Sputum Conversion as a Predictor to Treatment Outcome in Tuberculosis Control in Kenya

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Abstract: _Introduction_: _Globally in 2017, the estimated tuberculosis (TB) morbidity stood at 10 million while 1.45 million people died due to TB. Among the contributors to the high number of adverse outcomes is delayed sputum conversion during treatment. However, little data about delayed sputum conversion in Kenya exists. The objective was to determine the relationship between month two smear conversion and treatment outcome and established associated risk factors._ _Method_: _This was a 3 year' retrospective cohort study of Pulmonary TB patients using routinely collected data available at the National TB Program, Kenya. Non-conversion was defined as persistent sputum smear positive PTB cases at the end of two months of treatment. Chi-square test for linear trend. A multilevel binary logistic regression models was considered with county as the level-2 variable to evaluate the impact of demographic, clinical and therapeutic data on treatment outcome._ _Results_: _The average age was 35.10 (14.82). Female constituted_ 34%. _Month 2 Sputum bacteriological non conversion was observed in_ 8.3% _of the cases notified. The positive predictive value of the month 2 sputum smear non-conversion for unfavourable outcomes was_ 13.1% (95% _CI: = [12.4 - 13.9])._ _Adjusted for sociodemographic and clinical characteristics, the odds for unfavourable outcomes were 5.18 (_95% _CI: [4.799 - 5.595]) higher among those that had not converted at the second month of treatment. Other variables significantly associated with higher odds for unfavourable outcomes included treatment history (aOR1.909;_ 95% _CI:[1.736 - 2.10]). Female gender aOR(0.752 (95%CI: [0.695 - 0.815]); HIV negative aOR(0.579 (95%CI: [0.535 - 0.626]) and Moderate malnutrition aOR(0.800 (95%CI: [0.730 - 0.878]), Normal aOR(0.601 (95%CI: [0.542 - 0.665]), Overweight aOR(0.463 95%CI: [0.354 - 0.608]), Obese aOR (0.478; 95%CI: [0.364 - 0.629]) all compared to severe malnutrition; are all protective of unfavorable outcomes._ _Conclusion_: _Bacteriologically confirmed cases, especially men and those with identified risk factors for non-conversion, should be closely monitored throughout their treatment period. National TB Program should robust the existing strategies to ensure patient adherence to mitigate smear non-conversion risk factors, and ensure treatment success._

Keywords: TB, conversion, Multi-level

1. Introduction

Globally in 2017, the estimated tuberculosis(TB) morbidity stood at 10 million while 1.45 million people died due to TB, majority (85%) of whom were from African and South East Asia regions [18]. While major milestones have been made in the fight against the mammoth TB, a lot still needs to be done to win. The End TB strategy (2015 - 2035) developed by World Health Organization (WHO) to end global TB epidemic, underscores in its pillars the target to reduce TB deaths by 95%. Treatment outcome remain a great area of focus in Tuberculosis control. Despite the high efficacy of the 6 month treatment regimen which has seen 54 million of lives saved [18],[17]), patients receiving this treatment are still prone to adverse outcomes.

Kenya has made tremendous strides in the fight against Tuberculosis. These include closing the gap between notified TB cases and the estimated incidence and development of data driven National Strategic Plan (NSP) 2018 - 2023. The third pillar in the NSP (patient centred approach) seeks to provide quality TB care and prevention of morbidity and mortality due to TB among patients. This happens at a time where while the Country has made enormous progress regarding successful treatment of drug susceptible patients, the treatment success rate is still below the target of 90% at 81% with deaths (6%) and patients being lost to follow up

(5%). The Country still faces burdensome prevalence of 426/100,000 population an indication that the country could be missing up to 50% of the patients; is listed as among the 30 high burden Countries for TB, TBHIV and DRTB; and not being able to meet the WHO mandated successful TB treatment outcome of 90% due to adverse outcomes being reported. A key pointer to Tuberculosis (TB) disease is the presence of bacilli in sputum. The latter two scenarios have been recognized as a predictor of unfavorable outcomes [8] , [10], [1] and [14]. Advancement in hierarchical models have paved way to considering population structures and dependencies leading to plausible results. In view of all these, it is therefore imperative to pay attention to smear conversion and treatment outcome and establish associated risk factors. This study therefore sought to determine whether sputum conversion is predictive of treatment outcomes.

2. Materials and Methods

2.1 Study design and Population

This was a retrospective cohort study. The study population was all pulmonary bacteriologically confirmed TB cases which had been notified as having tuberculosis disease in the periods 2014, 2015, 2016 and 2017 of our review to the National TB program (NTP) of Kenya. Variables of interest included patients' socio-demographic characteristics, smear

results during follow up and treatment outcome at the end of treatment.

2.2 Definitions

Treatment Outcome Treatment outcome as provided by WHO TB definition and reporting framework is categorized as: Cured which refers to a pulmonary TB patient with bacteriological confirmation at the beginning of treatment who was smear negative or culture-negative in the last month of treatment and on at least one previous occasion; treatment completed refers to a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion (Either Month 2 or Month 5) were negative, either because tests were not done or because results are unavailable; treatment failure refers to a TB patient whose sputum smear or culture is positive at month 5 or later during treatment; died refers to a TB patient who dies for any reason before starting or during the course of treatment; lost to follow-up refers to a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more. We further classified these outcomes as favorable (cured or treatment completed) or unfavorable (died, loss to follow up or failure).

Conversion The sputum conversion refers to when smear-positive pulmonary TB (PTB+) cases registered in a specified period convert to smear negative after the standard two months of the intensive phase of treatment (Felix, et al., 2012). Hence in the study, delayed conversion will be participants who will not have converted at the end of 2nd month of treatment while early conversion refers to patients who will have converted to smear negative by end of 2nd month of treatment.

In the study, Positive predictive value (PPV) as the proportion of TB patients in whom treatment was unfavorable among all those with sputum non conversion at month 2.

2.3 Data

TB cases reported in years 2014, 2015 and 2016 were used in this study. This was sourced from TIBU, the national electronic web based system at National TB Program. The details of TIBU are given elsewhere [16] [13] but in brief, TIBU is a case based electronic data collection system.

At the facility level,once a patient is diagnosed and initiated on treatment, their details which include baseline covariates (age, gender, type of TB, treatment outcome,date of start of treatment and HIV status) and Sputum smear test (done in four occasions (month 0 (diagnosis), at month 2, at month 5 and at month 6) among other variables are documented in the register. Sub County TB and Leprosy Coordinators (SCTLCs) then transcribe these patient details from the TB facility register to tablet computers that run on android operating system and is fitted with sim-card to connect to the internet through mobile phone network. The case based data are then transmitted directly to the National database (TIBU) via the mobile network. Because this is national data coming from various facilities in different counties, individual record was level-1 while variable county was level-2.

This data was exported from the TIBU system into analyzable format in an excel sheet. This was then imported to STATA version 13 and R software for data cleaning and analysis.

Th variables of interest were unfavorable outcome (derived from treatment outcome variable by combining patients who were lost to follow up or had died) and sputum smear result (a repeated measure).

Patients who were diagnosed as extra pulmonary (EPTB) or had their initial smear as not done were excluded from the study.

2.4 Statistical Analysis

We employed bivariate analysis to understand the population characteristics and how the converts and non-converts differed. Chi square statistics and the p-values were used to check for significance of each potential risk factor in the bivariate analysis.
This was followed by evaluating the positive predictive value and of a positive month 2 sputum smear (non-conversion) for unfavourable treatment outcomes. This was calculated through the proportion of patients with a positive month 2 sputum smear out of those who had unfavourable outcomes

We then employed hierarchical logistic regression to evaluate the relationship between the response variable (unfavorable outcome) and the selected socio-demographic and clinical variables while exploring the between County variance. This was guided by the response variable which is a binary indicator of whether an individual had a favorable outcome or not.
From the TB data, we observed that the data has two level structure:
- Level 1 are the individual TB patients
- Level 2 is the County

Given that
Y_{ij} = is an indicator of individual i at County j
j = 1,...,47
n = number of individuals
i = 1,...,n

We considered four models. The first model was a null model; the second model considered only random effects for the "County"; the third model included month 2 smear conversion as an explanatory variable while considered model 3 with additional baseline covariates.

We begun by fitting an intercept only model.

Level 1
$$Y_{ij} \sim Ber(pi_ij)$$
$$logit(pi_ij) = \alpha_0$$
In the second model, each individual had their own intercept which summarized $P(Y_ij = 1)$ across the j measurements.

Level 1
$$Y_{ij} \sim Ber(pi_ij)$$
$$logit(pi_ij) = \alpha_0 + u_{0j}$$

Level 2

$$\beta_{0i} \sim N(\mu, \tau_u{}^2)$$

Where α_0 is shared by all Counties while the random effect u is specific to County j.

In the third model, we introduced smear conversion into the second model as an explanatory variable

$$logit(pi_i j) = \alpha_0 + \beta_1 convert_i j + u_{0j}$$

In the fourth model, we included baseline covariates into the third model.

$$logit(pi_i j) = \alpha_0 + \beta_1 convert_i j + \beta_1 hivstatus_i j + \beta_1 sex_i j + \beta_1 treatmenthistory_i j$$
$$+ \beta_1 foodsupport_i j + \beta_1 bmi_i j + u_{0j}$$

Multilevel model was used to avoid parameter under-estimation [6]. We used glmer command within the lmer function to estimate a mixed effects logistic regression model with HIV status, BMI category, age group, convert, sex and treatment history, as patient level predictors and County as level 2. The estimates were based on laplace approximation of the likelihood. To avoid warning messages of possible nonconvergence, we did specify a different optimizer with the argument control=glmerControl(optimizer="bobyqa").

Data analysis were performed using both R software version 3.4.0 (JM-base package available online) and Stata Corp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

2.5 Protocol approval

The study protocol did not require approval by the Institutional Review Board (IRB) as the study did not involve contact with human subjects.

2.5.1 Inclusion and Exclusion criteria

Inclusion criteria
1) Pulmonary confirmed TB cases
2) Cases in two categories of HIV status: positive and negative

Exclusion criteria
1) Cases not assigned a treatment outcome during the period of study

3. Results

The total number of pulmonary bacteriologically confirmed patients notified to NTP between 2014 and 2016 and were recruited into the study were 101,518. The average age was 33.72 (CI: [33.64, 33.80]). Out of all the cases enrolled, female constituted 34% while male constituted 66% . Sputum bacteriological conversion was observed in 93,103 (91.7%) of the cases notified. Over the study period, respectively 9.1% of male, 6.8% of female and 93,103 (8.3%) of all cases registered sputum smear non-conversion at two months of TB treatment. The agegroup 25 - 34 had the highest burden 34598 (34.8%) (males: 34.2% ; females: 33.8%). Patients with previous history of treatment constituted 8.4% . Malnutrition (both severe and moderate) was at 48%(males: 52.7%; females: 40.0%) of all the study population. Co-infection was at 24.5% (males: 20.1% ; females: 33.1%). Only 20.1% of the patients received therapeutic food. It should be noted that the huge proportion of patients not receiving food support is as a result of a policy to provide therapeutic food to only the malnourished group. All variables considered were independently statistically significantly (P<0.001) associated with sputum smear non-conversion at two months of TB treatment. At 9.1% , males cases had a significantly (P<0.001) higher rate of two-month sputum smear non-conversion than females at 6.8% . Among the age groups, those aged between 45 - 54 years (10.3%) reported a significantly (P<0.001) higher rate of non-conversion relative to other age groups. As expected, non-conversion was significantly highest among previously treated patients (8.8% ; P<0.001). HIV-negative cases registered statistically significantly (P<0.001) higher non-conversion (8.8%) than HIV-positive cases (6.9%) and those with HIV status unknown (6.6%). Non-conversion was also significantly higher in patients receiving therapeutic food at (9.2%) than those not receiving at (8.0%)(P<0.001).

Table 1: Descriptive Statistics

Characteristic	Category	Overall	Delayed Converters	Converters	p-value
		(n=101,518)	(n = 8,415)	(n = 93,103)	
Age group	0 -14	2497 (2.46)	118 (4.72)	2379 (95.27)	
	15-24	22611 (22.27)	1448 (6.4)	21163 (93.59)	
	25-34	34598 (34.08)	2926 (8.45)	31672 (91.54)	
	35-44	22864 (22.52)	2045 (8.94)	20819 (91.05)	0.000
	45-54	11069 (10.9)	1139 (10.28)	9930 (89.71)	
	55-64	4841 (4.77)	449 (9.27)	4392 (90.72)	
	65+	3038 (2.99)	290 (9.54)	2748 (90.45)	
Sex	Male	67,218 (66.21)	6087 (9.05)	61131 (90.94)	
	Female	34,300 (33.79)	2328 (6.78)	31972 (93.21)	0.000
HIV status	Pos	24853 (24.48)	1708 (6.87)	23145 (93.12)	
	Neg	74252 (73.14)	6547 (8.81)	67705 (91.18)	0.000
	Unknown	2413 (2.38)	160 (6.63)	2253 (93.36)	
TB History	New	92975 (91.58)	7660 (8.23)	85315 (91.76)	
	Prev. Treated	8543 (8.42)	755 (8.83)	7788 (91.16)	0.050
Food support	Yes	21390 (21.07)	1978 (9.24)	19412 (90.75)	
	No	80128 (78.93)	6437 (8.03)	73691 (91.96)	0.000
BMI	Severe Mal	15585 (15.35)	1642 (10.53)	13943 (89.46)	

	Moderate Mal	33561 (33.06)	3182 (9.48)	30379 (90.51)	
	Normal	38266 (37.69)	2738 (7.15)	35528 (92.84)	0.000
	Overweight	3254 (3.21)	155 (4.76)	3099 (95.23)	
	Obese	4586 (4.52)	225 (4.9)	4361 (95.09)	
	Not Evaluated	6266 (6.17)	473 (7.54)	5793 (92.45)	
Sector	OFB	2406 (2.37)	175 (7.27)	2231 (92.72)	
	Prisons	1723 (1.7)	103 (5.97)	1620 (94.02)	
	Public	82635 (81.4)	7046 (8.52)	75589 (91.47)	0.000
	Private	14754 (14.53)	1091 (7.39)	13663 (92.6)	
DOT By	CV	1362 (1.34)	118 (8.66)	1244 (91.33)	
	Household	90531 (89.18)	7519 (8.3)	83012 (91.69)	
	HCW	9526 (9.38)	773 (8.11)	8753 (91.88)	0.000
	Not done	99 (0.1)	5 (5.05)	94 (94.94)	

The positive predictive value of the second month-SSM non-conversion for unfavourable outcomes was 13.1% CI: 12.4% - 13.9%)

Table 2: Positiv Predictive Value

Positive predictive value	13.10 %	12.40 %	13.90%

3.1 Hierarchical logistic regression caterpillar plot

The caterpillar plot below examines estimates of the county effect shown in rank order together with 95% confidence intervals. Substantial number of Counties do not overlap the red horizontal line indicating that occurrence of unfavourable outcomes is significantly above average for Counties above the line and below average for Counties below the zero line.
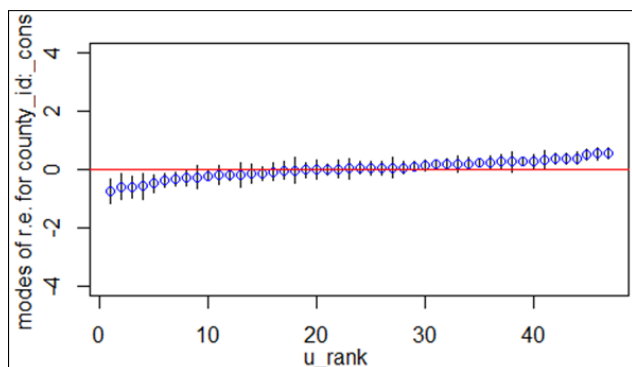

Figure 1: Caterpillar plot

3.2 Odd ratio estimates for two-level binary logistic regression models for predicting unfavorable outcome among TB patients in Kenya

The data had two level hierarchical struture with 101,518 individuals nested within 47 Counties at level 2. We considered treatment history, sex, HIV status,food support,age and BMI at level 1 and County at level 2. We fitted null model, a model with random effect only, model 3 which included smear conversion as an explanatory variable and model 4 which included other baseline covariates. Model 4 proved to be the best fit model (AIC was the least). Adjusted for sociodemographic and clinical characteristics, the odds for unfavourable outcomes were 5.18 higher (95%CI: [4.799 - 5.595]) among those that had not converted at the second month of treatment (Table 3). Other variables significantly associated with higher odds for unfavourable outcomes included treatment history aOR(1.909 (95 % CI: [1.736 - 2.10]). Female gender aOR(0.752 (95%CI: [0.695 - 0.815]); HIV negative aOR(0.579 (95%CI: [0.535 - 0.626]) and Moderate malnutrition aOR(0.800 (95%CI: [0.730 - 0.878]), Normal aOR(0.601 (95 % CI: [0.542 - 0.665]), Overweight aOR(0.463 95 % CI: [0.354 - 0.608]), Obese aOR(0.478; 95%CI: [0.364 - 0.629]) all compared to severe malnutrition; are all protective of unfavorable outcomes (Table 3).

Table 3: Odd ratio estimates for two-level binary logistic regression models for predicting unfavorable outcome among TB patients in Kenya

Fixed Effects	Category	Model 1	Model 2	Model 3	Model 4
Intercept 1		-3.302***	-3.39715 ***	0.026	0.051
Convert	Yes			Ref	Ref
	No			5.302 CI(4.917,5.716)	5.181 CI(4.799,5.595)
HIV Status	Pos				Ref
	Neg				0.579 CI (0.535,0.626)
	Unknown				0.613 CI (0.478,0.787)
Sex	Male				Ref
	emale				0.752 CI (0.695,0.815)
TB history	New				Ref
	Prev. Treated				1.909 CI (1.736,2.10)
Food Support	Yes				Ref
	No				0.935 CI (0.859,1.018)
BMI	< 16.0				Ref
	16.0 - 18.4				0.800 CI (0.730,0.878)
	18.5 - 24.9				0.601 CI (0.542,0.665)
	25.0 - 29.9				0.463 CI (0.354,0.608)
	>30.0				0.478 CI (0.364,0.629)
Age group	0 - 14				Ref

15 - 24				0.928 CI (0.667,1.293)
25 - 34				1.193 CI (0.857,1.663)
35 - 44				1.038 CI (0.739,1.460)
45 - 54				1.172 CI (0.840,1.634)
55 - 64				1.190 CI (0.833,1.699)
65+				1.357 CI (0.934,1.970)
AIC		31142	30978.2	29472.3	28815.5

* Model 1 is null model * Model 2 No predictors but only random effects for the "County" * Model 3 Model 2 + month 2 conversion * Model 4 Model 3 + additional baseline covariates

4. Discussions

The study focused on the relationship between smear month 2 conversion as a prognostic marker for end of treatment outcome among notified TB patients in Kenya.

Smear non-conversion was lowest compared to results shown in [10], [8], [15]. This high conversion rates could be explained by adoption of WHO recommended intervention strategies such as direct observe therapy, patient centred care and availability of funding to combat the disease. While the occurrence of sputum smear non-conversion at the end of 2 months of treatment may not be a useful marker for predicting a patient′s treatment outcome the result demonstrated that smear conversion was associated with unfavorable outcomes among TB patients. This is consistent with the findings from [15], [9] [12] which showed second month sputum smear to be a poor predictor of unfavorable outcomes. This may be due to the fact that after month 2 non-conversion, patients are more likely to convert to smear negative through the treatment curve. More so, a lot of interventions have been put in place to trace; treatment supporter; which ensure adherence to treatment. As recommended by National treatment guidelines, all the patients with month two smear positive results are subjected to culture, a gold diagnostic test, which confirms the results from microscopy. This is because microscopy picks bacilli whether dead or alive [7]. The study however was not able to validate this as either adherence to the recommendation was low or due to poor documentation of culture results. Demographic and clinical factors play significant roles in predicting treatment response, and influenced sputum smear conversion at two months post-treatment.

In previous studies, these demographic and clinical factors have also been reported as independently associated with the odds of unfavorable outcomes. Controlling for a number of baseline covariates and clustering effect from the County: Conversion was found to be associated with treatment outcome among TB patients. Male [10] ,[3], [14], [5]. Possible explanations could be delayed treatment initiation among the males [11] and possibly non-adherence to treatment.

HIV status [14] , [2], [11]. It could be that that the various interventions received by HIV-positive patients also had a positive effect on these patients when they are initiated TB treatment, consequently influencing their treatment outcomes.

Age group [10], [3], [11]. Progressive age-related immune dysregulation and delayed TB diagnosis [11], [4] could possibly account for the observed two-month sputum smear non-conversion among older patients in the current study. Hence a pointer for consistent need to and rigorous clinical management of the elderly.

treatment history was found to be associated treatment outcome where patients who had previous history of TB were two times more likely to experience an unfavourable outcome as compared to new patients. BMI was also associated with treatment outcome [5].

Provision of food support was protective of unfavorable outcomes. the importance of developing composite prognostic markers that can predict end-of-treatment outcomes in the early stage of MDR-TB treatment that may have the potential to guide clinical decision making.

The strengths of this study were the large number of cases studied, robust surveillance system (TIBU) and the adherence to the conduct and reporting of the routine data. Limitations include the usual operational problems of working with routine programmatic records that may have inaccuracies and inconsistencies.

5. Conclusion

Sputum smear non conversion of at the end of 2 months of treatment may not be a useful marker for predicting a patient's treatment outcome. The recommendation however to conduct month 2 smear should be conducted to ensure improved surveillance. Non conversion, Male, HIV status, Elderly and previously treated patients were independently and significantly associated with unfavorable outcomes. These factors should be paid attention as they will lead to unfavourable outcomes.

We recommend that:
- National DB to include smear month 3 results
- National TB Program to enforce documentation of culture results for smear positive patients at month 2
- Fast track digitization of laboratory register to facilitate real time access of smear results hence better monitoring of the same.
- Evaluation of nutrition interventions to ensure favorable outcomes
- A need to identify interventions which will mitigate the risk of non-conversion to maximize indicators for TB treatment success rate. Targeted interventions should focus on (i) revamp TB treatment adherence counselling and support, and (ii) improve follow-up of high-risk groups, especially men patients with previous history of TB. Investing in digitization of laboratory recording tools so as to fast-track laboratory results relay which will assist to improve

follow-up and TB indicators for treatment outcomes.

6. Acknowledgments

7. Competing Interests

The authors declare that they have no competing interests. Availability of Data and Materials The datasets analyzed during the current study are available from the corresponding author on reasonable request and further approval from the national TB Program, Ministry of Health Kenya.

8. Ethics Approval

Approval was obtained from the National Tuberculosis Program of Kenya. TB patient privacy and confidentiality were strictly maintained through removing personal identifying information and using unique patient identifiers.

9. Funding

10. Abbreviations

Table 4: Abbreviations

TB	Tuberculosis
SMM	Sputum smear microscopy
PTB	Pulmonary Tuberculosis
CI	Confidence interval
ll	Lower limit
up	Upper limit
OR	odds ratio
DST	Drug susceptibility test
AUC	Area under curve
NTP	National tuberculosis Program

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