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# Quarterly Trends of TB Treatment Outcomes as Xpert MTB/Rif Rolled Out in Manicaland, Zimbabwe for 2017 and 2018

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**ABSTRACT**

**Background:** The World Health Organization target is to reduce to zero the number of death due to Mycobacterium tuberculosis by the year 2035. The earlier TB treatment is commenced, the less chance of a TB associated death and the higher the chance of successful treatment outcomes.

**Objective:** The objective of the study was to evaluate quarterly trends of TB treatment outcomes as Xpert MTB/Rif testing services rolled out in Manicaland for 2017 and 2018.The study gave an opportunity for the Zimbabwe National TB Program to generate some evidence showing implementation of the intervention, Xpert MTB/Rif diagnostic test.

**Method:** In the retrospective study , a total of 3277 TB patient variables were captured from facility TB registers .The population was all TB patients recorded in the 304 health facilities as having received TB treatment between 1 January 2017 and 31 December 2018. The scope of the study did not include capturing the full range of variables that are determinants of TB treatment outcomes.

**Results:** The study demonstrates that the proportion of TB treatment outcome of died had a steady decrease from quarter one of 2017, which had 30/238 (12.6%) to quarter two 2018 which had 41/431 (9.5%). Then quarter three of 2018 the outcome died had a slight increase to just slightly above 10.0% , before going back to just below 10.0% in quarter four of 2018. The proportion of cured for 2017 first quarter was 90/238(37.8%) and that for 2018 quarter four was 147/313 (47.0%). TB treatment outcome of treatment completed for 2017 quarter one was 91/238(38.2%) then for 2018 quarter one, it was 205/464(44.1%).There was no noticeable trend in the two TB treatment outcomes of cured and treatment completed during the eight evaluated quarters.

**Conclusion:** Overall the TB treatment outcome of died showed a decreasing trend over the eight quarters. In order to avoid inferring the decrease to Xpert MTB/Rif roll out, more variables that are determinants of TB treatment outcomes have to be analysed in future studies.

**KEYWORDS:** Tuberculosis; Trends; Treatment; Outcome

## INTRODUCTION

The World Health Organization (WHO) End tuberculosis (TB) Strategy has expanded the Sustainable Development Goals (SDGs) to reduce TB deaths by 95% and new cases by 90% between 2015 and 2035.[1]The earlier TB treatment is commenced, the less chance of a TB associated death and the higher the chance of successful TB treatment outcomes. Successful TB treatment outcomes in clinically diagnosed patients receiving TB treatment is lower compared to patients with bacteriologically confirmed TB receiving TB treatment, irrespective of HIV status and age.[2] The need for early commencement to treat patients confirmed to be infected with TB comes with the necessity for early diagnosis of TB. The roll out of, a rapid molecular diagnostic method for **Mycobacterium tuberculosis (MTB) which simultaneously detects rifampicin (Rif) resistance pattern (Xpert** MTB/Rif) changed TB landscape , since it has higher sensitivity meaning TB is detected earlier than when smear microscopy diagnosis was in use. Benefits of early TB diagnosis to both patients and their families may be due to: 1) decreased morbidity resulting in increased quality of life at the end of treatment; 2) reduced amounts of money used during the period of seeking a confirmed diagnosis; and 3) less chance of transmission .[3]

The evaluation of quarterly trends of TB treatment outcomes as Xpert MTB/Rif rolled out had not been systematically

carried out under programmatic conditions in Manicaland. For the purposes of this study TB treatment outcomes such as the number of patients cured, treatment completed, treatment failure and died were as defined by WHO.[4] There are many determinants of TB treatment outcomes including : type of TB, method used for TB diagnosis, time taken to commencement of treatment, treatment regimen, model of treatment care and support, existing co morbidities, level of management of co morbidities, Tuberculosis disease is the major cause of death among adolescents co-infected with HIV. [5]

A study in India did not look at many other determinants of TB treatment outcomes such as co morbidities like diabetics where an Indian study reported 30% fewer unsuccessful treatment outcomes (aOR (0.95 CI): 0.72 (0.64−0.81)) and 2.8 times higher odds of 'no recurrence' (aOR (0.95 CI): 2.83 (2.60−2.92)) among patients with optimal glycemic control at baseline .[6]

In a study carried out in Zambia the TB treatment outcomes established were; death 5.5%, lost to follow-up 2.9%, and 3.2% treatment failure. [7] In .a study carried out in Ghana TB patients who were HIV positive had lower successful TB treatment outcomes than HIV negative 70% (83/107) compared to 91.2% (382/419) respectively. In the same study, 21.5% (23/107) HIV positive TB patients died compared to 5.5% (23/419) for HIV negative TB patients. [8]In Cape Town, it was found that the reason for TB treatment commencement changed from a positive smear microscopy in 67% and 21% HIV negative and HIV positive patients respectively to Xpert MTB/Rif positive in 84 % and 67% in HIV negative and HIV positive patients respectively. [9]

In a study carried out in Ethiopia the TB treatment outcomes of treatment completed and died, were established to be 137/281(48.8%) and 14/281 (5%) respectively. [10]

In a study carried out in Kalifi , Kenya overall poor treatment outcomes were 776 (5.3%) loss to follow up, 415 (2.8%) transferred out, 103 (0.7%) treatment failure 30 (0.2%) multidrug resistance and 1,074 (7.3%) deaths .It was also established that during the last three months of treatment, being a female (aHR 0.83 (95%CI 0.70–0.97)) was negatively associated with poor treatment outcomes . While in the same last 3 months of treatment completion, being of an elderly age ≥50 years (aHR 1.26 (95%CI 1.02–1.55), a TB retreatment patient (aHR 1.57 (95%CI 1.28–1.93), were positively associated with poor treatment outcomes,[11]

Another study in Kenya showed effect of type of TB diagnostic method used on TB treatment outcomes, meaning analyzing patient clinical outcomes while comparing the method of diagnosis. The median age for the 12 856 patients enrolled was 37 [IQR 28 − 50] years. Males comprised the majority i.e. 7639 (59%), while 11 339 (88%) were pulmonary TB cases HIV positivity was 3791 (29%). From the 6472 (50%) clinically diagnosed patients, 4521/6472 (70%) of them had a negative sputum or Xpert MTB/Rif test. Comparing method of TB diagnosis namely clinically and bacteriologically diagnosed patients, there were no significant differences in defaulting (P= 0.70) or transfer out (P= 0.19). The treatment outcome of death was significantly higher among clinically diagnosed patients: 639 (9.9%) deaths compared to 285 (4.5%) amongst the bacteriologically diagnosed patients; aHR 5.16 (95%CI 2.17 − 12.3) P< 0.001.[2]

A mathematical model evaluated potential health and economic consequences of implementing Xpert MTB/Rif in five southern African countries—Botswana, Lesotho, Namibia, South Africa, and Swaziland—where drug resistance and TB-HIV co infection are prevalent, The mathematical model projected that implementation of Xpert MTB/Rif would avert 132 000 (95% CI: 55,000–284,000) TB cases and 182 000 (97,000–302,000) TB deaths in southern Africa over the first 10 years following introduction, and would reduce prevalence by 28% (14%–40%) by 2022, with more modest reductions in incidence .[12]

In 2017 Zimbabwe experienced 8300 deaths associated with TB .Mupfumi et al in 2014 found a non-significant decrease in mortality on drug resistant Mycobacterium tuberculosis (DRTB) patients using centralized Genexpert analyser, 6% and 10% 95% (CI -9%- 2% ) p value 0.19 respectively.[13]

This study sought to establish whether there were any changes in percentages of TB treatment outcomes recorded in Manicaland Province TB Facility registers between 2017 and 2018 comparing against the method of TB diagnosis ( whether clinically diagnosed or diagnosed by Xray or bacteriologically confirmed by either smear microscopy or by Xpert MTB/Rif). Clinically diagnosed meant patient could have negative Xray, Negative smear microscopy and negative Xpert MTB/Rif results, yet is commenced on TB treatment based on clinical presentation only, or the patient might not even have full panel of negative diagnostic results, but is commenced on TB treatment without any one of the following positive results; Xray or smear microscopy or Xpert MTB/Rif. 2017 is the period when roll out of Xpert MTB/Rif gradually took place from 5% to 100% by quarter one of 2018 (quarter five).[3] Before first quarter 2018, when there was 100% implementation of the intervention, the TB diagnostic algorithm in use was targeted Xpert MTB/Rif. Targeted Xpert MTB/Rif algorithm only processed the following selected or targeted groups, that is presumptive TB patients who were HIV positive, or less than 5 years or older than 60 years or those who had any conditions that lowered their immunity, while the rest were processed using smear microscopy. The operational definition of Xpert MTB/Rif roll out in the context of this paper was using Xpert MTB/Rif to analyze all presumptive TB specimens regardless of HIV status, thus moving away from targeted Xpert MTB/Rif for the previously stated selected group and smear microscopy as TB diagnostic tool for HIV negative population who didn't fit the inclusion criteria. What changed during Xpert MTB/Rif roll out was only the diagnostic algorithm, while the

TB screening tool as well as the TB screening points in 2017 and 2018 remained the same.

The intervention was Xpert MTB/Rif roll out and the population was TB patients who were commenced on TB treatment between 2017 and 2018. The aim of this study was to evaluate quarterly trends of TB treatment outcomes as Xpert MTB/Rif rolled out in Manicaland for 2017 and 2018.The findings would be used to inform the Zimbabwe National TB Program.

## MATERIALS AND METHODS

The retrospective study was carried out in Manicaland, one of the ten provinces in Zimbabwe. The province has a total area of 36,459 square kilometres. It is the second most populous province after Harare with a population total of 1.75million (Census, 2012).[13] It is the third most densely populated province after Harare and Bulawayo. According to the Zimbabwe District Health Information System (DHIS2), Manicaland province has a total of 304 health facilities. These health facilities form clusters that are served by fifteen Genexpert testing sites. One of the fifteen Genexpert testing sites Rusape General Hospital has two Genexpert analyzers, bringing total Genexpert machines in Manicaland to sixteen. Mutasa district , Makoni district , Chimanimani district , Nyanga district , Buhera district and Chipinge district, all have two each while Mutare district has four Genexpert analyzers. All Genexpert testing sites also offer smear microscopy. Smear microscopy is also performed at fifteen additional microscopy centres. All 304 facilities despite level of operation, provide TB investigations and treatment.

The population was all TB patients recorded in the 304 health facilities to have received TB treatment between 1 January 2017 and 31 December 2018. With the change in TB testing algorithm, the 304 facilities that provided TB screening services remained the same and the same TB screening tool was in use throughout. Data collection period started in October 2019 and ended in December 2021. The data was collected from paper based Facility TB registers at health facilities. Each morning the data collectors would ride on any program vehicles that were going to health facilities on any business. The variables captured included demographic factors such as sex, age, HIV status, and other diagnostic factors, for example sputum smear results, pulmonary or extrapulmonary (EPTB) disease, Xpert MTB/Rif results as well as the algorithm in use. The variables were entered into an excel sheet, with enrolment numbers that were anonymised, to maintain confidentiality. Ethical authorisation was received from Africa University Research Ethical Committee as well as from the Manicaland Provincial Medical Directorate. The study is Medical Research Council of Zimbabwe reference number A/ 2385.

## RESULTS

In total 3277 (Table 1) TB patient details were enrolled. The median age was 38. Proportion of female to male patients was, with missing

**Table 1:** Type of TB

| Type of TB | Frequency | Percent |
|---|---|---|
| **1** | 2,802 | 85.5 |
| **2** | 392 | 12.0 |
| **4** | 83 | 2.5 |
| **Total** | 3277 | 100.0 |

**Table 2:** TB Treatment Outcomes Including Missing Outcomes

| Outcome | Frequency | Percentage |
|---|---|---|
| **Died** | 298 | 9.1 |
| **Treatment Failure** | 62 | 1.9 |
| **Loss to Follow Up** | 66 | 2.0 |
| **Transfer** | 62 | 1.9 |
| **Treatment completed** | 1008 | 30.8 |
| **Cured** | 1018 | 31.1 |
| **Not Evaluated** | 8 | 0.2 |
| **Other (eg stopped by doctor)** | 2 | 0.1 |
| **Missing** | 753 | 23.0 |
| **Total** | 3 277 | 100.0 |

Table 2 shows the two most common TB treatment outcomes were cured 1018/3277 (31.1%) followed by treatment completed 1008/3277 (30.8%). The worst outcome which is died comprised 298/3277(9.1%) that were captured in TB registers. There was missing outcomes data for 753/ 3277(22.3%). Due to the inclusion of the proportion with missing TB treatment outcome results, the rates in table 2 were lower, than those from annual TB review report of 2017 and 2018.

**Table 3:** Frequency of The HIV Status

| HIV Status | Frequency | Percentage |
|---|---|---|
| **Negative** | 1252 | 38.2 |
| **Positive** | 1676 | 51.1 |
| **Unknown or missing** | 349 | 10.7 |
| **Total** | 3277 | 100,0 |

Table 3 shows the HIV status of the 3277 patients treated for TB. 1252/3277(38.2%) were HIV negative. 1676/3277(51.1%) of the patients treated for TB were HIV positive, while 349/3277(10.7%) had HIV status of unknown or missing field.

**Table 4:** MTB Versus HIV Status

| MTB | HIV Status 0 | HIV Status 1 | HIV Status 2 | Total |
|---|---|---|---|---|
| **0** | 91 | 174 | 16 | 286 |
| **1** | 563 | 747 | 1929 | 1 509 |
| **2** | 5 | 1 | 2 | 8 |
| **3** | 24 | 45 | 4 | 73 |
| **4** | 26 | 40 | 3 | 69 |
| **5** | 15 | 18 | 3 | 36 |
| **6** | 1 | 2 | 0 | 3 |
| **7** | 527 | 644 | 122 | 1293 |
| **Total** | 1 252 | 1 676 | 349 | 3 277 |

**Key for MTB** 0: Not detected, 1: Detected, 2: Mantoux, 3: Xray, 4: Genexpert not done, 5: Clinically diagnosed, 6:Other, 7: Missing
**Key for HIV Status** 0 HIV Negative 1 HIV Positive 2 Unkown or missing

**Table 5:** Initial TB Diagnosing Method Used by Quarter

| | QUARTER | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| **MTB** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| **Not detected** | 24 | 20 | 14 | 26 | 44 | 67 | 49 | 42 | 286 |
| **Detected** | 49 | 84 | 11<br>3 | 13<br>1 | 27<br>7 | 29<br>1 | 23<br>2 | 33<br>2 | 1<br>509 |
| **Mantoux** | 0 | 1 | 1 | 0 | 4 | 0 | 1 | 1 | 8 |
| **Xray** | 4 | 8 | 9 | 8 | 19 | 8 | 10 | 10 | 73 |
| **Genexpert not done** | 5 | 7 | 4 | 4 | 7 | 19 | 13 | 13 | 69 |
| **Clinically diagnosed** | 11 | 3 | 3 | 2 | 8 | 5 | 1 | 1 | 36 |
| **Other** | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 |
| **Missing** | 18 | 17 | 16 | 17 | 20 | 14 | 10 | 10 | 1 |
| **Total** | 7<br>28<br>1 | 1<br>29<br>4 | 0<br>30<br>4 | 4<br>34<br>5 | 8<br>56<br>8 | 8<br>53<br>8 | 7<br>41<br>3 | 7<br>53<br>4 | 293<br>327<br>7 |

**Key for Quarter:** 1: Quarter 1 of 2017, 2: Quarter 2 of 2017,3: Quarter 3 of 2017, 4: Quarter 4 of 2017, 5: Quarter 1 of 2018, 6: Quarter 2 of 2018, 7: Quarter 3 of 2018, 8: Quarter 4 of 2018.

The table 5 shows that, as the Xpert MTB/Rif primary diagnostic test rolled out from Quarter one 2017 to Quarter four 2018 the initial diagnosis based on MTB detected was increasing directly proportional to Genexpert MTB from 49/281 (17.4%) to 332/534(62.2%). The proportion with reason for TB treatment as clinical diagnosis changed from Quarter one 2017 to Quarter four 2018 as follows 11/281 (3.9%) and 3/534 (0.6%). Testing for association p value of <0.001 showed there was a statistically significant association between Initial TB diagnosing method used and Genexpert MTB/ Rif roll out as represented by quarters of the 2 years. Proportion of patients commenced on TB treatment as a result of MTB detected result increased. On the other hand the proportion of patients commenced on TB treatment despite a MTB not detected result oscillated. Pearson chi2(49) = 376.0453 Pr = <0.001

**Table 6:** HIV Status Versus Type of TB

| | Type of TB | | | Total |
|---|---|---|---|---|
| **HIV STATUS** | 1 | 2 | 3 | |
| 0 | 1080 | 148(11.8%) | 24 | 1 252 |
| 1 | 1410 | 224(1 3.4%) | 42 | 1 676 |
| 2 | 312 | 20 | 17 | 349 |
| Total | 2 802 | 392 | 83 | 3277 |

**Key for Type of TB**: 1: Pulmonary TB 2: EPTB 3: Missing
**Key for HIV Status:** 0: HIV negative, 1: HIV positive, 2: Unknown or Missing

Table 6 shows that 224/1676(13.4%) HIV positive had EPTB while 148/1252(11.8%) HIV negative had EPTB, showing HIV negative were less likely to have EPTB.

**Table 7:** TB Treatment Outcome by Type of TB

| Treatment | Type of TB (N=3277) | | | Total |
|---|---|---|---|---|
| **Outcome** | 1 | 2 | 3 | |
| **1** | 250 (7.6%) | 42(1.3%) | 6(0.2%) | 298 |
| **2** | 57(1.5%) | 3(0.1%) | 2(0.1%) | 62 |
| **3** | 49(1.5%) | 14(0.4%) | 3(0.1%) | 66 |
| **4** | 56(1.5%) | 6(0.2%) | 0 | 62 |
| **5** | 817(24.9%) | 179(5.5%). | 12(0.4%) | 1 008 |
| **6** | 931(28.4%) | 71(2.2%) | 16(0.5%) | 1018 |
| **7** | 6(0.2%) | 2(0.1%) | 0 | 8 |
| 8 | 2(0.1%) | 0(%) | 0 | 2 |
| 9 | 634(19.3%) | 75(2.3%) | 44(1.3%) | 753 |
| Total | 2,802 | 392 | 83 | 3277 |

**Key for Type of TB**: 1: Pulmonary TB 2: EPTB 3: Missing
**Key for Treatment Outcome**: 1: Died, 2: Treatment failure, 3: Defaulted or loss to follow up, 4: Transfer, 5: Treatment completed, 6: Cured, 7: Not evaluated, 8: Other, 9: Missing

Table 7 shows that whereas the TB treatment outcome with the highest proportion was cured 931/3277(28.4%) for PTB. For EPTB the TB treatment outcome with the highest proportion was treatment completed179/3277(5.5%).

**Percentage TB Treatment Outcome Trends/Quarter**

For the trend analysis we assumed the 753/3277(22.3%). missing TB treatment outcomes were by chance and excluded them in the trend analysis. Once results with missing TB treatment outcomes were excluded the remaining 2524 TB treatment outcome trend analysis by quarter became more comparable with the annual TB review reports.

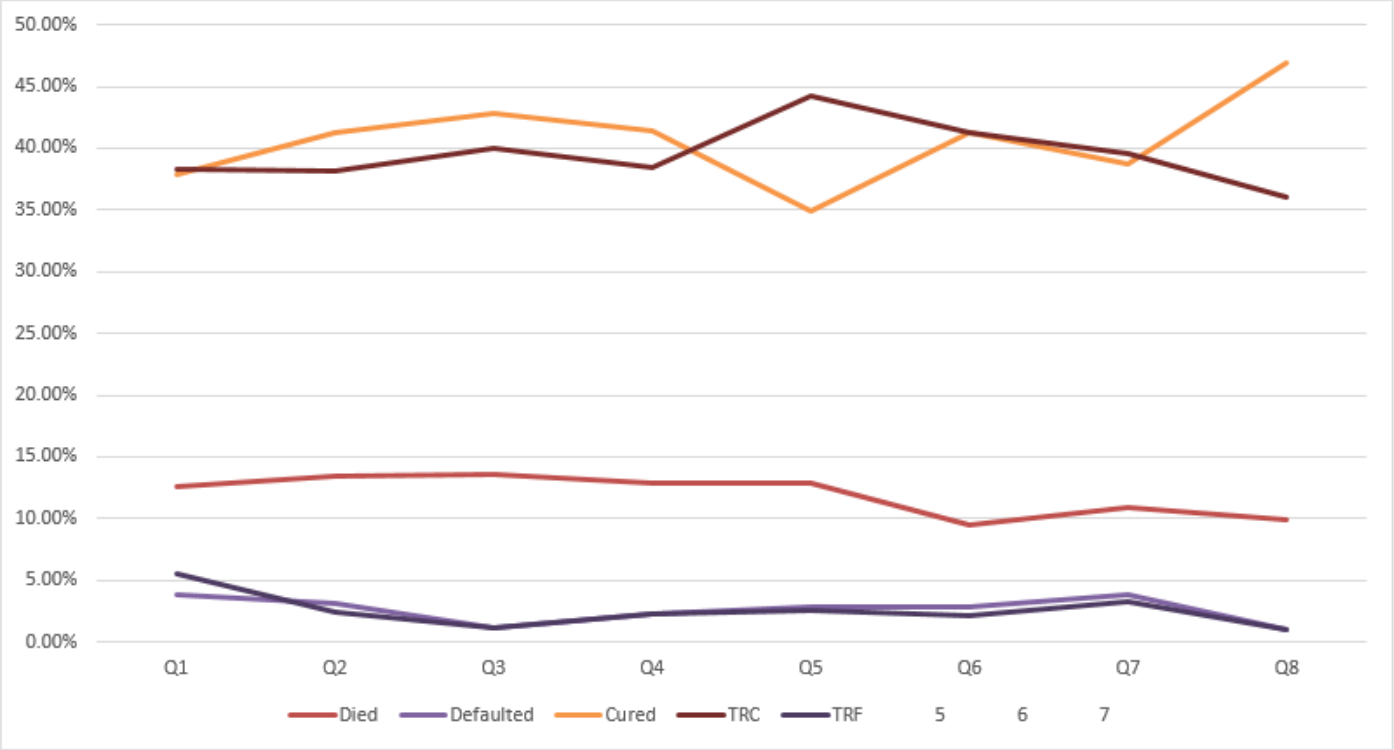


**Figure 1:** Percentage TB Treatment Outcome Trends/Quarter

TRF=treatment failure

TRC= treatment completed

**Key for Quarter:** 1: Quarter 1 of 2017, 2: Quarter 2 of 2017, 3: Quarter 3 of 2017, 4: Quarter 4 of 2017, 5: Quarter 1 of 2018, 6: Quarter 2 of 2018, 7: Quarter 3 of 2018, 8: Quarter 4 of 2018.

Figure 1.shows that the proportion of TB treatment outcome of died had a steady decrease from quarter one of 2017 30/238(12.6%) to quarter two 2018 41/431 (9.5%). Then quarter three of 2018 the outcome died had a slight increase to just slightly above 10.0% , before going back to just below 10.0% in quarter four of 2018. To avoid inference that roll out of diagnostic test algorithm had a positive effect on the outcome died, as trend showed a steady decrease in deaths, more variables that are determinants of TB treatment outcomes will need to be captured, in future studies. The proportion of cured for the period 2017 first quarter was 90/238(37.8%) and for 2018 quarter four was 147/313 (47.0%). TB treatment outcome of treatment completed for 2017 quarter one and for 2018 quarter one was 91/238 (38.2%) and 205/464(44.1%), respectively. There was no noticeable trend in the two TB treatment outcomes of cured and treatment completed.

**Testing for association**

Testing for association between HIV status and TB treatment outcome showed a statistically significant association with a p value of <0.001. Testing for significance of association between MTB Rif roll out and TB treatment outcome showed a statistical significance with p value, <0.001. There was statistically significant association between HIV status and type of TB (i.e. PTB or EPTB). There was statistically significant association between type of TB and TB treatment outcome, with p value <0.001.

## DISCUSSION

The findings of mean age 38 years were similar to those established in a previous study in Kenya. Findings predicted by literature were TB outcome cured that comprised 1018/3277 (31.1%) which was similar to cured 90/281(32%), found in a study carried out in Ethiopia. Findings that differ from expectations, were TB treatment completed 1008/3277 (30.8%), which differed from treatment completed of

137/281(48.8%) found in a study carried out in Ethiopia. The worst outcome which is died comprised highest of 34/250 (13.6%) to lowest 41/431(9.5 %) with overall average of 298/2524(11.8%) that were captured in TB registers, differed from died 14/281 (5%) established by Tesema et al. 10 At the same time the findings established that previous study in Ethiopia of 5% , as well as that established in Kalifi , Kenya of 7.3%, for TB treatment outcome died show better progress towards the ultimate target of zero TB death.10,11

At the time data collection occurred from October to December 2019, there was missing outcomes data for 753/3277(22.3%).There is need to address 22.3% outcome that was still missing in facility TB registers, yet 6 months for quarter four cohort ended in June 2019 and recording period window September 2019. The transcription of laboratory results or TB treatment out comes into the Facility TB registers should be given a timeline, just like statistics is given the timeline that by the end of the next month of each quarter everything should have been compiled. This will eliminate cases where fields are left blank for long until they are just reported as not evaluated. The limitations of the study was that the study did not include evaluation of other factors besides TB detection algorithm, that could influence TB treatment outcomes, like among others, the type of direct observed treatment model of each patient, as well as the adherence counselling sessions received by patient.

## CONCLUSION

In conclusion the findings have answered the research question which was what were the trends of quarterly TB treatment outcomes as Xpert MTB.Rif rolled out in Manicaland for 2017 and 2018? The research demonstrates decrease of bad TB treatment outcomes .Overall the trend showed a steady decrease in the TB treatment outcome died... Transcription of TB treatment out comes into the Facility TB registers takes place long after the expected timelines, for example 6 months for quarter four cohort ended in June 2019 and recording period window September 2019.

To avoid inferred influence to the variables collected namely age, sex, HIV status, type of TB, method of diagnosis, a wider number of variables, that also have an influence on the dependent variable TB treatment outcomes, needed to be collected.

Limitation of the study was that the other variables that influence TB treatment outcome, that is determinants of TB treatment outcomes, were not captured. The information generated shows there is slow progress towards projected targets.

## RECOMMENDATIONS

Future study to focus on full panel of determinants of TB treatment outcomes such as existing co-morbidities, level of management of the co morbidities, type of TB, time taken to commencement of TB Treatment, TB regimen, and treatment model, . NTP to continue provision of primary diagnostic test in a bid to reduce TB deaths and increase successful TB treatment outcomes. That transcription of laboratory results or TB treatment out comes into the Facility TB registers be given a timeline, (like weekly disease surveillance statistics is given the timeline) that by the end of the next month of each quarter everything should have been compiled. This will eliminate cases where fields are left blank for long.

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