Pre-treatment lost to follow-up tuberculosis patients, Chongwe, Zambia, 2017: a retrospective cohort study

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Setting: Four tuberculosis (TB) diagnostic health facilities of the Chongwe District, Zambia.

Objective: To determine the frequency of bacteriologically confirmed TB patients lost to follow-up (LTFU) before treatment from January to December 2017.

Design: This is a retrospective cohort study involving the review of TB registers. Information on presumptive TB patients who tested positive either by smear microscopy or Xpert® MTB/RIF assay was extracted from the laboratory TB registers of the TB diagnostic facilities and cross-matched with the TB treatment registers of TB treatment facilities.

Results: Two hundred and seventeen bacteriologically confirmed TB patients were found in the laboratory TB registers. Of these, 145 (67%) were males and seven (3%) were children; 177 (81%) patients were diagnosed using Xpert, while the remaining 40 (19%) were diagnosed using sputum smear microscopy. A total of 71 (33%) were not linked to treatment. Those diagnosed using smear microscopy were 2.5 times (95% CI 1.1–5.3) more likely to be LTFU before treatment than those diagnosed using Xpert.

Conclusion: About one third of TB patients who were not linked to treatment could potentially extend the duration of bacilli transmission in their communities. National TB control programmes should consider including LTFU patients before treatment in routine monitoring and evaluation.

Tuberculosis (TB) remains one of the world's leading causes of death and a major health challenge. It is the ninth leading cause of death worldwide and the leading cause from a single infectious agent.¹ In 2016, an estimated 10.4 million people fell ill with TB and close to 1.4 million of them died due to it.¹ Of the estimated 10.4 million TB cases, only 61% (6.3 million) were reported. It is estimated that about 4 million TB cases were missed in 2017.¹ Many of those persons missed will either die or follow some unknown treatment but most will continue infecting others and thereby hindering efforts to eliminate TB as a public health problem. In some countries, limited notification on TB patients from the private sector may be an issue.

Rapid case detection of sputum smear-positive TB patients and starting anti-TB treatment have been fundamental measures of the TB control strategy since 1993 when the World Health Organization (WHO) adopted the DOTS strategy. Patients presumed to have

TB may drop out of care during the case-finding process ('lost to follow-up [LTFU] during the diagnostic period'), before starting treatment ('pre-treatment LTFU,' previously known as 'initial default') or after treatment has started.² Bacteriologically confirmed TB patients who do not start treatment pose a potential risk of extended TB transmission to others, and bringing these patients into care could reduce this risk.

The rapid increase of TB in Zambia from 1985 onwards is mainly attributed to the human immunodeficiency virus (HIV) epidemic, but other factors such as population growth, urban overcrowding and poverty have also contributed. To address the dual epidemics, the Zambia Ministry of Health introduced TB-HIV collaborative activities, whereby all TB patients are offered HIV counselling and testing services (HTS) and all PLHIV are screened for active TB disease. The main objective of the TB-HIV collaborative services is to reduce the burden of TB-HIV co-infection by offering comprehensive TB-HIV treatment, care and support.³

With a TB incidence of 376 per 100 000 population and HIV prevalence of 11.6%, Zambia is one of the 30 countries with the highest per capita burden of TB and HIV. The notification rate and absolute number of TB cases have been declining over the last decade.³ However, this is not a true decline as it is based on routine data collected in health facilities. According to the WHO, estimated TB incidence in Zambia in 2017 was 361/100 000, whereas the TB notification rate is 218/100 000 for 2017.⁴ One of the reasons why TB cases are missed is poor linkage between health services such as laboratory and treatment units. More efforts are required to find the missing cases of TB, some of which may be people LTFU.

Although efforts to reduce the number of LTFU patients after initiating treatment have been emphasised, researchers and policy makers have paid little attention to reducing the number of pre-treatment LTFU patients, and the magnitude of this problem has not been fully assessed, partially because it has not been included in routine reporting by national TB control programmes (NTPs). A recent systematic review revealed a high (18%) frequency of pre-treatment loss to follow-up in sub-Saharan Africa.⁵ The review also concluded there was a paucity of evidence on the magnitude of pre-treatment loss to follow-up and recommended urgent evaluation of this problem. Also, there are no data on pre-treatment loss to follow-up in Zambia.

The objectives of the present study were to determine the frequency of pre-treatment loss to follow-up

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KEY WORDS

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in the Chongwe District from January to December 2017, and to make recommendations to the NTP on pre-treatment loss to follow-up.

STUDY POPULATION, DESIGN AND METHODS

Chongwe, a district (2017 population: 177 491) in Lusaka Province of Zambia, is served by 40 health facilities with five TB diagnostic centres. Four of these TB diagnostic centres, namely Chongwe District Hospital (CDH), and Ngwerere, Kanakantapa and Chongwe Rural Health Centres (RHCs), are publicly owned, while another (ZAF 71 RHC) is a military health facility. About 90% of the notified TB cases are diagnosed at Chongwe RHC (CRHC) and CDH. TB patients confirmed by the laboratories are referred to the TB treatment units of these health centres (HCs) and other HCs for treatment.

The major role of the TB diagnostic centres is to provide laboratory services for the diagnosis of TB and notify the NTP through the district health office (DHO). In this study, hospitals or clinics with TB diagnostic facilities (laboratory infrastructure, equipment and personnel) are referred to as 'TB diagnostic centres'. All the TB diagnostic centres in this study also serve as TB treatment centres, although not every TB treatment centre performs the functions of a TB diagnostic centre. All patients with presumptive TB are referred to the TB diagnostic centres for confirmation of TB disease. Diagnosis of TB in Zambia is based on finding at least one of two sputum smear samples positive for acid-fast bacilli (AFB) using Ziehl-Neelsen (ZN) staining, fluorescence microscopy or Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA).³ The method of TB diagnosis in Chongwe has been mainly sputum AFB microscopy until recently, when GeneXpert machines were commissioned. However, with the recent recommendations for using rapid molecular tests such as the Xpert for TB diagnosis^{3,6} and AFB microscopy for treatment monitoring, the district has seen an increase in the acquisition and use of Xpert. Three of the four public health TB diagnostic centres had Xpert machines at the time of this study. HCs without laboratory facilities refer sputum samples or patients to one of the nearest diagnostic centres for laboratory confirmation of TB disease. Some facilities outside the Chongwe District also make use of these diagnostic facilities by way of sample or patient referral systems. The main role of the TB treatment centres is to continue administering anti-TB treatment to patients and monitor them appropriately. At the completion of treatment, all TB treatment centres report patients' treatment outcomes to the diagnostic centres for onward reporting to the DHO and NTP.

In our study, a patient LTFU before treatment, formerly called an 'initial defaulter', was defined as a presumptive TB patient who was bacteriologically confirmed to have TB, either using smear microscopy or Xpert, or both and who had not started anti-TB treatment within 1 month of laboratory diagnosis. The study period was from 1 January to 31 December 2017.

This is a retrospective cohort study involving the review of TB registers. The study population was made up of all patients who were bacteriologically diagnosed with pulmonary TB in the four TB diagnostic centres in Chongwe District. Patients whose reasons (diagnosis or treatment follow-up) for attendance were missing were excluded from the review to avoid collecting vague and inaccurate data. The investigators first reviewed the laboratory TB registers at the four health facilities and extracted data on presumptive TB patients who were bacteriologically confirmed to have TB. The variables included name, sex, age, date of the labo-

ratory examination, laboratory serial number, residential address and TB test results of the patients. These data were then stored in an Excel (Microsoft, Redmond, WA, USA) file as a line list. The investigators then crosschecked with the TB treatment registers of the same four HCs and HCs of surrounding areas, and any other assigned treatment units. This procedure was extended to other facilities even if there was no indication that the patients had been referred there. This is because the treatment centres might also refer the patients elsewhere depending on patients' choice and accessibility of treatment services. When the name was found in one of the TB registers, the date of the registration on the TB treatment register was copied to the line list and the name was crossed out. Those who were not found in any TB treatment registers in the Chongwe District were considered to be pre-treatment LTFU. Once the names of the confirmed TB patients were cross-matched with the TB treatment registers of facilities in the Chongwe District, the names were removed from the line list and were permanently eliminated. Until then, the list was kept under lock and key to ensure confidentiality.

The proportion of pre-treatment LTFU patients was calculated as the number of the pre-treatment LTFU patients in the line list divided by the number of bacteriologically confirmed TB patients in the study period.

Statistical analyses, including a confidence interval (CI) for a population proportion, calculation of a relative risk (RR) and 95%CIs, were conducted using R Software (The R Foundation of Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

This survey was conducted as part of the review and monitoring activities of routine TB case finding in relation to TB control and there was no direct interaction with patients. The investigators sought research permission from the Zambia National Health Research Authority, Lusaka, and ethical clearance from Ethics and Research (ERES) Converge Institutional Review Board, Lusaka, Zambia (Ref No 2018-MAY-015) and the Research Institute of Tuberculosis, Tokyo, Japan (RIT/IRB: 28-7).

RESULTS

We found a total of 245 patients in the TB laboratory registers who had bacteriologically confirmed TB at the four TB diagnostic facilities from 1 January 2017 to 31 December 2017. Of these, 17 were duplicates (i.e., they had the same names with the same addresses and the same age), and these were eventually excluded from the analysis to avoid double counting. A further 11 (4.4%) were from outside the Chongwe District, and so were excluded from analysis for logistical reasons. Of the remaining 217 eligible patients, 178 (82%) were diagnosed using Xpert, while the rest were found using sputum AFB microscopy. At the time of this study, the first line of diagnosis was Xpert according the latest guidelines; however, Xpert use was influenced by other factors such as the availability, functionality and accessibility of Xpert. One hundred and forty-five (67%) patients were males and seven (3%) were aged <15 years. The median age was 33 years (range 1.5–84); 22 patients (9.6%) had no age indicated in the registers. Of the 217 bacteriologically positive TB patients in the laboratory registers, 71 (32.7%, 95%CI 26.5–39.4) were not linked to treatment (pre-treatment LTFU patients) (Table).

Figure 1 shows distribution of the proportion of pre-treatment LTFU patients by month. Loss to follow-up before treatment peaked in February and was lowest in August. Figure 2 gives the numbers and the proportions of the sex and age distributions of

TABLE Number of confirmed patients and number who started TB treatment with positive sputum results by facility, Chongwe, Zambia, 2017

Name of facility	Bacteriologically confirmed TB patients	Xpert	Microscopy	Started on treatment
Chongwe District Hospital	56	43	13	34
Chongwe RHC	155	135	20	107
Kanakantapa RHC	1	0	1	1
Ngwerere RHC	5	0	5	4
Total, <i>n</i> (%)	217 (100)	178 (82)	39 (18)	146 (67)

TB = tuberculosis; RHC = rural health centre.

pre-treatment LTFU patients. There were more male pre-treatment LTFU patients, with a peak in the 35–44 years age group. Figure 3 shows the proportions of pre-treatment LTFU patients by grading of positivity and laboratory method. The proportion of pre-treatment loss to follow-up was greater in patients who were diagnosed using smear microscopy (18/36, 50.0%, 95%CI 32.9–67.1) than in those diagnosed using Xpert (53/177, 29.9%, 95%CI 23.3–37.3; RR 2.5, 95%CI 1.1–5.3).

DISCUSSION

We studied pre-treatment loss to follow-up in the Chongwe District, Zambia, from January to December 2017, and found that the proportion of pre-treatment loss to follow-up was 33%. Those patients diagnosed using smear microscopy were 2.5 times more likely to be pre-treatment loss to follow-up than those diagnosed using Xpert.

According to health care workers in the field, two of the factors that contributed to these findings were referral to neighbouring districts with no proper documentation⁵ and long turnaround time for the sample results, as seen, for example, in a South African study by Mwansa-Kambafwile.⁷

These findings were similar to those of a systematic review and meta-analysis that reported a range of 4–38% pre-treatment loss to follow-up in 23 studies.⁵ The proportion of pre-treatment loss to follow-up in our study was higher than in the studies by Ram et al. (16%),⁸ Onyo et al. (16.7%),⁹ Cele et al. (17.9%),¹⁰ Wali et al. (21%)¹¹ and Botha et al. (26%).¹² A higher proportion of pretreatment loss to follow-up (38%) was also reported in Ghana.¹³

Pre-treatment loss to follow-up had seasonal fluctuations, with a peak in February (peak rainy season in Chongwe) and a base in August (the dry season), suggesting that road conditions may contribute to pre-treatment loss to follow-up in Chongwe. Presumptive TB patients diagnosed using smear microscopy were more likely to be LTFU before treatment than those diagnosed using Xpert, possibly because the turnaround time for smear microscopy is longer than that for Xpert and presumptive TB patients may not come back for the results. Since laboratory workers need intensive training for smear microscopy, whereas Xpert is easier for them to handle, produces results within 2–3 h and is not labour-intensive, greater use of Xpert may contribute to a reduction in patients LTFU. This is in line with the current guidelines that recommend the use of rapid diagnostic testing in TB diagnostic algorithms.^{3,6,14}

FIGURE 1 Proportion of bacteriologically confirmed TB patients LTFU before treatment by month, Chongwe, Zambia, 2017. TB = tuberculosis; LTFU = lost to follow-up.

FIGURE 2 **A)** Number of pre-treatment LTFU patients by sex and age group, Chongwe, Zambia, 2017. **B)** Proportion of pre-treatment LTFU patients by sex and age, Chongwe, Zambia, 2017. LTFU = lost to follow-up.

The strength of our study is that routine data collected at facilities were analysed to measure the magnitude of pre-treatment loss to follow-up. In addition, this is the first study aimed at investigating the magnitude of pre-treatment loss to follow-up in Zambia.

However, the study had some limitations. First, this was a retrospective study with no direct patient interaction, making it almost impossible to investigate patient-related factors that contributed to the high proportion of pre-treatment loss to follow-up. Nor did the study take into account the distance and travel time

FIGURE 3 Proportion of patients lost to follow-up before treatment by positivity grade of each detection method, Chongwe, Zambia, 2017. *1–9 AFB = actual number of *Mycobacterium tuberculosis* seen per field under microscopy.

from the patients' residences to the TB diagnostic and treatment centres for quantitative analysis as to whether these factors were associated with the outcomes. There is a need to conduct a qualitative study involving both health care workers and patients to establish the cause of the high proportion of pre-treatment loss to follow-up.^{15,16} There is also need to conduct similar studies prospectively and retrospectively involving large amounts of data like a study from South Africa¹⁷ and over a long period of time with distance and travel time analysis⁹ to obtain more representative data for Zambia. Furthermore, we may need more data from urbanised settings to compare the findings, as the setting in this study was mostly rural. The other limitation was that 11 patients from outside the district were excluded from the study, and this may have affected the findings. However, assuming that they all started treatment, the proportion of LTFU patients would be 28%, while assuming that all of them did not start treatment would put the proportion of LTFU patients at 38%.

CONCLUSION

About one third of bacteriologically positive TB patients were not linked to treatment and could potentially extend the period of TB transmission to others in the communities. Since the NTP does not routinely require reporting of pre-treatment loss to follow-up, the impact of missing TB cases as a result of non-reporting cannot be measured. NTPs should consider including pre-treatment LTFU patients in routine monitoring and evaluation of TB programmes.¹⁸

References

- World Health Organization. Global tuberculosis report, 2017. WHO/HTM/TB/2017.23. Geneva, Switzerland: WHO, 2017.
- World Health Organization. The definitions and reporting framework for tuberculosis—2013 revision. Geneva, Switzerland: WHO, 2014. http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. Accessed February 2020.
- National Tuberculosis and Leprosy Programme, Ministry of Health, Republic of Zambia. Tuberculosis manual. 5th ed. Lusaka, Zambia: MoH, 2017.
- Ministry of Health, Republic of Zambia. National TB prevalence survey 2013–2014 Report, Lusaka, Zambia: MoH, 2015.
- MacPherson P, Houben R M G J, Glynn J R, Corbett E L, Knanzer K. Pre-treatment lost to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2014; 92: 126–138.
- Global Laboratory Initiative, Stop TB Partnership. GLI model TB diagnostic algorithms. Geneva, Switzerland: Stop TB Partnership, 2018. http://stop.tb.org/wg/gli/assets/documents/GLI_algorithms.pdf. Accessed February 2020.
- Mwansa-Kambafwile J, Maitshotlo B, Black A. Microbiologically confirmed tuberculosis: factors associated with pre-treatment loss to follow-up and time to treatment initiation. *PLoS One* 2017; 12(1): e0168659.
- Ram S, Kishore K, Batio I, et al. Pre-treatment loss to follow-up among smear-positive pulmonary tuberculosis cases: a 10-year audit of national data from Fiji. *Public Health Action* 2012; 2: 138–141.
- Onyo E F, Kuaban C, Lin H-H, et al. Pre-treatment loss to follow-up of pulmonary tuberculosis patients in two regions of Cameroon. *Int J Tuberc Lung Dis* 2018; 22: 378–384.
- Cele L P, Knight S, Webb E, Tint K, Dlungwaneb T. High level of initial default among smear positive pulmonary tuberculosis in eThekweni health district, KwaZulu-Natal. *South Afr J Infect Dis* 2016; 31: 41–43.
- Wali A, Kumar A M V, Hinderaker S G, et al. Pre-treatment loss to follow-up among smear-positive TB patients in tertiary hospitals, Quetta, Pakistan. *Public Health Action* 2017; 7: 21–25.
- Botha E, den Boon S, Lawrence K-A, et al. From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. *Int J Tuberc Lung Dis* 2008; 12(8): 936–941.
- Afutu F K, Zachariah R, Hinderaker S G. High initial default in patients with smear-positive pulmonary tuberculosis at a regional hospital in Accra, Ghana. *Trans R Soc Trop Med Hyg* 2012; 106: 511–513.
- Stop TB Partnership. The paradigm shift. Global plan to end TB 2016–2020. Geneva, Switzerland: Stop TB Partnership, 2015. http://www.stoptb.org/assets/documents/global/plan/globalplantoendtb_theparadigmshift_2016-2020_stoptbpartnership.pdf. Accessed February 2020.
- Soomro M H, Qadeer E, Mørkve O. Barriers in the management of tuberculosis in Rawalpindi, Pakistan: a qualitative study. *Tanaffos* 2013; 12(4): 28–34.
- Tadesse T, Demisse M, Berhane Y, Kebede Y, Abebe M. Long distance travelling and financial burdens discourage tuberculosis DOTs treatment initiation and compliance in Ethiopia: a qualitative study. *BMC Public Health* 2013; 13: 424.
- Claassens M M, du Toit E, Dunbar R, et al. Tuberculosis patients in primary care do not start treatment. What role do health systems delays play? *Int J Tuberc Lung Dis* 2013; 17: 603–607.
- Fatima R, Qadeer E, Hinderaker S G, et al. Can the number of patients with presumptive tuberculosis lost in the general health services in Pakistan be reduced? *Int J Tuberc Lung Dis* 2015; 19(6): 654–656.

Contexte : Quatre structures de diagnostic de la tuberculose (TB) dans le district de Chongwe, Zambie.

Objectif : Déterminer le nombre de patients TB perdus de vue (LTFU) avant le traitement ayant une confirmation bactériologique de janvier à décembre 2017.

Schéma : Etude rétrospective de cohorte impliquant la consultation des registres TB. Les informations relatives aux patients présumés TB qui ont été positifs par microscopie de frottis ou test Xpert® MTB/RIF ont été extraites des registres du laboratoire de TB et croisés avec les registres de traitement de la TB dans les structures de traitement.

Résultats : Parmi les 217 patients TB confirmés par bactériologie et identifiés dans les registres du laboratoire TB, 145 (67%) ont été des

hommes et 7 (3%) ont été des enfants. Ont été diagnostiqués 177 (81%) patients par Xpert, tandis que 40 (19%) ont été diagnostiqués par microscopie de frottis de crachats. Un total de 71 (33%) n'a pas été lié au traitement. Les patients diagnostiqués par microscopie de crachats ont été 2,5 fois (IC95% 1,1–5,3) plus susceptibles d'être perdus de vue avant le traitement que ceux diagnostiqués par Xpert.

Conclusion : Environ un tiers des patients TB n'a pas été connecté à la prise en charge et ces patients ont pu potentiellement allonger la durée de la transmission des bacilles dans leurs communautés. Les programmes nationaux de lutte contre la TB devraient envisager d'inclure les patients LTFU avant le traitement en suivi et évaluation de routine.

Marco de referencia: Cuatro establecimientos de diagnóstico de la tuberculosis (TB) en el distrito Chongwe de Zambia.

Objetivo: Determinar la pérdida durante el seguimiento (LTFU) antes de iniciar el tratamiento de los pacientes con diagnóstico de TB y confirmación bacteriológica de enero a diciembre del 2017.

Método: Fue este un estudio de cohortes retrospectivo a partir del análisis de los registros de TB. La información sobre los pacientes con presunción de TB que obtuvieron resultados positivos ya sea de la baciloscopia o la prueba Xpert® MTB/RIF se extrajo de los registros de laboratorio en los establecimientos de diagnóstico de la TB y se cotejó con los datos de los registros de tratamiento de los centros de tratamiento de la TB.

Resultados: En los registros de los laboratorios de TB se encontraron 217 pacientes con diagnóstico de TB y confirmación bacteriológica.

De estos, 145 (67%) eran de sexo masculino y siete (3%) eran niños. El diagnóstico se obtuvo en 177 pacientes (81%) con la prueba Xpert y en los 40 restantes (19%) mediante la baciloscopia del esputo. Setenta y un pacientes (33%) no se vincularon a los servicios de tratamiento. La LTFU anterior al tratamiento fue 2,5 veces más frecuente en los pacientes diagnosticados mediante baciloscopia (IC95% 1,1–5,3) que en los pacientes diagnosticados con la prueba Xpert.

Conclusión: Cerca de un tercio de los pacientes con TB no se vinculó a los servicios de tratamiento, lo cual pudo prolongar la transmisión de los bacilos en sus comunidades. Es necesario que los Programas Nacionales contra la TB tengan en cuenta la inclusión de los pacientes con LTFU anterior al tratamiento en el seguimiento y la evaluación sistemáticos.