td>1998–2001</td>
<td>India</td>
<td>PHCs</td>
<td>≥ 2 positive smears</td>
<td>2 years</td>
<td>833</td>
<td>3 months</td>
<td>3 months</td>
<td>Retrospective linking of laboratory register and patient records</td>
<td>713 (86)</td>
</tr>
<tr>
<td>Gopi, 2005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2001–2003</td>
<td>India</td>
<td>One PHC</td>
<td>Smear positive, not further specified</td>
<td>31 months</td>
<td>1049</td>
<td>2 months</td>
<td>2 months</td>
<td>Prospective reconciliation of laboratory and treatment registers</td>
<td>893 (85)</td>
</tr>
<tr>
<td>Sai Babu, 2008&lt;sup&gt;14&lt;/sup&gt;</td>
<td>2006</td>
<td>India</td>
<td>20 districts in Andhra Pradesh state</td>
<td>≥ 2 positive smears</td>
<td>3 months</td>
<td>15 361</td>
<td>Cross-sectional: identification of all initial defaulters in one quarter of 2006</td>
<td>ND</td>
<td>Extraction of data from laboratory register; home tracing of patients with missing treatment information</td>
<td>14 676 (96)</td>
</tr>
<tr>
<td>Razia, 2011&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2009</td>
<td>Pakistan</td>
<td>One district, including 16 peripheral centres and five tertiary centres</td>
<td>Smear positive, not further specified</td>
<td>1 year</td>
<td>1698</td>
<td>Up to one year</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>1597 (84)</td>
</tr>
<tr>
<td>Rao, 2009&lt;sup&gt;15&lt;/sup&gt;</td>
<td>2007–2008</td>
<td>Pakistan</td>
<td>Chest clinic, Karachi</td>
<td>Smear positive, not further specified</td>
<td>5 months</td>
<td>224</td>
<td>Patients prospectively recruited during a 5-month period; time before tracing undertaken not defined</td>
<td>ND</td>
<td>Telephone tracing of patients who did not return for treatment</td>
<td>162 (72)</td>
</tr>
<tr>
<td>Rao, 2011&lt;sup&gt;40&lt;/sup&gt;</td>
<td>2010</td>
<td>Pakistan</td>
<td>Chest clinic, Karachi</td>
<td>Smear positive, not further specified</td>
<td>6 months</td>
<td>1121</td>
<td>Up to 6 months</td>
<td>ND</td>
<td>Telephone tracing of patients who did not return for treatment</td>
<td>947 (84)</td>
</tr>
<tr>
<td>Korbibitsyn, 2010&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2008–2009</td>
<td>Tajikistan</td>
<td>Four districts</td>
<td>Smear positive, not further specified</td>
<td>1 year</td>
<td>254</td>
<td>Up to one year</td>
<td>ND</td>
<td>Retrospective linking of laboratory and treatment registers</td>
<td>209 (82)</td>
</tr>
<tr>
<td>Uthairoravit, 2003&lt;sup&gt;22&lt;/sup&gt;</td>
<td>1995</td>
<td>Thailand</td>
<td>Provincial referral hospital</td>
<td>≥ 1 positive smear</td>
<td>60 months</td>
<td>212</td>
<td>“Mid-1996” to “the end of 2000”. Reported in yearly cohorts</td>
<td>ND</td>
<td>Prospective linking of laboratory, treatment register and medical records</td>
<td>168 (79)</td>
</tr>
</tbody>
</table>

(...continued)
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).

Table 1 shows the characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year(s) study conducted</th>
<th>Country</th>
<th>Setting</th>
<th>Recruiting period</th>
<th>No. with diagnosis of tuberculosis</th>
<th>No. with diagnosis of smear-positive disease</th>
<th>No. with smear-positive disease</th>
<th>Recruitment criterion</th>
<th>Follow-up period</th>
<th>Method used to confirm start of treatment</th>
<th>Temporal definition of pre-treatment loss to follow-up</th>
<th>No. with pre-treatment loss to follow-up period</th>
<th>No. (% of patients initiating treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buu, 2003 25</td>
<td>2000</td>
<td>Viet Nam</td>
<td>District tuberculosis units</td>
<td>1 year</td>
<td>3859 (84)</td>
<td>78 (2)</td>
<td>706 (18)</td>
<td>≥ 1 month</td>
<td>smear-positive</td>
<td>2 month</td>
<td>Retrospective linkage of laboratory and treatment registers</td>
<td>Retrospective linkage of laboratory and treatment registers</td>
<td>4280 (21)</td>
</tr>
<tr>
<td>Pan, 2012 26</td>
<td>2001–2010 Fiji</td>
<td>Fiji</td>
<td>Laboratories and DOTs sites</td>
<td>9 years</td>
<td>690</td>
<td>579 (84)</td>
<td>579 (84)</td>
<td>≥ 1 month</td>
<td>smear-positive</td>
<td>1 month</td>
<td>Retrospective linkage of laboratory and treatment registers</td>
<td>Retrospective linkage of laboratory and treatment registers</td>
<td>30</td>
</tr>
</tbody>
</table>

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. In some studies smear positivity was defined as at least 1, 2, 27–29, 30–31, 34–42 or at least 22, 24, 34 positive smears, whereas others did not provide any definition.

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), 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.

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 four studies, patients with a diagnosis of tuberculosis were identified as part of ongoing epidemiological surveillance or were prospectively recruited for follow-up from a chest clinic or from primary-health-care centres. The recruitment periods ranged from 3 months, to 90 months. Only 9 studies22–25, 27, 29–51, 53, 57 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 and to follow-up, some studies did not report on data from a single clinical site. Studies that reported on data from a single clinical site22, 25, 27, 29, 33, 37–39, 41–42 had higher rates of pre-treatment loss to follow-up (range: 14–38%) than studies reporting on national or regional data (range: 4–25%).

In total, 10 studies18, 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.20 Tracing rates were rather poor on average. The proportion of patients who could not be traced ranged from 0%21 to 77%.22 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. 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. 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-
Factors associated with an increased risk of pre-treatment loss to follow-up were male sex, older age, living in an urban area, diagnosis in a hospital or stationary clinic (rather than a mobile clinic), geographical location of the tuberculosis laboratory (regional versus local), and being diagnosed with smear-negative but culture-positive tuberculosis. However, distance to treatment site was not associated with the risk of pre-treatment loss to follow-up in Ghana.

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, and the other eight were based on structured patient interviews, either in person or by telephone. 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. 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). Other reasons were disease-related (e.g., weakness and fatigue).

### 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. 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 and experience high morbidity and mortality.

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. Although tracing was suboptimal in most

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### 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Selection</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creek</td>
<td>Botswana</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>Dembele</td>
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<td>+</td>
</tr>
<tr>
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<td>Ghana</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>Glynn</td>
<td>Malawi</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
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<td>Malawi</td>
<td>***</td>
<td>+</td>
</tr>
<tr>
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<td>***</td>
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</tr>
<tr>
<td>Uchenna</td>
<td>Nigeria</td>
<td>***</td>
<td>+</td>
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<tr>
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<td>South Africa</td>
<td>***</td>
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</tr>
<tr>
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<td>South Africa</td>
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<tr>
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<td>South Africa</td>
<td>***</td>
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<tr>
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<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Davis</td>
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<td>***</td>
<td>+</td>
</tr>
<tr>
<td>Chadambuka</td>
<td>Zimbabwe</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Balasubramanian</td>
<td>India</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Gopi</td>
<td>India</td>
<td>**</td>
<td>+</td>
</tr>
<tr>
<td>Sai Babu</td>
<td>India</td>
<td>**</td>
<td>+</td>
</tr>
<tr>
<td>Razia</td>
<td>Pakistan</td>
<td>***</td>
<td>+</td>
</tr>
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<tr>
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<td>Pakistan</td>
<td>***</td>
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<tr>
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<td>Tajikistan</td>
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<td>Thailand</td>
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<td>+</td>
</tr>
<tr>
<td>Buu</td>
<td>Viet Nam</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>Ram</td>
<td>Fiji</td>
<td>***</td>
<td>+</td>
</tr>
</tbody>
</table>

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### Reasons for loss to follow-up

- A study can be awarded a maximum of one star for each of three items within the “selection” and “outcome” categories.
- Assessment of patient selection comprised three items (those that score stars are shown): (i) representativeness of the cohort (true 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).
- 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); (iii) adequacy of follow-up (complete, follow-up > 80%, follow-up < 80%, no description).

---

### 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. 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 and experience high morbidity and mortality.

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. Although tracing was suboptimal in most
Pre-treatment loss to follow-up in tuberculosis patients

Peter MacPherson et al.

Systematic reviews

In 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.49

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) microscopy51 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" for subsequent monthly tracing of those whose smear results had not been received and of smear-positive patients who had not returned for treatment.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>No. lost to follow-up before treatment</th>
<th>% (95% CI)</th>
<th>No. of treatment status unknown</th>
<th>% (95% CI)</th>
<th>No. traced elsewhere</th>
<th>% (95% CI)</th>
<th>No. deceased</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynn30</td>
<td>Malawi</td>
<td>40</td>
<td>0.00–0.09</td>
<td>0</td>
<td>0.00–0.09</td>
<td>40</td>
<td>0.63 (0.47–0.77)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Nyirenda32       | Malawi        | 502                                     | 0.73 (0.63–0.83) | 40 | 0.34 (0.26–0.44) | 27 (outside district) | 0         | 0.34 (0.26–0.44) | 27 (outside district) | 0  
| Squire10         | Malawi        | 20                                      | 0.16 (0.05–0.38) | 3  | 0.14 (0.03–0.29) | 0           | 0         | 0.14 (0.03–0.29) | 0  
| Botha24          | South Africa  | 58                                      | 0.65 (0.43–0.88) | 9  | 0.39 (0.29–0.49) | 13 (outside area) | 0         | 0.39 (0.29–0.49) | 13 (outside area) | 0  
| Gopi31           | India         | 156                                     | 0.55 (0.43–0.68) | 77 | 0.59 (0.49–0.70) | 38 (private) | 0         | 0.59 (0.49–0.70) | 38 (private) | 0  
| Sai Babu34       | India         | 685                                     | 0.59 (0.55–0.62) | 55 | 0.55 (0.49–0.61) | 6 (private) | 0         | 0.55 (0.49–0.61) | 6 (private) | 0  
| Rao33            | Pakistan      | 62                                      | 0.55 (0.46–0.65) | 18 | 0.41 (0.33–0.49) | 15 (private) | 0         | 0.41 (0.33–0.49) | 15 (private) | 0  
| Korobitsyn38     | Tajikistan    | 45                                      | 0.60 (0.45–0.73) | 18 | 0.41 (0.33–0.49) | 15 (private) | 0         | 0.41 (0.33–0.49) | 15 (private) | 0  
| Buu25            | Viet Nam      | 349                                     | 0.50 (0.45–0.55) | 174 | 0.50 (0.45–0.55) | 175 (private) | 0         | 0.50 (0.45–0.55) | 175 (private) | 0  

CI, confidence interval; NS, not stated.

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

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 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. 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...
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.

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

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Outcomes reported under current WHO targets</th>
<th>After including tuberculosis patients lost to follow-up before treatment</th>
<th>Outcomes reported under current WHO targets</th>
<th>After including tuberculosis patients lost to follow-up before treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>100,000</td>
<td>100,000</td>
<td>100,000</td>
<td>100,000</td>
</tr>
<tr>
<td>Cases detected, no. (%)</td>
<td>70,000 (70)</td>
<td>85,366* (85)</td>
<td>70,000 (70)</td>
<td>80,460* (80)</td>
</tr>
<tr>
<td>Tuberculosis patients lost to follow-up before treatment, no. (%)</td>
<td>Unknown</td>
<td>15,366 (18)</td>
<td>Unknown</td>
<td>10,460 (13)</td>
</tr>
<tr>
<td>Cases started on treatment, no. (%)</td>
<td>Unknown</td>
<td>70,000 (82)*</td>
<td>Unknown</td>
<td>70,000 (87)*</td>
</tr>
<tr>
<td>Patients cured, no. (%)</td>
<td>59,500 (85)</td>
<td>59,500 (70)*</td>
<td>59,500 (85)</td>
<td>59,500 (74)*</td>
</tr>
<tr>
<td>Deceased tuberculosis patients, no. (%)</td>
<td>4,200* (6)</td>
<td>12,498* (12)</td>
<td>210* (3)</td>
<td>325* (3)</td>
</tr>
</tbody>
</table>

WHO, World Health Organization.

* Calculated as [1 – (1 – fraction lost to follow-up before treatment)] × number of cases detected. For Africa: [1 – 0.087] × 70,000; for Asia: [1 – 0.87] × 70,000.

* 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.

* 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.

* Number obtained from WHO country database.

* 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: 4,200 + (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.

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Competing interests: None declared.

ملخص النتائج

الفقدان في مرحلة ما قبل العلاج المقرر متابعته في مرضى السلفي البلدان المنخفضة الدخل وبلدان الشريحة الدنيا من الغرض تقدير حجم الفقدان المقرر متابعته في مرضى السل الذين تمت إيجاد نتائجهم قبل بدء العلاج والخسائر بين المرضى الذين تم تبعهم.

الحديث المترتب على البلدان التي تمت توزيع المرضى في مرض السل في البلدان المنخفضة الدخل وبلدان الشريحة الدنيا من الغرض تقييم حجم الفقدان المقرر متابعته في مرضى السل الذين تمت إيجاد نتائجهم قبل بدء العلاج والحصائل بين المرضى الذين تم تبعهم.

الدروس التي تم البحث في قواعد بيانات Global Health و Ovid و Medline عن الدراسات التي تم نشرها في الفترة من 1 يناير 1994 إلى 1 يناير 2013 ووصفت النتائج في مرحلة ما قبل العلاج المقرر متابعته في مرضى السل الذين تمت إيجاد نتائجهم في مرحلة ما قبل العلاج المقرر متابعته في مرحلة ما قبل العلاج المقرر متابعته من 4/3 إلى 8/3. وكان هناك شائع في دراسات أفريقيا (النسبة المرجحة للخسائر العشوائية: 18/3).
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患者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,用于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导致肺结核控制工作。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。
Результаты
Было выявлено 23 исследования, соответствующие критериям включения в данный анализ, которые охватывали в целом 34 706 мозгополитивных или культурополитивных 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% в 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. Используя лишь, 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 занимают 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 in 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 cumplieran 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.

References
Systematic reviews
Pre-treatment loss to follow-up in tuberculosis patients


