

# Urban-Rural Disparities in Treatment Outcomes Among Recurrent TB Cases in Zambia

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## Research article

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# Abstract

Setting Southern province, Zambia. Background At least 13 – 20% of all Tuberculosis (TB) cases are recurrent TB. Recurrent TB patients have high risk of Multi-Drug Resistant TB (MDR-TB). Objective To estimate the prevalence of recurrent TB among TB cases and compare risk of unfavorable treatment outcomes between rural and urban settings. Methods In a retrospective cohort study, we used mixed effects logistic regression to assess associations between explanatory and outcome variables. Primary outcome was all-cause mortality and exposure was setting (rural/urban). Results Overall 3,566 recurrent TB cases were diagnosed among 25,533 TB patients. The prevalence of recurrent TB was 15.3% in urban and 11.3% in rural areas. Death occurred in 197 (5.5%), 103 (2.9%) were lost to follow (LTFU), and 113 (3.2%) failed treatment. Rural settings had 70% higher risk of death (aOR: 1.7; 95% CI: 1.2 2.7). Risk of LTFU was twice higher in rural than urban (aOR: 2.0 95% CI: 1.3 3.0). Compared to HIV-uninfected, HIV-infected individuals on Antiretroviral Treatment (ART) were 70% more likely to die (aOR: 1.7; 95% CI: 1.2 3.1). Conclusion Recurrent TB prevalence was generally high in both urban and rural settings. The risk of mortality and LTFU was higher among rural patients. We recommend a well-organized Directly Observed Therapy strategy adapted to setting.

## Introduction

Tuberculosis (TB) remains a major problem in the world and a leading killer among infectious diseases.<sup>1</sup> In 2017 there were 10 million cases of TB and 1.6 million deaths among TB cases.<sup>1</sup> Multi-Drug Resistant TB (MDR-TB) poses a big threat to TB control because of the expensive and limited treatment options and high mortality. MDR-TB is common among patients with recurrent TB, that is individuals who were previously treated with TB drugs for more than one month and once again have been diagnosed with TB disease.<sup>2</sup>

It is estimated that 13% of all the TB cases reported to the World Health Organization (WHO) in 2017 were due to recurrent TB.<sup>3</sup> In high Human Immunodeficiency Virus (HIV) burden settings, TB recurrence rates are as high as 20% following standard treatment.<sup>4,5</sup> Recurrent TB can result from reactivation of the original *Mycobacterium tuberculosis* or from re-infection with a different strain.<sup>6</sup>

Zambia is a country with a high prevalence of TB (455 cases per 100,000 population) and high prevalence of HIV infection (12% among adults between 15 – 59 years).<sup>7,8</sup> The extent of recurrent TB and treatment outcomes of recurrent TB cases have not been fully described. Distinctions must be made between new and recurrent cases as well as the subgroups of recurrent cases because they are essential for monitoring the TB epidemic and TB program performance.<sup>10</sup>

The burden of TB disease is generally considered to be higher in urban settings than rural settings due to overcrowding, high HIV prevalence and occupational transmission.<sup>7</sup> However, health care service delivery is better in urban populations because health facilities are easy to reach whereas rural patients must travel long distances.<sup>11,12</sup> Additionally, urban settings have more skilled health care providers with more clinical experience in the management of TB and HIV and access to better diagnostics. In contrast, most TB patients in urban settings are from deprived communities and social disadvantages such as slums which may contribute to poorer TB treatment outcomes.<sup>11</sup>

We examined the prevalence of recurrent TB among TB cases notified to the National TB Program (NTP) in southern province of Zambia. We assessed for risk factors associated with death, loss to follow up and failure among recurrent TB patients in rural and urban settings.

## **Methods**

### **Study design**

A retrospective cohort study was conducted by analyzing data collected in the NTP in southern province of Zambia.

### **Study Setting and population**

The study was conducted in a predominantly rural setting (85%) with a high TB case notification rate (>300 cases per 100,000 population per year).<sup>13</sup>

All adults and children who were treated for recurrent TB between January 2006 and June 2014 were included in the analysis. Recurrent TB was defined as a case of TB disease diagnosed in a patient who had been treated before for more than 1 month with TB drugs.<sup>2</sup>

### **Study exposure**

The study assessed factors associated with death, treatment failure and loss to follow up (LTFU) among patients treated for recurrent TB. The main exposure was health facility location classified as either rural or urban. The definition of rural or urban was based on the Ministry of health and Central Statistical Office of Zambia classification of health facilities.<sup>14</sup> A rural area is a location where the source of livelihood for at least 75% of the population is agriculture and agriculture allied activities and the health facility in the area serve a catchment population of less

than 30,000.<sup>14</sup> Urban health facilities are facilities that are located in urban settings and serve catchment populations of over 30,000.<sup>14</sup>

### **Study outcomes**

The primary outcome was all-cause mortality which is death from TB disease or any other cause before the patient successfully completed treatment. Death was verified by the attending physician through death certificate or verbal report from treatment supporters or the patient's next of kin.

The secondary outcomes were LTFU and treatment failure. LTFU was defined as a patient having missed more than two months of consecutive doses.<sup>2</sup> Treatment failure was defined as patient being smear positive after more than 5 months of treatment.<sup>2</sup>

### **Covariates**

The following clinical and demographic characteristics were evaluated as risk factors for death: age, sex, HIV status and ART in TB/HIV co-infected patients, treatment delay and clinical classification of disease. Clinical Pulmonary TB was a situation where the attending clinician made a diagnosis of pulmonary TB and decided to give the patient a full course of anti-TB treatment without bacteriological confirmation; Bacteriologically confirmed TB was when the diagnosis and treatment was supported by biological specimen such as by Acid-Alcohol Fast Bacilli (AAFB) smear microscopy, culture or GeneXpert.<sup>2</sup>

### **Data collection and data integrity**

We abstracted clinical and demographic data on the TB cases that had been recorded in the NTP register at every outpatient visit. Data entries were subjected to quality control, including removal of duplicate data entries, outliers in continuous variables, date parameters and ambiguous or erroneous entries in categorical entries. Verification of extracted records with source data was done in a randomly selected subset of 10 patients for every 100 entries from each site. After quality control, all available records for TB patients registered at the participating health centers between January 2006 and January 2013 were screened for inclusion.

### **Statistical analysis**

Data were described using frequency counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables. In the primary analysis we

estimated the odds ratio and the 95% confidence intervals for death among rural cases compared with urban cases. We first estimated the crude odds ratio and then stratified to assess for confounding and interaction. For associations between explanatory variables and the primary and secondary outcomes we used mixed effects logistic regression accounting for clustering by district. The data were cleaned and analyzed using Stata v.14.

### **Ethical considerations**

Ethical approval was obtained from the Macha Research Trust ethics committee, the University of Georgia institutional review board and regulatory authority from the Zambia National Health Research Authority.

## **Results**

### **Case enrollment**

Data from 25,533 TB patients was abstracted, of whom 3,566 (13.9%) were recurrent TB cases. Of these recurrent TB cases 2,573 (72.2.3%) were in urban areas and 992 (27.8%) in rural areas (Figure 1). After excluding recurrent TB cases whose treatment outcomes were not documented because they transferred to another facility before the end of treatment, there were 2,565 (72.1%) recurrent TB cases in urban areas and 990 (27.9%) in rural areas.

### **Prevalence of recurrence among TB cases**

The overall prevalence of recurrent TB was 14% (95% CI; 13.5 14.4). In urban setting the prevalence was 15.3% (n = 2,573; 95% CI: 14.8 15.9) and 11.3% (n = 992; 95% CI: 10.7 12.0) in rural areas (Table 1). TB recurrence in HIV negative TB cases was 10.0% (n = 499; 95% CI: 9.2 10.9) and 16.1% (n = 2,216; 95% CI: 15.5 16.7) in HIV seropositive positive recurrent TB cases. In men prevalence of recurrent TB was 13% (n = 1506; 95% CI: 12.4 13.6) and 14.9% (n = 2,049; 95% CI: 14.3 15.5) in women.

### **Demographic and clinical characteristics**

The mean was 36.3 years (Standard deviation (SD) = 14.8) and most of the recurrent TB cases were male (n = 2,019; 56.9%) Of the total cases 2,745(77%) were recurrent cases due to relapse, 31 (0.9%) were recurrence after LTFU, 29 (0.8%) were recurrence after failure and 106 (3.0%) were classified as others (Table 2).

Of all the HIV seropositive cases of recurrent TB that were analyzed 1,712 (78.8%) cases were in urban areas whereas 461 (21.2%) were in rural areas (Table 2). Most patients received treatment within the first 14 days of registering in the TB clinic (n=3,135; 88.2%).

### **Treatment outcomes**

Of the 3,555 patients who were included in the analysis 265 (7.5%) were cured and 2,877 (80.9%) completed treatment (Table 3). In the urban areas 111 (4.3%) cases died, 95 (3.7%) cases experienced treatment failure and 52 (2.0%) were LTFU. In the rural areas 51 (5.2%) died, 18 (1.8%) experienced TB treatment failure and 51 (5.2%) were LTFU.

### **Univariable and multivariable analysis results**

In both the univariable and multivariable analysis place of TB treatment was statistically associated with all-cause mortality (Table 4). After adjusting for sex, age group, microbiological confirmation, and HIV status, recurrent TB cases treated in the rural settings were 70% more likely to die while on TB treatment. (aOR: 1.7, 95% CI: 1.2 2.7). HIV positive patients on ART 70% more likely to die when compared to HIV negative patients (aOR 1.7; 95% CI: 1.4 - 3.7).

For secondary outcomes of LTFU and TB treatment failure analyzed separately rural areas had worse TB treatment outcomes. After adjusting for calendar year of treatment, HIV and ART status recurrent TB patients in the rural areas were twice more likely to be LTFU as compare to those in urban areas (aOR 2.0, 95% CI: 1.3 3.0) (Table 5). For recurrent TB treatment failure, patients in rural areas were 70% more likely to experience treatment failure (aOR 1.7, 95% CI: 0.7 5.1) (Table 6).

## **Discussion**

In this retrospective cohort of TB patients, the overall prevalence of recurrent TB of 14% is high and similar to other sub-Saharan Africa countries.<sup>16</sup> It is higher in urban (15.3%) than in rural areas (11.3%). Recurrent TB prevalence was higher among HIV seropositive individuals than HIV seronegative individuals (16.1 vs 11.8). Recurrent TB cases receiving treatment in rural areas were 70% more likely to die when compared to patients treated in urban areas. The risk LTFU was twice higher in rural areas than urban areas.

Overall the prevalence of recurrent TB was high and similar to other sub-Saharan African settings with high HIV prevalence.<sup>4</sup> The prevalence was slightly higher in urban areas than rural areas. High prevalence of recurrent TB can be driven by either a high rate of exogenous re-infection

or high rate of relapse of the initial *M. tuberculosis* infection. In this study, high prevalence of TB in the general population and among HIV seropositive individuals provides a suitable environment for high exposure to *M. tuberculosis* and consequently a high potential of re-infection. Because of the limited laboratory capacity, distinction between exogenous re-infection and true relapse cases could not be made. However, previous molecular studies in similar settings have demonstrated that a large proportion of recurrent TB cases among HIV patients are caused by exogenous reinfection. In a cohort of South African gold-mine workers, HIV-1 infection was strongly associated with re-infection but not with relapse. This finding has programmatic and public health consequences because even with effective TB treatment regimens TB recurrence can be more common in population with high HIV prevalence as long as exposure to *M. tuberculosis* is high.<sup>4,17</sup> Another study in Uganda showed that recurrent TB occurring more than 2 years after completing TB treatment was mainly due to re-infection whereas recurrence occurring within 2 years of treatment was due to relapse. Unfortunately, the NTP registers do not capture the dates when the last TB treatment was completed and hence it was not possible to ascertain the time interval between TB episodes.<sup>16</sup>

The risk of death was higher in rural areas than urban areas. Generally, patients in rural areas have worse TB treatment outcomes than patients in the urban areas including LTFU.<sup>11,18</sup> Our study presents data on recurrent TB and provides a valid assessment of recurrent TB treatment outcomes presented separately for death, treatment failure and LTFU. For recurrent TB patients understating the magnitude of LTFU is critical because recurrent TB patients who are LTFU are likely to progress to MDR-TB and are a potential risk to further transmission of the multi-drug resistant *M. tuberculosis*. Although the prevalence of recurrent TB was lower in rural than urban settings, LTFU was higher in rural settings. This implies that rural settings are at increased risk of creating next generation of MDR-TB cases.

Most studies that have assessed risk factors associated with unfavorable TB treatment outcomes found that urban areas generally have better outcomes because of better organized patient follow up systems and relatively easy access to health care services.<sup>19-21</sup> A qualitative study conducted in Uganda highlighted geographical barriers in rural areas as one of the barriers for delivery of routine TB diagnostic and treatment services.<sup>20</sup> Interviews highlighted physical remoteness of their homes from the clinic and the tough terrain encountered during travel as the principal barrier to accessing timely TB evaluation and treatment.<sup>20</sup> Challenges in accessing diagnostic and treatment services have potential of influencing TB treatment outcomes and increasing mortality among TB patients. Additionally, urban settings have a high prevalence of TB

and HIV and have more healthcare providers as compared to rural settings.<sup>12</sup> Therefore health workers in the urban areas have more clinical experience in managing TB and HIV.

The strength of this study is that it describes recurrent TB cases from a large cohort of TB cases at multiple rural and urban sites in a setting with high prevalence of both TB and HIV. Additionally, the paper highlight some of the gaps in the program and clinical case management of recurrent TB. The gaps herein highlighted are likely to be found in most NTPs in sub-Saharan Africa.

### **Limitations**

As in any real-world data or observational studies our analysis was subject to some limitations. An obvious weakness of this analysis was errors in the recorded data and missing which could not be validated. To address this potential selection bias, we conducted a sensitivity analysis by comparing baseline characteristics of those included in the analysis and those excluded. The two sample populations were similar on most aspects. Hence selection bias was very unlikely.

### **Public health relevance**

We have shown that recurrent rates of TB are high in both rural and urban settings with rural areas having worse treatment outcomes as compared to urban areas. Therefore, a well-organized patient monitoring system such as effectively administered Directly Observed Treatment Short-course (DOTS) can help early detection of recurrent cases and reduce mortality and LTFU. DOTS must be adapted to the setting.

## **Conclusion**

Prevalence of recurrent TB was high in both rural and urban areas in the southern part of Zambia. The burden was higher in urban areas than rural areas. However, TB recurrent cases in rural areas experienced higher mortality and worse treatment outcomes as compare to patients in urban areas. We strongly recommend effective DOTS adapted to the setting.

## **Declarations**

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## **Authors contributions**

SM (study concept and data analysis). SM, JNM, CCW, KM, CK (study design, development of data collection tools, data interpretation, manuscript writing and manuscript review). SM, JNM, CCW, KM, CK, VCM, KD, CL, XY (study implementation, data collection, data cleaning, manuscript writing and critical revision the manuscript). SM, CCW, VCM, KD, CL, XY, JNM (critical revision of data analysis and interpretation). All the authors read and approved the manuscript for publication.

## **Availability of data and materials**

The data that support the findings of this study are available from the national TB control program at the provincial health office in southern province Zambia, but restrictions apply to the availability of these data, which were used under license for the current study and are currently not publicly available. Data can be made available for other authors upon request and with the permission and approval of the Ministry of Health and the Zambia National Research Authority.

## **Ethics approval**

This study was approved by the Zambia National Health Research Authority and the institutional review boards at Macha Research Trust and the University of Georgia. We conducted analysis of anonymized routinely collected program data, hence all the institutional review boards waived informed consent.

## **Consent for publication**

Not applicable

## **Competing interests**

The authors declare that they have no competing interests.

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## Tables

Table 1: Prevalence of Tuberculosis retreatment cases by different characteristics among patients who were treated for tuberculosis

<b>Patient characteristics</b>	<b>total number of TB cases</b>	<b>recurrent cases</b>	<b>Prevalence in % (95% CI)</b>
<b>Overall</b>	25,533	3,566	14.0 (13.5 14.4)
Urban site	16,791	2,574	15.3 (14.8 15.9)
Rural site	8,742	992	11.3 (10.7 12.0)
<b>Age</b>			
10 & below	3,259	280	8.6 (7.7 9.6)
11 - 18	2,641	272	10.3 (9.1 11.5)
19 - 55	16,835	2,614	15.5 (15 16.1)
56 & older	2,769	400	14.5 (13.1 15.8)
<b>Sex</b>			
Female	11,569	1506	13 (12.4 13.6)
Male	13,726	2,049	14.9 (14.3 15.5)
<b>HIV status</b>			
negative	11,709	1382	11.8 (9.2 10.9)
positive	13,795	2,216	16.1 (15.5 16.7)
Note: In this table we estimate the prevalence using the overall number of cases before excluding cases who did not have the outcomes of interest at the end of follow (patients who transferred out and the TB treatment outcome was not documented).			

Table 2: Clinical and demographic characteristics of recurrent TB cases treated for drug susceptible TB in Zambia, southern province

Characteristic	Level	Total	Urban areas	Rural areas
		n (percent)	n (percent)	n (percent)
<b>Sex</b>	Female	1,482 (41.7)	1045 (40.7)	437 (44.1)
	male	2,019 (56.9)	1473 (57.4)	546 (55.2)
	Missing	54 (1.52)	47 (1.8)	7 (0.7)
<b>Age group*</b>	10 & below	128 (3.6)	93 (3.6)	35 (3.5)
	11 - 18	140 (3.9)	103 (4.0)	37 (3.7)
	19 - 55	2,185 (79.2)	2064 (80.5)	751 (75.9)
	56 & older	403 (11.3)	259 (10.1)	144 (14.6)
	Missing	69 (1.9)	46 (1.8)	23 (2.3)
<b>Microbiological confirmation</b>	clinical	2,519 (70.9)	1874 (73.1)	639 (64.6)
	confirmed	1,036 (29.1)	689 (26.9)	347 (35.1)
<b>Reason for retreatment</b>	Relapse patients	2,745 (77.2)	2126 (82.9)	619 (62.5)
	Other	644 (18.1)	330 (12.9)	314 (31.7)
	Treatment after default patients	31 (0.8)	28 (1.1)	3 (0.3)
	Treatment after failure patients	29 (0.82)	15 (0.6)	14 (1.4)
	Missing	106 (3.0)	66 (2.6)	40 (4.0)
<b>Site of disease</b>	Pulmonary	2,937 (82.6)	2086 (81.3)	851 (86.0)
	Extra-pulmonary	537 (15.1)	418 (16.3)	119 (12.0)
	Missing	81 (2.3)	61 (2.4)	20 (2.0)
<b>Delay</b>	14 days & less	3,135 (88.2)	2286 (89.1)	849 (85.8)
	15 days and more	420 (11.8)	279 (10.9)	141 (14.2)
<b>Calendar year</b>	<2010	1,884 (53)	1336 (52.1)	548 (55.4)
	2010 & after	1,671 (47)	1229 (47.9)	442 (44.7)

<b>Facility type</b>	Hospital	1,353 (38.1)	926 (36.1)	427 (43.1)
	Health Center or clinic	2,202 (61.9)	1639 (63.9)	563 (56.9)
<b>HIV status</b>	Negative	1382 (38.9)	853 (61.7)	529 (38.3)
	Positive	2,173 (61.1)	1712 (78.8)	461 (21.2)
*Age group (<10, 11 - 18, 19 - 55 and > 55) classification was based a WHO pediatric treatment guidelines and other previous studies of TB treatment outcomes <sup>23,24</sup>				

Table 3: TB treatment outcomes among recurrent TB cases in rural and urban settings in southern province, Zambia

		<b>Urban</b>	<b>Rural</b>
<b>Treatment outcomes</b>	Total number (percent)	n (percent)	n (percent)
Cure	265 (7.5)	176 (6.9)	89 (9.0)
Completed	2,877 (80.9)	2131 (83.1)	746 (75.4)
Failure	113 (5.5)	95 (3.7)	18 (1.8)
Died	197 (2.9)	111 (4.3)	86 (8.7)
LTFU	103 (3.2)	52 (2.0)	51 (5.2)

Table 4: Estimates of the risk of death (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

Characteristics	Total	Died	Crude	Adjusted
			OR (95% CI)	OR (95% CI)
<b>Location</b>				
Urban	2,574	111	1	1
Rural	991	86	2.1 (1.5 2.8)	1.7 (1.2 2.7)
<b>Sex</b>				
Female	1,482	112	1	1
Male	2,019	85	0.5 (0.4 0.7)	0.6 (0.4 1.0)
<b>Age group*</b>				
Below 55	2721	171	1	
>55	403	26	1.0 (0.8 1.3)	
<b>Microbiological confirmation</b>				
clinical	2519	62	1	
confirmed	1036	135	1.1 (0.8 1.5)	0.6 (0.4 1.0)
<b>Site of disease</b>				
pulmonary	2937	169	1	
Extra-pulmonary	537	24	0.8 (0.5 1.2)	
<b>Delay</b>				
<=14 days	3135	174	1	
>15 days	420	23	1.2 (0.6 1.5)	
<b>Facility type</b>				
<b>Calendar</b>				
<=2010	1884	106	1	
>2010	1671	91	0.9 (0.7 1.3)	
<b>HIV</b>				
Seronegative	1382	367	1	
Seropositive + ART	1187	610	1.6 (1.4 3.7)	1.7 (1.4 3.7)
Seropositive no ART	986	114	2.3 (1.8 6.8)	2.3 (1.6 6.0)

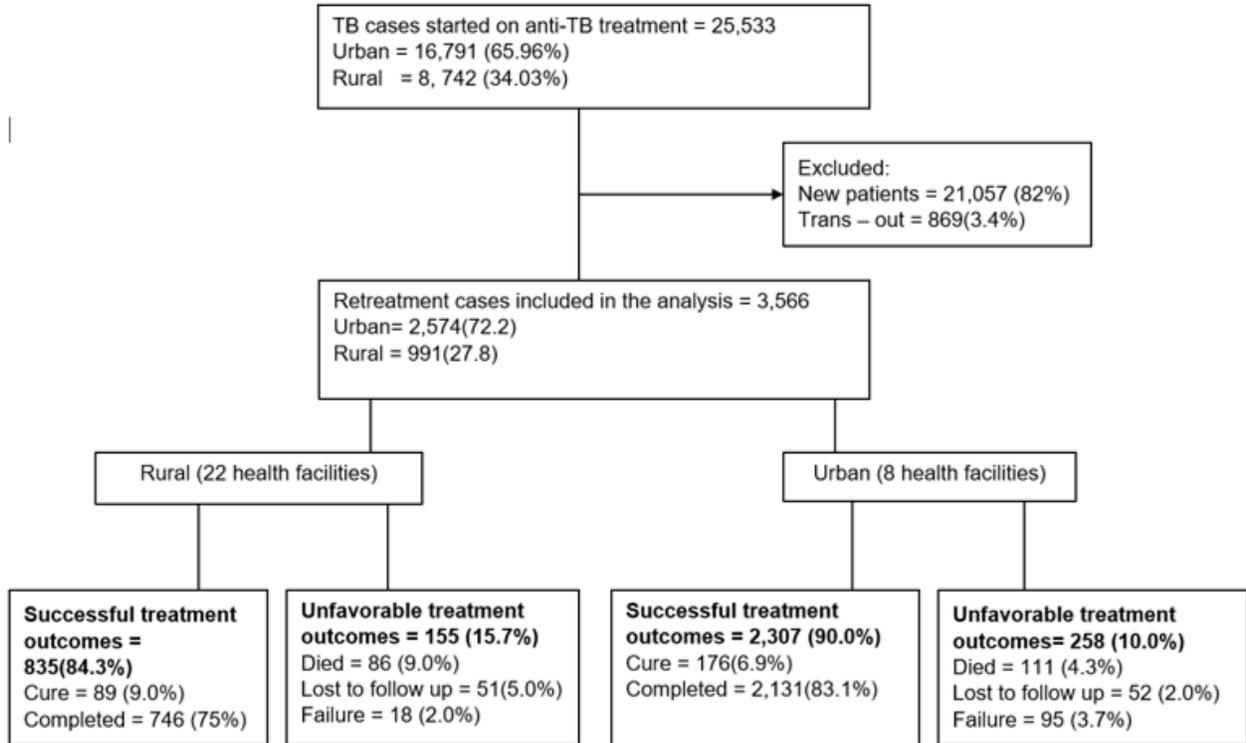
Table 5: Estimates of the risk of LTFU (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

Characteristic	total	LTFU	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Setting</b>				
Urban	2,565	52	1.0	
Rural	990	51	1.9 (1.1 3.4)	2.0 (1.3 3.0)
<b>Sex</b>				
Male	2,019	53	1.0	
Female	1,482	50	0.8 (0.5 1.2)	
<b>Age group</b>				
Below 55	2721	90	1.0	
Above 55	403	13	0.9 (0.8 1.2)	
<b>Calendar year</b>				
Before 2010	1,884	53	1.0	
After 2010	1,671	50	0.99 (0.7 1.5)	1.1 (0.7 1.5)
<b>Treatment delay</b>				
Less than 14 days	3,135	92	1.0	
14 days and more	420	11	0.8 (0.4 1.4)	
<b>Classification of TB</b>				
Microbiology confirmed	1,036	40	1.0	
clinical	2,460	63		
<b>HIV and ART status</b>				
HIV negative	1,382	57	1.0	
HIV seropositive on ART	1,187	39	0.9 (0.6 1.3)	0.8 (0.5 1.2)
HIV seropositive no ART	986	7	0.9 (0.7 1.4)	0.9 (0.8 1.4)

Table 6: Estimates of the risk of treatment failure (OR) in recurrent TB patients in southern province Zambia according to demographic and clinical characteristics.

Characteristic	total	Treatment failure	Crude OR (95% CI)	Adjusted OR (95% CI)
<b>Setting</b>				
Urban	2,565	95	1.0	
Rural	990	18	1.4 (0.5 3.9)	1.7 (0.7 5.1)
<b>Sex</b>				
Male	2,019	60		
Female	1,482	50	0.8 (0.5 1.2)	
<b>Age group</b>				
Below 18 years	268	10	1.0	
18 - 55	2,815	86	0.7 (0.4 1.5)	
Above 55	403	17	1.3 (0.5 2.9)	
<b>Calendar year</b>				
Before 2010	1,884	54	1.0	
After 2010	1,671	59	1.2 (0.8 1.8)	
<b>Treatment delay</b>				
Less than 14 days	3,135	90		
14 days and more	420	23	2.1 (1.2 3.4)	1.7 (0.9 2.4)
<b>Classification of TB</b>				
Microbiology confirmed	1,036	63		
clinical	2,460	50	0.3 (0.2 0.4)	0.4 (0.2 0.6)
<b>HIV and ART status</b>				
HIV negative	1,382	45	1.0	
HIV seropositive on ART	1,187	27	0.7 (0.5 1.4)	0.7 (0.4 1.2)
HIV seropositive no ART	986	41	0.8 (0.4 1.2)	1.0 (0.6 1.7)

## Figures



**Figure 1**

Consort diagram showing the selection of retreatment TB patients and a summary of TB treatment outcomes