Sputum smear non-conversion among adult persons with bacteriologically confirmed pulmonary tuberculosis in rural eastern Uganda

Jonathan Izudi⁎, Imelda K. Tamwesigire, Francis Bajunirwe

Department of Community Health, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda

ARTICLE INFO

Keywords:
Persons with tuberculosis
Smear positive tuberculosis
Sputum smear conversion
Treatment success rate
Tuberculosis patients
Uganda

ABSTRACT

Rationale: Failure to convert sputum at two months of treatment among persons with bacteriologically confirmed pulmonary tuberculosis (BC-PTB) indicates poor response to treatment but data are limited on its assessment.

Objective: We determined the frequency and factors associated with sputum smear non-conversion at two months among persons with BC-PTB in eastern Uganda.

Methods: We abstracted data of adult persons with BC-PTB, from routinely available records from TB registers at 10 clinics in eastern Uganda. We determined factors that are independently associated with sputum smear non-conversion using logistic regression analysis. We expressed the results as odds ratio (OR) with 95% confidence interval (CI).

Measurements and main results: Of 516 persons with BC-PTB, 81 (15.7%) did not achieve sputum smear conversion at two months of TB treatment. Higher Mycobacterium tuberculosis (MTB) load and treatment at a private-not-for-profit (PNFP) facility compared to government health facility were significantly associated with sputum smear non-conversion. A one unit (+1) increase in MTB load based on ZN stain counts was associated with a 48% increase in the odds of sputum smear non-conversion with adjusted odds ratio (AOR), 1.48 (95% CI, 1.02–2.18). TB treatment at private-not-for-profit health facility was associated with a two-fold increase in the odds of sputum smear non-conversion (AOR, 2.03; 95% CI, 1.01–3.92).

Conclusions: Our study shows that sputum smear non-conversion is common at two months of treatment in this population. It is more likely among patients with higher baseline MTB load and those treated at PNFP facilities. Strategies targeting patients with these risk factors are needed to enhance sputum smear conversion.

1. Introduction

Millions of people continue to fall sick and die of tuberculosis (TB) in both developed and developing countries despite the availability of effective treatment and cure [1,2]. The 2019 global TB report indicates that 10 million people developed TB disease in 2018 and an estimated 1.5 million of them died [1]. For persons with bacteriologically confirmed pulmonary TB (BC-PTB) who have been started on treatment, the World Health Organization (WHO) recommends sputum smear follow-up tests at two or three, five, and six or eight months [3] to establish treatment response and to promptly detect treatment failure as well as drug resistance. Good response to TB treatment is indicated by sputum smear conversion, a change in baseline sputum smear results from detectable to non-detectable Mycobacterium tuberculosis (MTB) bacilli.

Currently, there is no optimal diagnostic for accurate monitoring of response to TB treatment. The available options include culture, GeneXpert, and sputum smear microscopy, which all have limitations. For instance, a systematic review and meta-analysis showed that both sputum smear microscopy and mycobacterial culture have low sensitivity and modest specificity in predicting treatment failure and relapse during TB treatment [4]. Also, culture takes several weeks to yield results and requires specialized equipment while GeneXpert test results are not accurate because it may detect deoxyribonucleic acid (DNA) from dead MTB for individuals previously treated for TB [5], thus compromising its specificity. Due to its poor specificity, recommendations have been made that the GeneXpert test should not replace the standard sputum smear microscopy and culture tests for monitoring treatment response [6]. Therefore, sputum smear microscopy, which comes with additional advantages of being cheaper and less time consuming compared to GeneXpert and culture, is used to monitor response to TB treatment in Uganda [7].

⁎ Corresponding author.
E-mail address: jonahzd@gmail.com (J. Izudi).

https://doi.org/10.1016/j.jctube.2020.100168

2405-5794/ © 2020 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
Sputum smear conversion is an important performance target for TB control programs because it determines cure and treatment success rates, two important favorable outcomes of TB treatment [8]. For instance, to declare a cure, the sputum smear result must be negative at six or eight months and on one previous occasion, either at five or two months of treatment [8]. Sputum smear non-conversion is a major threat to public health because non-converters remain infectious and may propagate TB transmission at household and community levels [9]. Estimates indicate that 80 to 90% of persons with BC-PTB achieve sputum smear conversion within two to three months of treatment initiation [10]. Certain persons do not achieve sputum smear conversion (sputum smear non-converters) for reasons such as advanced age [11–13], high baseline MTB load [11,13,14], and infection with human immunodeficiency virus (HIV) [15].

In Uganda, data on sputum smear non-conversion among persons with BC-PTB remain scarce. The purpose of this study was therefore to investigate factors associated with sputum smear non-conversion at two months of treatment among adult (≥15 years old) persons with BC-PTB in rural Uganda. The data will support the design of context-specific interventions that are useful in improving the quality of TB services at the district.

2. Methods

2.1. Data source

The data source and study setting for this study are described elsewhere [16]. Briefly, the data are part of a large mixed-methods study conducted in the Teso region of eastern Uganda comprising four districts of Soroti, Kumi, Ngora, and Serere. The study participants were obtained from treatment registers for persons with TB, treated across 10 health facilities with high patient loads, namely ≥100 persons with TB per year. We abstracted data for persons with TB treated between January 2015 and June 2018. Data were collected at hospitals or health center IV facilities. A health center IV is a county level health facility serving a population of about 100,000. The study sites in Soroti district were Soroti Regional Referral Hospital, Princess Diana Memorial Health Center (HC) IV, and Tiriri HC IV. For Serere district, they were Serere and Apapai HC IVs as there was no district hospital. In Ngora district, the Ngora HC IV and Ngora hospital were the study sites while in Kumi district, the sites were Kumi HC IV, Kumi hospital, and Atutur hospital. Most of the study sites were government health facilities except Kumi and Ngora hospitals were private-not-for-profit (PNFP) health facilities. The data were abstracted between April and May 2019 by trained research assistants.

2.2. Anti-tuberculosis regimen

Each health facility has a TB diagnostic and treatment (DTU) unit to provide TB diagnostic, treatment, and preventive services, mostly managed by either a medical, clinical, or nursing officer. The TB DTUs use the national TB treatment and control guidelines in managing persons with TB, and the treatment is divided into two phases: an intensive and continuation phase. However, the treatment guidelines have changed over time. Prior to August 2017, persons with new BC-PTB diagnosis were treated with either an eight months regimen that consisted of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol as a fixed dose combination for two months in the intensive phase and HE for six months in the continuation phase (2RHZE/6HE), or with a six months regimen that comprised of RHZE for two months in the intensive phase and RH for four months in the continuation phase (2RHZE/4RH) [17]. Response to treatment was monitored with sputum smear microscopy at two, five, and six or eight months. Previously treated persons with BC-PTB were treated with an eight months regimen that consisted of two months of RHZE as fixed dose combination (FDC) tablet and daily Streptomycin (S) injection for two months and RHZE for one month in the intensive phase. In the continuation phase, a FDC of RHE tablets was used for five months (2RHZE/1RHZE/5RHE) [17]. Therefore, the response to treatment was monitored at three, five, and eight months for these patients.

In 2017, the WHO revised the TB treatment guideline and the changes were adopted by the Uganda National TB and Leprosy Control Program (NTLP). In the revised guideline, which took effect in Uganda in August 2017, both previously treated persons and those with new BC-PTB diagnosis are managed with the same six month regimen, 2RHZE/4RH, provided Rifampicin resistance has been excluded by GeneXpert test [18]. Accordingly, response to treatment is monitored by sputum smear microscopy testing at two, five, and six months in both categories of persons with TB.

2.3. Sputum smear microscopy monitoring procedure

Persons with BC-PTB provided a sputum smear sample at two, five, and six months of treatment for monitoring purposes. Each sample was examined under direct microscopy using the Ziehl-Neelsen (ZN) staining technique for acid-fast bacilli (AFB). In this procedure, sputum samples were spread centrally on examination slides using a continuous rotational movement until sputum smear sizes of about 20 mm by 10 mm was achieved.

The slides were then placed on a dryer with the smeared surfaces facing upwards for about 30 min to enable air drying, heat fixed and covered with carbofuchsin stain. The slides were then heated until the onset of vaporization, and the heated stains were allowed to remain on the slides for five minutes before it was washed off with clean water. Thereafter, the slides were covered with 3% acid alcohol until they were sufficiently decolorized, washed well with clean water again, and then covered with malachite green stain for one to two minutes. The malachite stain was washed off with clean water and thereafter, the back surface of the slides were wiped clean before they were air dried on a drying rack. Lastly, each slide was examined under microscopy using 100X oil immersion objective. The number of MTB in the sputum smear samples were quantified as follows: 1 + for AFB less than 100 per 100 immersion fields, 2 + for 1–10 AFB per field at least in 50 fields, and 3 + for more than 10 AFB per field at least in 20 fields [19].

2.4. Study design and eligibility criteria

We conducted a cross-sectional analysis for adult persons with BC-PTB retrieved from the registers and treated between January 2015 and June 2018. They were assessed for sputum conversion at two months following the date of treatment initiation. We excluded the following: 1) persons with clinically diagnosed and extra pulmonary TB as well as those below 15 years of age as their response to treatment was not monitored by sputum smear microscopy; 2) persons with multi-drug resistant TB (MDR-TB) because this form of TB is not drug susceptible and often requires specialized treatment at referral sites; 3) persons who never received sputum smear monitoring at two months since this was the primary outcome; 4) previously treated persons with BC-PTB who were managed using the eight months TB regimen (2RHZES/1RHZE/5RHE); because they had received sputum smear monitoring test at three months. The inclusion of such persons would result into differences in sputum smear conversion relative to those with new BC-PTB diagnosis who had received sputum smear monitoring at two months. We restricted our analysis to persons with new BC-PTB diagnosis managed using either 2RHZE/4RH or 2RHZE/HE, and previously treated persons with BC-PTB managed using 2RHZE/4RH, because they all receive sputum testing at two months of treatment, which provides a harmonized time point for assessment of sputum smear conversion. We adhered to the Strengthening of the Reporting of Observational Studies in Epidemiology (STOBE) guideline in reporting the findings [20,21].
2.5. Measurements

We extracted the following variables: district of residence, type of health facility ownership measured as government or private-not-for-profit; level of health facility measured as Health Center IV (sub county level health facility), district and referral hospital; participant age, sex, type of person with BC-PTB measured as new or previously treated; baseline MTB load, TB regimen measured as 2RHZE/6HE or 2RHZE/4RH; HIV sero-status, type of directly observed therapy short course (DOTS) measured as facility versus community-based DOTS; and treatment supporter availability (yes or no). We categorized health facilities located within 5 km radius to the main trading town as peri-urban, otherwise they were considered rural. Using the WHO threshold for treatment success rate (TSR) of at least 90%, districts with a TSR above 90% were categorized as high TSR district and the rest as low TSR districts.

2.6. Data analysis

In the univariate analysis, we summarized categorical data into frequencies or percentages, and numerical data into means and standard deviations. The primary outcome variable was sputum smear non-conversion at two months of TB treatment measured as a binary outcome, yes or no. Persons with BC-PTB who remained sputum smear positive at two months of TB treatment were considered sputum smear non-converters.

In the bivariate analysis, we tested differences in proportion of sputum smear non-conversion with categorical variables such as sex using the Chi-square test for large cell counts, otherwise the Fisher’s exact test was used. To test mean differences in sputum smear non-conversion with numerical variables like age, we used the Student’s t-test when data were normally distributed, and the Wilcoxon rank sum test was used for skewed data. Variables with probability values (p values) less than 5% were considered statistically significant. We considered variables that carried important clinically prognosis such as HIV infection and new versus previously treated persons with BC-PTB for univariate and multivariate binary logistic regression analyses. We reported the results both as unadjusted odds ratio (uOR) and adjusted odds ratios (aOR) with the 95% confidence interval (95% CI).

We performed sensitivity analysis to examine the effect of excluding persons with missing baseline MTB load because their diagnosis was by GeneXpert. We examined the effect of analyzing MTB load as a categorical variable, and then as a continuous variable. All analyses were performed in R statistical software version 3.5.2 [22].

2.7. Human subjects’ issues and ethics approval

We received ethics approval from Mbarara University of Science and Technology Research Ethics Committee, MUST-REC (reference number 03/11-18) and the Uganda National Council for Science and Technology (HS 2531). We received a waiver of patient consent from MUST-REC to access secondary data because it was not possible to reach and obtain informed consent from the large number of study participants. To ensure confidentiality of data and information, individual identifiers such as names and registration numbers were made anonymous in the data abstraction and analysis stages.

3. Results

3.1. Study profile

We retrieved records of 3025 persons with TB treated across 10 study sites. Of these, 1881 were first excluded because they were not persons with BC-PTB as shown in the study profile in Fig. 1 below. Of 1144 persons with BC-PTB, 21 were excluded: 14 were below 15 years of age and 7 had MDR-TB. Of the remaining 1123 persons with BC-PTB, 607 were excluded with reasons: 568 did not receive sputum smear microscopy test at two months of TB treatment and 39 were previously treated persons with BC-PTB managed using 2RHZE/IRHZE/5RHE. Overall, 516 records for adult persons with BC-PTB were analyzed.

3.2. Socio-demographic and clinical characteristics of participants

The average age of all the participants was 38.4 ± 15.6 years, with no statistically significant difference between sputum smear converters and non-converters and the results are shown in Table 1. Of 516 participants, 81 (15.7%) were sputum smear non-converters at two months of TB treatment. Among patients from the PNFPs, a significantly larger proportion of them were sputum smear non-converters (19.8%) compared to the converters (9.4%), with p = 0.011. The distribution of sputum smear converters and non-converters did not differ by district TSR (p = 0.896). In districts with low TSR, the proportion of sputum smear non-converters (77.9%) was similar to converters (76.5%). The proportion of sputum smear non-converters was slightly higher among patients who had received treatment at government health facilities (80.2%), at referral hospital level of care (37.0%) and peri-urban health facilities (65.4%) compared to PNFP health facilities, district hospital or HC IV level of care, and rural health facilities, respectively but the differences were not significant.

3.2.1. Factors associated with sputum smear non-conversion at two months among persons with bacteriologically confirmed pulmonary tuberculosis

In unadjusted binary logistic regression analysis (Table 2), results showed that sputum smear non-conversion was more likely when TB treatment was at PNFP health facility than at government health facility (uOR, 2.37; 95% CI, 1.23–4.39), and among patients with higher baseline MTB load with 51% increase in the odds of non-conversion for a unit (1+ on ZN stain) increase in MTB load (uOR, 1.51; 95% CI, 1.05–2.22). Although not statistically significant, our analysis indicated that sputum smear non-conversion was more likely for the following persons with BC-PTB: those above 35 years old (uOR, 1.26; 95% CI, 0.79–2.04), those with history of previous treatment of TB (uOR, 1.18; 95% CI, 0.39–2.94), those living with HIV (uOR, 1.16; 95% CI, 0.67–1.94), and of male sex (uOR, 1.37; 95% CI, 0.82–2.34).

In the adjusted logistic regression analysis (Table 2), sputum smear non-conversion was more likely to occur among patients who received TB treatment at PNFP health facility compared to those at a government health facility (aOR, 2.03; 95% CI, 1.01–3.92). A one unit (1+ on ZN stain) increase in baseline MTB load was associated with a 48% increase in the odds of non-conversion (aOR, 1.48; 95% CI, 1.02–2.18). However, the other factors namely location of health facility, HIV infection, and type of BC-PTB were not significantly associated with sputum smear non-conversion.

4. Discussion

Our study in rural eastern Uganda shows that at least 15% of persons with BC-PTB did not achieve sputum smear conversion at two months. We found high baseline MTB load and treatment of TB at private-not-for-profit (PNFP) healthcare facilities are associated with sputum smear non-conversion. The magnitude of sputum smear conversion falls between 80 and 90% [10], which is within the WHO recommended threshold for sputum smear conversion for persons with new BC-PTB diagnosis when the TB control program is performing well [23]. The magnitude of sputum smear conversion is similar to estimates in previous epidemiological studies in several sub-Saharan African countries [11,13,15], and Sri Lanka [24]. The proportion of persons with BC-PTB who were sputum smear non-converters at two months of TB treatment is small. Since not all persons with BC-PTB achieve SSC by two months of treatment, drug susceptibility testing using GeneXpert remains critical in ruling out possible MDR-TB in sputum smear non-converters as recommended [3].
Fig. 1. Study profile for sputum smear non-conversion among adult persons with bacteriologically confirmed pulmonary tuberculosis in rural eastern Uganda. Note: BC-PTB: Bacteriologically confirmed pulmonary tuberculosis.

Table 1
Socio-demographic and clinical characteristics of participants.

| Characteristics                        | Level                      | Total, n = 516 | Yes, n = 435 | No, n = 81 | p value |
|----------------------------------------|----------------------------|----------------|--------------|------------|---------|
| Category of district of study          | High TSR                   | 115 (22.3)     | 96 (22.1)    | 19 (23.5)  | 0.896   |
|                                        | Low TSR                    | 401 (77.7)     | 339 (77.9)   | 62 (76.5)  |         |
| Type of health facility                | Government                 | 459 (89.0)     | 394 (90.6)   | 65 (80.2)  | 0.011   |
|                                        | Private-not-for profit     | 57 (11.0)      | 41 (9.4)     | 16 (19.8)  |         |
| Year of TB treatment                   | 2015                       | 184 (35.7)     | 154 (35.4)   | 30 (37.0)  | 0.988   |
|                                        | 2016                       | 95 (18.4)      | 81 (18.6)    | 14 (17.3)  |         |
|                                        | 2017                       | 126 (24.4)     | 106 (24.4)   | 20 (24.7)  |         |
|                                        | 2018                       | 111 (21.5)     | 94 (21.6)    | 17 (21.0)  |         |
| Level of health facility               | Health Center IV           | 185 (35.9)     | 157 (36.1)   | 28 (34.6)  | 0.178   |
|                                        | District hospital          | 108 (20.9)     | 85 (19.5)    | 23 (28.4)  |         |
|                                        | Referral hospital          | 223 (43.2)     | 193 (44.4)   | 30 (37.0)  |         |
| Location of health facility            | Rural                      | 127 (24.6)     | 99 (22.8)    | 28 (34.6)  | 0.034   |
|                                        | Peri-urban                 | 389 (75.4)     | 336 (77.2)   | 53 (65.4)  |         |
| Age group (years)                      | ≤ 35                       | 261 (50.6)     | 224 (51.5)   | 37 (45.7)  | 0.500   |
|                                        | > 35                       | 255 (49.4)     | 211 (48.5)   | 44 (54.3)  |         |
| Sex                                     | Male                       | 340 (65.9)     | 282 (64.8)   | 58 (71.6)  | 0.292   |
|                                        | Female                     | 176 (34.1)     | 153 (35.2)   | 23 (28.4)  |         |
| Type of persons with BC-PTB            | New                        | 488 (94.6)     | 412 (94.7)   | 76 (93.8)  | 0.955   |
|                                        | Previously treated         | 28 (5.4)       | 23 (5.3)     | 5 (6.2)    |         |
| Baseline MTB load                      | 1+                         | 67 (23.7)      | 58 (20.9)    | 31 (31.3)  | 0.021   |
|                                        | 2+                         | 116 (37.5)     | 131 (34.4)   | 15 (35.1)  |         |
|                                        | 3+                         | 126 (40.8)     | 164 (44.0)   | 31 (31.3)  |         |
| HIV infected                            | No                         | 382 (74.0)     | 324 (74.5)   | 58 (71.6)  | 0.686   |
|                                        | Yes                        | 134 (26.0)     | 111 (25.5)   | 23 (28.4)  |         |
| Type of Directly Observed Therapy Short Course (DOTS) | Facility | 16 (3.1)       | 13 (3.0)     | 3 (3.7)    | 0.726   |
|                                        | Community                  | 500 (96.9)     | 422 (97.0)   | 78 (96.3)  |         |
| Treatment supporter present            | Yes                        | 461 (89.3)     | 386 (88.7)   | 75 (92.6)  | 0.403   |
|                                        | No                         | 55 (10.7)      | 49 (11.3)    | 6 (7.4)    |         |
Table 2
Unadjusted and adjusted Binary logistic regression analysis of factors associated with sputum smear non-conversion among people with BC-PTB.

| Characteristics                              | Level          | Binary logistic regression analysis |
|----------------------------------------------|----------------|-------------------------------------|
|                                              |                | uOR (95% CI)                        | aOR (95% CI)                        |
| Type of health facility                      | Government     | 1                                   | 1                                   |
|                                              | Private-not-for profit | 2.37 (1.23–4.39) | 2.03 (1.01–3.92)*          |
| Location of health facility                  | Rural          | 1                                   | 1                                   |
|                                              | Peri-urban     | 0.56 (0.34–0.94)*                   | 0.89 (0.39–2.22)                  |
| Age group in years                           | ≤ 35           | 1                                   | 1.26 (0.79–2.04)                  |
|                                              | > 35           | 1                                   | 1                                   |
| Type of person with BC-PTB                   | New            | 1                                   | 1                                   |
|                                              | Previously treated | 1.18 (0.39–2.96) | 2.38 (0.50–8.61)         |
| Baseline MTB load on ZN stain counts         | One unit (1+) increase | 1.51 (1.05–2.24)* | 1.48 (1.02–1.81)*          |
| HIV infected                                 | No             | 1                                   | 1                                   |
|                                              | Yes            | 1.16 (0.67–1.94)                    | 2.24 (0.48–8.06)                  |
| Sex                                          | Female         | 1                                   | 1                                   |
|                                              | Male           | 1.37 (0.82–2.34)                    |                                     |

Note: 1) *p < 0.05; **p < 0.001; ***p < 0.0001 at 5% significance level; 2) All odds ratio (ORs) and 95% confidence intervals (CI) are in brackets 3) aOR: Adjusted Odds Ratio; 4) uOR: Unadjusted odds ratio. 5) Odds Ratios are exponentiated coefficients.

This study shows that higher baseline MTB load is associated with increased likelihood of sputum smear non-conversion, consistent with several studies [13,24–28]. High baseline MTB load is associated with higher numbers of bacilli in the lungs, and such persons tend to have extensive lung cavitation [29]. The patients with a higher pre-treatment MTB load might benefit from rigorous treatment adherence counseling and psychosocial support to ensure that they take their medicines correctly and not further increase their probability of remaining infectious after the first two months of treatment. Health workers need to prioritize these patients in the sputum smear monitoring and follow up to ensure they achieve sputum smear conversion.

Evidence from elsewhere shows that health and healthcare related performance are influenced by the kind of ownership of health facilities [30]. Our study shows that TB treatment at PNFP health facilities is associated with higher odds of sputum smear non-conversion compared to treatment at government health facilities. In our context, no study has compared treatment outcomes among persons with TB treated at PNFP versus government healthcare facilities but most existing studies have compared treatment outcomes between PFP and government health facilities [31,32].

In low and middle income countries, particularly for countries in SSA, a systematic review and meta-analysis reports that PNFP health facilities tended to be more responsive and to offer better clinical practice especially compliance with clinical guidelines than government health facilities [33], but have incompetent healthcare providers in terms of knowledge tests or exams [33]. It is therefore highly likely that persons with BC-PTB treated at government health facilities tend to benefit from better quality TB services compared to those treated at PNFP health facilities. Such differences in quality of care translate into reduction in sputum smear non-conversion at government than PNFP health facilities.

Our data shows no difference in sputum smear conversion between previously treated persons with BC-PTB and persons with new BC-PTB diagnosis. The findings are not in agreement with the results of an earlier study conducted in India [34]. A recent systematic review and meta-analysis reports that a high pill burden and longer treatment duration among previously treated persons with BC-PTB compromises treatment adherence and leads to suboptimal rates of cure and success [35]. However, in the present study, both previously treated and untreated persons with BC-PTB were managed using same regimen that lasted for six months. The similar pill burden may explain the lack of a difference in sputum conversion. Our data also shows that HIV infected persons with BC-PTB were no different in achieving sputum smear conversion compared to HIV uninfected persons. Our finding is consistent with the results of an earlier study performed in Dar es Salaam, Tanzania [36]. The lack of difference in sputum smear conversion may be an indicator for strengthened HIV and TB treatment integration [19].

4.1. Study limitations

Our study has a number of limitations that should be considered in the interpretation of results. We analyzed secondary data initially collected for routine clinical care so the number of variables were limited to enable comprehensive examination of SSC among persons with BC-PTB. For instance, variables known to influence SSC such as tobacco smoking [26], diabetes mellitus [26,37,38] adherence to treatment [37], and changes in body weight that occurs during TB treatment [39] were not available in the patient database. Although we were able to exclude seven persons with MDR, we could not exclude all persons with MDR-TB from this study because diagnosis was performed largely using sputum smear microscopy test.

Accordingly, assuming some participants had MDR-TB at baseline, the observed lack of difference in SSC between previously treated and untreated persons with BC-PTB would not hold. As the analysis was restricted to sputum smear conversion status at two months, our conclusions might not reflect those at five and six months of treatment. Also, we acknowledge that sputum smear microscopy is not the best in monitoring response to TB treatment due to low sensitivity and modest specificity in predicting treatment failure and relapse. The measurement of sputum smear conversion depends on the healthcare systems’ factors such as staff competence and skills to conduct sputum smear monitoring tests and to accurately report sputum smear non-conversion on time. The lack of data on health systems is another limitation. These factors have the potential to influence the outcome and were not measured in our study. However, these limitations do not override the rigor with which this study was designed and conducted. Importantly, we made attempts to verify all sputum smear results that were recorded in the TB unit registers using the laboratory register results. All the 10 study sites participate in routine external quality assurance of the national TB control program so the sputum smear results recorded in the registers are reliable.

4.2. Conclusions and recommendations

Our study showed that sputum smear conversion at two months of TB treatment among adult persons with BC-PTB in eastern Uganda falls within the expected proportion of 80 to 90%. Patients with higher baseline MTB load and those on treatment of TB at PNFP health facility compared to government health facility carried higher odds for sputum smear non-conversion at two months. TB control programs should develop strategies targeting these high risk individuals to reduce the risk for emergence of MDR-TB.
Ethical statement

We received ethics approval from Mbarara University of Science and Technology Research Ethics Committee, MUST-REC (reference number 03/11-18) and the Uganda National Council for Science and Technology (HS 2531). We were granted a waiver of patient consent by MUST-REC to access secondary data because it was not possible to reach and obtain informed consent from the large number of study participants. To ensure confidentially of data and information, individual identifies such as names and registration numbers were anonymized at data abstraction and analysis stages.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Jonathan Izudi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Visualization, Writing - original draft, Writing - review & editing. Imelda K. Tamwesigire: Methodology, Supervision, Writing - review & editing. Francis Bajunirwe: Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Acknowledgements

We are grateful to the German Academic Exchange Services (DAAD) for awarding the primary author a doctoral scholarship at Mbarara University of Science and Technology. We thank the District Health Officers of Soroti, Kumi, Serere, and Ngora districts for granting us administrative clearance that enabled data collection at respective study sites. We appreciate the support provide to us by the District Tuberculosis and Leprosy Supervisors of Serere, Soroti, Kumi, and Ngora districts as well as the Tuberculosis Focal Persons at respective study sites. We thank the Research Assistants for their immense support.

References

[1] World Health Organization, Global Tuberculosis Report 2019. 2019: Geneva, Switzerland.
[2] World Health Organization. Tuberculosis. 2019 [cited 2019 2 Nov]; Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
[3] Hopewell PC, et al. International standards for tuberculosis care. Lancet Infect Dis 2006;6(11):710–25.
[4] Horne DJ, et al. Spatum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis. Lancet Infect Dis 2010;10(6):387–94.
[5] World Health Organization. Treatment of tuberculosis: guidelines. World Health Organization; 2010.
[6] Friedrich SO, et al. Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment. Lancet Respir Med 2013;3(6):462–70.
[7] Frieden, T. Toman’s tuberculosis. Case detection, Treatment and Monitoring, 2004.
[8] World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. 2017: Geneva, Switzerland. p. 8.
[9] Tiwari S, Kumar A, Kapoor S. Relationship between sputum smear grading and sputum conversion rate and treatment outcome in the patients of pulmonary tuberculosis undergoing dots–a prospective cohort study. Indian J Tuberc 2012;59(3):135–40.
[10] Frieden T. Toman’s tuberculosis: case detection, treatment and monitoring questions and answers. World Health Organization; 2004.
[11] Singla R, et al. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc Lung Dis 2003;7(1):58–64.
[12] Dominguez-Castellano A, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. Int J Tuberc Lung Dis 2005;7(5):412–8.
[13] Kuhah C, et al. Non conversion of sputum smears in new smear positive pulmonary tuberculosis patients in Yaoundé, Cameroon. East Afr Med J 2009;86(5).
[14] Parkh R, et al. Time to sputum conversion in smear positive pulmonary TB patients on category I DOTS and factors delaying it. J Assoc Physicians India 2012;60(8):22–6.
[15] Kayigamba FR, et al. Adherence to tuberculosis treatment, sputum smear conversion and mortality: a retrospective cohort study in 48 Rwandan clinics. PLoS ONE 2013;8(9).
[16] Izudi J, Tamwesigire IK, Bajunirwe F. Treatment supporters and level of health facility influence completion of sputum smear monitoring among tuberculosis patients in rural Uganda: a mixed-methods study. Int J Infect Dis 2020;91:149–55.
[17] Republic of Uganda, Manual of the National Tuberculosis and Leprosy Programme. 2010, Ministry of Health: Kampala, Uganda.
[18] Republic of Uganda, Uganda National Tuberculosis and Leprosy Control Program: Manual for management and control of Tuberculosis and Leprosy. 2017, Ministry of Health: Kampala. p. 22–30.
[19] Republic of Uganda, Uganda national tuberculosis and leprosy control programme. Manual for management and control of tuberculosis and leprosy. 2017. p. 31–33.
[20] Vandeneschbroeck JP, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4(10):e297.
[21] Von Elm E, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12(12):1495–9.
[22] R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2018 [cited 2019; Available from: https://www.R-project.org/.
[23] World Health Organization. Compendium of indicators for monitoring and evaluating national tuberculosis programs. Geneva World Health Organization, 2004.
[24] Jayakody W, et al. Characteristics and outcomes of tuberculosis patients who fail to smear convert after two months in Sri Lanka. Public Health Action 2013;3(11):26–30.
[25] Bisognin F, et al. Predictors of time to sputum smear conversion in patients with pulmonary tuberculosis under treatment. New Microbiol 2019;42(3):175.
[26] Anandaraj R, et al. Factors influencing delay in sputum smear conversion among new smear-positive pulmonary tuberculosis patients of Duvangere tuberculosis unit. Int J Med Sci Public Health 2017;6(11):1565–71.
[27] Commesie E, et al. Determinants of sputum smear nonconversion in smear-positive pulmonary tuberculosis patients in Suriname, 2010–2015. Pan Am J Public Health 2019;5(es8):1–8.
[28] Djomna FN, et al. Delay in sputum smear conversion and outcomes of smear-positive tuberculosis patients: a retrospective cohort study in Bafoussam, Cameroon. BMC Infect Dis 2015;15(1):139.
[29] Babalik A, et al. Factors affecting smear conversion in tuberculosis management. Med Sci 2012;1(4):351–62.
[30] Republic of Uganda, Health Sector Development Plan 2015/2016–2019/2020. 2015, Ministry of Health: Kampala, Uganda. p. 34–35, 39.
[31] Nohuti L, et al. Public and private providers’ quality of care for tuberculosis patients in Kampala, Uganda. Int J Tuberc Lung Dis 2001;5(11):1006–12.
[32] Konde-Lule J, et al. Private and public health care in rural areas of Uganda. BMC Int Health Human Rights 2010;10(1):29.
[33] Herrera CA, et al. Does ownership matter? An overview of systematic reviews of the performance of private for-profit, private not-for-profit and public healthcare providers. PLoS ONE 2014;9(12).
[34] Vasudevan K, Jayakumar N, Gnanasekaran D. Smear conversion, treatment outcomes and the time of default in registered tuberculosis patients on RNTCP DOTS in Pondcherry, Southern India. J Clin Diagnostic Res: JCDR 2015;3(e86):1.
[35] Izudi J, et al. Treatment success rate among adult pulmonary tuberculosis patients in sub-Saharan Africa: a systematic review and meta-analysis. BMJ open 2019;9(9):e029400.
[36] Senkoro M, Mfinanga GS, Moroke O. Sputum microscopy and culture conversion rates among smear positive pulmonary tuberculosis patients by HIV status in Dar es Salaam, Tanzania. BMC Infect Dis 2010;10(210):1.
[37] Shariff MN, Safian N. Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: a case control study. Int J Mycobacteriol 2015;4.s 3 2 3 – 3 2 9.
[38] Mi F, et al. Diabetes mellitus and tuberculosis: pattern of tuberculosis, two-month smear conversion and treatment outcomes in Guangzhou, China. Tropical Med Int Health 2013;18(11):1379–85.
[39] Filate M, Mehari Z, Alemu MY. Longitudinal body weight and sputum conversion in patients with tuberculosis, Southwest Ethiopia: a retrospective follow-up study. BMJ Open 2018;8(e019676):1–6.