Tuberculosis case finding in South Africa
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Tuberculosis Patients In Primary Care Do Not Start Treatment. What Role Do Health System Delays Play?

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ABSTRACT

Setting
Primary healthcare facilities in five provinces of South Africa.

Objective
To investigate the association between the proportion of sputum results with a prolonged smear turnaround time and the proportion of smear positive TB cases who are initially lost to follow-up.

Design
The unit of investigation was a primary healthcare facility and the outcome was the initial loss to follow-up rate per facility which was calculated by comparing the sputum register with the TB treatment register. A prolonged turnaround time was defined as more than 48 hours from when the sputum sample was documented in the sputum register until the receipt of the result at the facility.

Results
The mean initial loss to follow-up rate was 25% (95%CI 22-28%). Turnaround time overall was inversely associated with initial loss to follow-up (p=0.008), when comparing Category 2 (33-66% turnaround time within 48 h) with Category 1 (0-32%) (OR 0.73, 95%CI 0.48-1.13, p=0.163) and when comparing Category 3 (67-100%) with Category 1 (OR 0.62, 95%CI 0.39-0.99, p=0.045). The population preventable fraction of initial loss to follow-up (when turnaround time was <48h in ≥67% of smear results) was 21%.

Conclusion
Initial loss to follow-up should be reported as part of the TB programme to ensure that patients are initiated on treatment to prevent transmission within communities.
INTRODUCTION

The management of tuberculosis (TB) in high prevalence settings such as South Africa depends on the rapid diagnosis and treatment of all infectious TB cases, especially those with smear positive disease (1-3). Patients with at least one positive smear should promptly be started on treatment (3,4). Although most TB programmes depend on passive case finding, National TB Programmes need to be active in developing strategies that make patients willing and able to access and attend its services (5).

Patients who are documented as sputum smear positive in the laboratory sputum register, but who do not appear in the TB treatment register and are therefore not registered as having started on treatment (6) may continue to spread tuberculosis in the community. However, in South Africa laboratory sputum registers are not routinely used because of the central structure of laboratories. Instead, sputum registers are used at facility level as advised (7). A study in Botswana (1) showed 27% of smear-positive TB patients had treatment delay or no evidence of treatment initiation and a study by Botha (8) documented an initial loss to follow-up (default) rate of 17% in selected facilities in the Western Cape, South Africa.

Health service related factors may constrain patient efforts to attend TB services (5). Edginton (9) demonstrated previous negative experiences at primary healthcare facilities in Gauteng, South Africa, are related to non-attendance of patients referred to these facilities. Documented service related factors associated with initial loss to follow-up (ILF) in Malawi are hospital admission, delays in the receipt of sputum results and misinterpretation by healthcare workers that negative smear results exclude tuberculosis (10).

Health systems delay can be defined as the sum of the time from contacting the health services to diagnosis (excluding patient delay) and time from diagnosis to initiation of treatment (11-13). One of the routine indicators in the South African National TB management guidelines is the sputum turnaround time (TAT) defined as the duration of time from taking a smear specimen from the patient (or receiving it at the facility if it is an early morning sputum) to receiving the result back at the facility (14). As TAT could be one of the factors contributing to delay in treatment initiation, the guidelines advise a target of 80% of smear results to be back at the facility within 48 hours. Improving TAT would, by definition, reduce the amount of time from the initial consultation to the final diagnosis (15) which suggests that fewer patients would be ILF because of delayed diagnosis. In addition, starting diagnosed patients on treatment rapidly by decreasing treatment initiation delay (11) may result in better treatment outcomes by decreasing loss to follow up during treatment.
A median time to initiation of treatment of five days in smear positive patients was demonstrated in the Western Cape, South Africa (11). It could be expected that if diagnosis is delayed by a long TAT with a corresponding delay in treatment initiation, loss to follow up may occur while patients wait for results and/or treatment initiation. The primary hypothesis of this study was therefore that in primary healthcare facilities there is an association between the proportion of sputum results with a prolonged smear TAT and the proportion of smear positive TB cases who are ILF. Secondly we hypothesized that there is an association between the proportion of patients with delayed initiation of treatment and a high ILF rate. To our knowledge, this is the first report of a study determining the association between TAT and ILF.

**METHODODOLOGY**

**Study Population**

133 primary healthcare facilities in five provinces of South Africa (Limpopo, Mpumalanga, Kwazulu-Natal, Northwest and Eastern Cape) were visited between May 2009 and September 2009. Preventive care and TB/HIV services are included in the services delivered at these facilities which were systematically selected with equal probability from a list of facilities supported by University Research Corporation (URC) as part of the TASC II (16) program. The TASC II program provided assistance to the South African National TB Programme to strengthen local capacity to detect, treat and prevent TB as well as integrate TB treatment with HIV management. Districts supported by the TASC II program were identified by the National TB Programme as poorly performing areas with regards to standard TB indicators. Facilities were either urban or rural, of various sizes (defined by number of TB patients) and made use of the centralised laboratory system, that is to say sputum samples and results had to be transported to and from laboratories.

**Definitions**

A person with a smear positive sputum result in the sputum register was defined as ILF when there was no documentation in the TB treatment register of starting treatment within one month of the receipt of the smear result by the facility. A prolonged TAT was defined as a TAT longer than 48 hours from when the sputum sample was documented in the sputum register until the receipt of the result at the facility. Treatment initiation delay was defined as treatment initiated more than five days after smear positive diagnosis as documented in the sputum register.
**Study design**

In this ecological study the unit of investigation was a primary healthcare facility and the outcome was the rate of ILF per facility, expressed as a percentage as in other literature on the topic (5,8,17). The ILF rate was calculated by comparing the sputum register with the TB treatment register. Individuals who had at least one smear positive result in the sputum register but who were not entered into the treatment register within one month of the facility receiving their results were regarded as ILF and used as the numerator. The total number of individuals who had samples sent for examination and were recorded as sputum smear positive in the sputum register for the same period was used as the denominator.

**Sample size**

The study was carried out as part of a larger study: thirty facilities were systematically selected per province except for the Northwest province where only sixteen facilities were supported by URC and all were selected. Three facilities were not visited because of time constraints.

**Data collection**

Each facility was visited by one of two research teams (trained and supervised to collect data accurately and consistently). Apart from the data needed for the ILF, the following determinants were captured: proportion of sputum smear results returned to the facility within 48 hours of being sent to the laboratory (as documented in the sputum register), proportion of smear positive TB patients started on treatment within five days of the facility receiving their sputum result (as documented in the sputum register and treatment register), whether it was rural or urban, in which province, whether it had a fast track/triage system for those eligible for TB examination and patients, and the number of TB patients per quarter (as a proxy for the size of the facility).

**Statistical analysis**

Data entry and analysis were performed using a SQL database and STATA 12. A multivariable binomial regression model was populated with data of 122 facilities. 11 facilities were excluded as they had missing outcome data. Because this evaluation was part of a bigger study, data on ILF were included only after the first data report (after the first six facility visits) when it was raised as a possible issue. At some of the other facilities data were missing because of incomplete or absent registers. There was no reason to suspect a different profile in the facilities not included in the analysis and the research team was retrained after the first data report to improve data accuracy and completeness.
Turnaround time (TAT) was divided into three categories depending on the proportion of sputum smear results returned to the facility within 48 hours. Category 1 indicated 0-32% of smear results were returned within 48 hours (52 facilities). Category 2 indicated 33-65% of smear results were returned within 48 hours (42 facilities). Category 3 indicated 66-100% of smear results were returned within 48 hours (28 facilities). These categories were selected rather than the standard two categories for TAT (<80% vs ≥80% returned within 48 hours) to obtain an even distribution of results since there were only seventeen facilities with a turnaround time ≥80%.

**Ethics**

The study was approved by the Stellenbosch University Health Research Ethics Committee and the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease.

**RESULTS**

122 primary healthcare facilities across five provinces of South Africa were included in the analysis (**Table 1**). The mean proportion of TB patients started on treatment within five days of the facilities receiving the results was 44% (95%CI 39-49%). The mean proportion of TB suspects whose results were returned to facilities within 48 hours was 43% (95%CI 38-48%). The mean number of TB patients per facility per quarter was 53 (95%CI 41-65). The proportion of facilities with a fast track/triage was 87% with the mean ILF for these facilities 24% (95%CI 21-27%). More than half (57%) of the facilities included in the study were rural with the mean ILF for these facilities 27% (95%CI 22-32%). The mean ILF rate was 25% across provinces varying from 21% to 28%.

The main determinant of ILF was the proportion of sputum smear results (%) returned to each facility within 48 hours of the sample being sent to the laboratory. **Figure 1** shows a non-linear relationship between the proportion of smear results returned to the facility within 48 hours as a continuous variable (%) and the ILF rate (%) in a lowess scatterplot. The relationship is inverse, in other words, the higher the TAT (the more results returned within 48 hours), the lower the ILF rate with coefficient $= -0.22$ (95%CI $-0.34$ $- 0.10$).
Table 1: Distribution of primary healthcare facility characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Median</th>
<th>95% CI</th>
<th>N (%)</th>
<th>Mean ILF</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Treatment start within 5 days(a)</td>
<td>44.4</td>
<td>42.9</td>
<td>39.4</td>
<td>49.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Results at facility within 48 hrs</td>
<td>42.8</td>
<td>40.0</td>
<td>37.8</td>
<td>47.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of TB patients per quarter(b)</td>
<td>52.8</td>
<td>27.5</td>
<td>40.6</td>
<td>65.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Binary variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast track/triage at facility (a)</td>
<td>Yes</td>
<td>98 (87%)</td>
<td>23.8</td>
<td>20.7</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>15 (12%)</td>
<td>35.0</td>
<td>25.8</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>Facility rural or urban</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rural</td>
<td>69 (57%)</td>
<td>26.7</td>
<td>22.2</td>
<td>31.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>53 (43%)</td>
<td>23.8</td>
<td>19.7</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td><strong>Categorical variable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Province</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>26 (21%)</td>
<td>23.0</td>
<td>17.0</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>23 (19%)</td>
<td>34.4</td>
<td>25.7</td>
<td>44.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28 (23%)</td>
<td>21.4</td>
<td>17.1</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>29 (24%)</td>
<td>28.8</td>
<td>19.8</td>
<td>39.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>16 (13%)</td>
<td>24.1</td>
<td>18.5</td>
<td>30.9</td>
<td></td>
</tr>
</tbody>
</table>

\(a\)missing value = 1, \(b\)missing values = 4, ILF: initial loss to follow-up rate (per cent)
When looking at univariable associations with ILF as outcome, in addition to TAT, the number of TB patients and whether there was a fast track/triage at a facility were significant (Table 2). TAT was categorised to ease interpretation after a significant association (OR=0.99, 95%CI 0.985-0.995, p<0.001) was established as a continuous variable. TAT was overall inversely associated with initial loss to follow-up (p=0.001) with an OR=0.57 (95%CI 0.38-0.85) and p=0.007 when comparing category 2 (33-66%) with category 1 (0-32%) and an OR=0.51 (95%CI 0.35-0.74) with p=0.001 when comparing category 3 (67-100%) with category 1 (0-32%).

Province 2 had a significantly higher odds for ILF in association with TAT compared to province 1 with OR=1.76 (95%CI 1.01-3.05) and p=0.045. However, province was not significantly associated with ILF overall (p=0.095). Whether treatment was started within five days of the facility receiving the result was borderline significant with OR=0.99 (95%CI 0.98-1.00) and p=0.054, and there was no association with the geographical location of the facility (rural or urban).

In the multivariable model TAT remained significant. Turnaround time overall was inversely associated with initial loss to follow-up (p=0.008), when comparing Category 2 (33-66% turnaround time within 48 h) with Category 1 (0-32%) (OR 0.73, 95%CI 0.48-
TB patients do not start treatment

1.13, p=0.163) and when comparing Category 3 (67-100%) with Category 1 (OR 0.62, 95%CI 0.39-0.99, p=0.045). The population preventable fraction of initial loss to follow-up (when turnaround time was <48h in ≥67% of smear results) was 21%, that is to say, the ILF rate would decrease by 21% in this population if the TAT is <48h in ≥67% of smear results (calculation not shown).

Table 2: Univariable and multivariable binomial regression model with initial loss to follow-up rate (%) as outcome

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Robust SE</td>
</tr>
<tr>
<td>Turnaround time within 48 hours (%)</td>
<td>overall p=0.001</td>
<td>overall p=0.008</td>
</tr>
<tr>
<td>Category 2 (33-66%)</td>
<td>0.57</td>
<td>0.12</td>
</tr>
<tr>
<td>Category 3 (67-100%)</td>
<td>0.51</td>
<td>0.10</td>
</tr>
<tr>
<td>Treatment started within 5 days (%) α</td>
<td>0.99</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of TB patients β</td>
<td>0.84</td>
<td>0.06</td>
</tr>
<tr>
<td>Fast track for TB patients at facility (Y/N) α</td>
<td>0.58</td>
<td>0.14</td>
</tr>
<tr>
<td>Facility rural or urban Province</td>
<td>overall p=0.095</td>
<td></td>
</tr>
<tr>
<td>Province 2</td>
<td>1.76</td>
<td>0.49</td>
</tr>
<tr>
<td>Province 3</td>
<td>0.91</td>
<td>0.21</td>
</tr>
<tr>
<td>Province 4</td>
<td>1.36</td>
<td>0.42</td>
</tr>
<tr>
<td>Province 5</td>
<td>1.07</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*reference categories not shown, α missing value = 1, β missing values = 4

DISCUSSION

We documented a mean ILF rate of 25% (22-28%) at primary healthcare facilities in five provinces of South Africa. Smear positive TB patients are the most infectious and this study indicates that one out of four of these patients were not started on treatment at the facility of diagnosis within one month of being diagnosed. This clearly highlights a challenge that needs to be addressed. It also suggests that ILF should be investigated in other settings, especially high-burden HIV settings where transmission to immunocompromised individuals may take place. This is underscored by a recent study from Ghana (18) indicating an ILF rate of 38% at a hospital. However, ILF cannot be addressed in isolation.
Chapter 4

The association between the sputum smear TAT and the ILF rate could be explained by health system and patient factors. For instance, if results are delayed, healthcare workers who may be already overwhelmed because of staff shortages, may find it difficult to keep track of all patients who should be contacted to initiate treatment. In turn, if patients do not receive their results within the specified time period of 48 hours, they may not return assuming that the result is negative. If they have to return to facilities on numerous occasions to enquire about results, they may not be enthusiastic about starting treatment.

This association could partially be addressed by decreasing the sputum smear TAT. However, in the South African system where laboratories are centralised, this may not be an easy target to achieve. Alternative strategies such as point-of-care diagnosis with microscopy or other diagnostics could be a solution and should be investigated (19). The recent introduction of short message service (SMS) printers at facilities may improve TAT, but if TAT is not addressed it could lead to an increase in severity of pulmonary TB as well as transmission within communities (20). One should however take into account that the association between TAT and ILF could be confounded by other variables, such as the number of staff available or the training of staff. It would be prudent to measure such confounders in future studies.

The province with the highest ILF rate (34%) showed a significant association between TAT and ILF in the univariable analysis (OR=1.76 with 95% CI 1.01-3.05 and p=0.045). In 2009, this was one of the provinces which reported the lowest level of satisfaction with public healthcare and where the utilisation rate of primary healthcare facilities for ≥5 year olds was lowest (21). The number of professional nurses was 118.5/100000 population, the second lowest amongst all provinces. These factors may have contributed to the high ILF at the facilities and TB management at provincial level should be effectively monitored to ensure equity of care for TB patients in all the provinces.

**Limitations**

This was an ecological study limited by the fact that only the TB treatment register of the specific facility where the sample was taken, was evaluated. TB patients might have started treatment elsewhere, which would mean the ILF rate was overestimated. Because of the sampling frame, study results would be generalisable to the population of health facilities supported by URC and not to all primary healthcare facilities in South Africa.
**Recommendations**

ILF should be reported as part of the TB programme to ensure that all patients are accounted for and traced to initiate treatment. Factors associated with ILF, such as a prolonged sputum smear TAT, should be addressed in the TB programme in order to decrease health system delay.

This study generated hypotheses about the etiology for high ILF rates. An intervention study could evaluate novel methods such as mobile technology to investigate the effect on TAT and time to initiation of treatment. Future research could include the linking of the electronic TB register with the National Health Laboratory System database in order to validate the results. Similar studies in other high burden TB/HIV settings with decentralised laboratory systems could indicate whether a decentralised system could perform better.
Chapter 4

REFERENCES


