**Submitted version- J AIDS**

**Title:**

**Clinical Impact of the Xpert MTB/RIF Assay on the Management and Treatment Outcomes of South African Patients with Multi-Drug Resistant Tuberculosis – a Prospective Descriptive Study**

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**Keywords**: multi-drug resistant tuberculosis, Xpert MTB/RIF, clinical impact, treatment outcomes, morbidity

**Word count**: Text: 3,382 words Abstract: 258 words

**References**: 29

**Displays**: Figures 2 Tables 4

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**ABSTRACT**

**Background:** The Xpert MTB/RIF Assay has been widely implemented in South Africa for rapid tuberculosis screening. However its usefulness in management and improving treatment outcomes in patients with Multi-Drug Resistant Tuberculosis (MDR-TB) remains undefined. We evaluated the impact of the introduction of Xpert MTB/RIF Assay on clinical management of patients with MDR-TB.

**Methods:** We enrolled 921 patients with MDR-TB, who presented to a specialist drug-resistant TB facility in KwaZulu-Natal, South Africa, pre- and post- rollout and implementation of Xpert MTB/RIF assay. Clinical, laboratory, chest radiograph and follow-up data from 108 patients with MDR-TB, post-introduction of the Xpert MTB/RIF assay (‘Xpert MTB/RIF’ Group) in November 2010 were analysed and compared with data from 813 MDR-TB patients from the pre-MTB/RIF assay period (‘Conventional Group’), July 2008 to July 2010. Primary impact measures was ‘Treatment success’ (WHO definition) at 24 months. Secondary outcomes were time to treatment initiation, radiological changes. Predictors of treatment success were analysed.

**Findings:** There were no significant differences in treatment success rates between the pre-Xpert MTB/RIF and post-Xpert MTB/RIF groups (54% vs 56·5%, p=0·681). Median time to treatment initiation was 20 days (IQR, 13-31) in the Xpert MTB/RIF assay group versus 92 days (IQR, 69-120) in the Conventional group (p<0·001). Patients on anti-retroviral therapy had higher treatment success rates (risk ratio (RR): 1·32, 95%CI: 1·08-1·62, p=0·007).

**Interpretation:** Whilst use of Xpert MTB/RIF assay significantly reduces the time to commencement of MDR-TB treatment, it had no significant impact on treatment outcomes of patients with MDR-TB. Studies on the impact of Xpert MTB/RIF assay usage on transmission of MDR-TB are required.

**Funding:** South African Medical Research Council.

**Ethics approval:** The study was approved by the South African Medical Research Council (SAMRC) Ethics Committee (Ref EC028-10/2012).

**INTRODUCTION**

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide and the emergence and continuing spread of multi-drug resistant TB (MDR-TB) is of great public health concern. Less than 10% of the estimated half a million MDR-TB incident cases emerging worldwide in 2013 were detected and reported.[1](#_ENREF_1) The protracted nature of conventional diagnostic tools, such as culture and drug susceptibility testing (DST), impede case finding and delay appropriate treatment initiation, which in turn potentially fuels transmission, increases morbidity and mortality, and amplifies resistance.

The advent of a PCR-based Xpert MTB/RIF assay, in 2010 represented a new breakthrough in TB diagnostics, simultaneously detecting both *Mycobacterium tuberculosis* (MTB) complex DNA and rifampicin resistance in just 2 hours.[2](#_ENREF_2) Although rifampicin resistance is not a complete surrogate marker for MDR-TB, it is considered the most important indicator of MDR-TB[3](#_ENREF_3). In December 2010, the World Health Organization (WHO) endorsed the Xpert MTB/RIF assay for use in TB endemic settings, and by the end of June 2014, 3,269 GeneXpert instruments (Cepheid, Sunnyvale, CA, USA) had been procured in the public sector across 108 countries.

South Africa has the third highest burden of TB after India and China, and fifth highest burden of MDR-TB globally. Over 60% of patients in South Africa are co-infected with HIV. South Africa rapidly rolled out and led the implementation of Xpert MTB/RIF assay, accounting for 56% of all Xpert MTB/RIF assay cartridges procured worldwide.[3](#_ENREF_3) There have been numerous studies evaluating the accuracy and operational implementability of Xpert MTB/RIF assay from various geographical regions in patients with all clinical types of TB.[2](#_ENREF_2),[4-6](#_ENREF_4) Xpert MTB/RIF assay gives a result operationally within 24 hours of obtaining sputum. The diagnostic accuracy of Xpert MTB/RIF assay has therefore been well validated, with an assay sensitivity of 89% and specificity of 99%[7](#_ENREF_7) when used as an initial test replacing smear microscopy. Xpert MTB/RIF assay sensitivity is greater when used as an initial test replacing conventional DST, detecting 95% of rifampicin resistant TB cases with a specificity of 98%.[7](#_ENREF_7)

Whilst the diagnostic advantages of Xpert MTB/RIF assay over conventional microbiological methods are apparent, its clinical usefulness in improving treatment outcomes in patients with Multi-Drug Resistant Tuberculosis (MDR-TB) remains undefined. Current assumptions in clinical management of MDR-TB patients with a positive Xpert MTB/RIF assay result are that since they are diagnosed early they will be more rapidly initiated on MDR-TB treatment; present with less severe parenchymal lung disease and morbidity; and that these benefits would translate into improved treatment outcomes compared to patients with MDR-TB diagnosed with conventional microbiological methods. The primary aim of this study was to evaluate the clinical impact on management and treatment outcomes of the use of the Xpert MTB/RIF assay in patients with MDR-TB.

**METHODS**

**Study design, participants and procedures**

We conducted a study of 921 patients with MDR-TB, who presented to a specialist drug-resistant TB facility in KwaZulu-Natal, South Africa, pre- and post-implementation of Xpert MTB/RIF assay (**Figure 1**). Clinical, laboratory, chest radiograph and follow-up data from 108 patients with MDR-TB, post-introduction of the Xpert MTB/RIF assay (‘Xpert MTB/RIF’ Group) in November 2010 were analysed and compared with data from 813 MDR-TB patients from the pre-MTB/RIF assay period (‘Conventional Group’), July 2008 to July 2010. Data for both cohorts were obtained through patient clinical charts at a specialist drug-resistant TB hospital in the KwaZulu-Natal Province, South Africa between 2008 and 2011. Eligible participants were adult patients (≥18 years of age) with pulmonary MDR-TB (as defined by the WHO[3](#_ENREF_3)), confirmed by conventional DST, receiving standard of care at this facility. Patients with resistance to a fluoroquinolone or second-line injectable agent were not eligible for study inclusion.

Prior to Xpert MTB/RIF assay implementation in South Africa, resistance testing was only performed when indicated (poor clinical response to first-line treatment or those with a previous history of TB). Patients diagnosed with MDR-TB or rifampicin resistance were referred to this facility if their place of residence lay within the catchment area. Patients were admitted as inpatients or outpatients, after being placed on an admission waiting-list and were treated with a standardized MDR-TB treatment regimen comprising an intensive phase, which includes an injectable agent that is administered for at least six months, followed by a continuation phase of oral drugs administered for approximately 18 months.[8](#_ENREF_8)

**Clinical management impact outcome measures**:

*Primary outcome* measure was ‘Treatment success’ (WHO definition)9,10 at 24 months since initiation of treatment.

*Secondary outcomes* were time to commencement of MDR-TB treatment and tuberculosis-related morbidity at treatment commencement (chest radiographs were used as a surrogate marker of disease severity). Factors predicting treatment success were also analysed.

**Data Collection**

Data for both cohorts were extracted from clinical chart reviews. Information on demographic characteristics, HIV, treatment, laboratory results and final treatment outcomes were collected prospectively. Baseline chest radiographs were used as a marker of disease severity and morbidity at the commencement of TB treatment and captured retrospectively.

**Definitions**

Treatment outcome was assessed at the end of therapy. Definitions are as described in the *WHO Guidelines for the programmatic management of drug-resistant tuberculosis*.[9](#_ENREF_9),[10](#_ENREF_10) Briefly:

*Cured*: A patient with MDR-TB is considered cured if they have completed treatment according to the programme’s protocol and had at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. ‘If only one positive culture is reported during this time, with no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

*Treatment completed*: A patient with MDR-TB ‘who has completed treatment according to the programme’s protocol, but does not meet the definition for cure because of lack of fewer than five cultures were performed in the final 12 months of treatment).

*Treatment Success* is defined as cumulative of “Cure” and “Treatment completed”.

*Default:* Treatment interruption, without medical approval, for at least 2 consecutive months.

*Treatment failure*: Patients were considered to have failed treatment if two or more of the five cultures performed in the final 12 months of therapy were positive, if any of the final three cultures were positive or a clinical decision was made to terminate treatment early due to poor clinical response or adverse events.

*Death:* All-cause mortality during MDR-TB treatment.

*Transferred out*: Patients whose treatment outcome was unknown due to transfer to another recording and reporting facility.

*Time to treatment initiation:* The time from initial sputum collection to MDR-TB treatment initiation.

**Chest radiograph analysis and scoring**

Chest radiographs were performed on all patients at this specialist facility on the day of treatment initiation. A random sample of 147 (78 in the Conventional group and 69 in the Xpert MTB/RIF assay group) baseline chest radiographs were scored by two independent medical practitioners trained in the reading of chest radiographs. The medical practitioners were blinded to the diagnostic group and scoring of the second reader. Chest radiograph scoring was based on a combination of the “NICE”[11](#_ENREF_11) and “Brust”[12](#_ENREF_12) scoring systems. Each lung field was divided into three zones (upper, middle and lower) and a score of 0 to 4 for each zone was recorded, on a standardized case report form. Radiographic scores were assigned based on disease severity: 0=no disease, 1=1-24% of the lung zone diseased, 2=25-49% of lung zone diseased, 3=50-74% of lung zone diseased and 4=75-100% of lung zone diseased. Scoring was performed for each of the following disease components per zone: nodules, infiltrates, cavities, bronchiectasis and fibrosis. Additional scores were allocated to chest radiographs in which pleural effusion, hilar lymphadenopathy and/or pneumothorax was present. Scores for all six zones across both lung fields were added with a total possible score of 125.

**Statistical analysis**

Fisher’s exact test was used for the analysis of categorical data, and unpaired t-tests or the Wilcoxon two-sample test was used for the analysis of continuous data. To measure the inter-reader variability or test agreement, we used Krippendorff’s alpha (α) and Bland-Altman diagrams. We considered α ≥ 0·800 to be good agreement, while α ≥ 0·667 to be an acceptable agreement.[13](#_ENREF_13) In the Bland-Altman plots, the limits of agreement were placed at a distance of two times the standard deviation of the differences. Multivariate log-binomial regression was used to identify predictors of TB treatment success. All statistical tests were 2-sided. Statistical analyses were performed using SAS, version 9·3 (SAS Institute, Cary, North Carolina).

**Ethics approval**:

The study was approved by the South African Medical Research Council (SAMRC) Ethics Committee (Ref EC028-10/2012).

**RESULTS**

**Figure 1** depicts the flow of patient enrolment into the two study groups. Of total of 187 patients who were eligible for inclusion at baseline in the Xpert MTB/RIF assay group 79 patients were excluded from analyses: 17 had no confirmatory DST result available, 23 were found to be negative for MDR-TB, 6 were found to have drug-sensitive TB, 17 were either isoniazid or rifampicin mono-resistant, and 16 exhibited other resistance profiles (poly-resistant, pre-XDR-TB or XDR-TB).

**Baseline demographic characteristics**

Age, gender, HIV and ART status were not significantly different between the two study groups (**Table 1**). In both, a large proportion of patients were HIV co-infected, 70·8% in the Conventional group and 78·7% in the Xpert MTB/RIF assay group.

**Treatment outcomes**

**Table 2** shows outcomes of treatment in both study groups. There were no significant differences in treatment success rates between the pre-Xpert MTB/RIF assay conventional group and post-Xpert MTB/RIF assay group (54% vs 56·5%, p=0·681). Cure rates were significantly higher in the Xpert MTB/RIF group compared to the Conventional group (45·4% vs 34·4%, p=0·032) while this trend was reversed for treatment completion (11.1% vs 19·6%, p=0.035). Importantly, default rates were significantly higher in the Conventional group (23·8%) than in the Xpert MTB/RIF assay group (18·5%) (p=0·038). Mortality was higher in the Xpert MTB/RIF assay group (19·4%) compared to Conventional group (13·9%) although this was not found to be statistically significant (p=0·415).

**Time to treatment initiation**

The median time to treatment initiation was significantly reduced by 78% in the Xpert MTB/RIF assay group compared to the Conventional Group. Median time to treatment initiation was 20 days (IQR, 13-31) in the Xpert MTB/RIF assay group versus 92 days (IQR, 69-120) in the Conventional group (p<0·001).

**Chest radiographic as a marker of morbidity at enrolment**

Baseline chest radiograph score per reader and Krippendorff’s (α) estimates are given in **Table 3a**. In the Conventional group, the median x-ray score for reader 1 and reader 2 was 10 (IQR, 6 - 13) and 10 (IQR, 6 - 12) respectively. Good inter-reader agreement was observed in this group: (α=0·96, 95% CI: 0·94-0·98). In the Xpert MTB/RIF assay group, the median x-ray score for reader 1 and reader 2 was 13 (IQR, 10 - 15) and 12 (IQR, 8 - 15) respectively. Similarly, there was a good inter-reader agreement in the Xpert MTB/RIF assay group (α=0·81, 95% CI: 0.70-0·89). Significantly higher scores were reported in the Xpert MTB/RIF assay group compared to the Conventional group (reader 1, p<0·001, reader 2, p=0·006) and the Bland-Altman plot shows between reader agreement (**Figure 2**). Since baseline morbidity was only evaluated for a subset of randomly selected patients, to exclude selection bias, sub-analyses confirmed that treatment outcomes between the Conventional and Xpert MTB/RIF assay groups were similar (**Table 3b**).

**Predictors of treatment success**

**Table 4** shows Multivariate log binomial regression analysis of factors associated with MDR-TB treatment success. HIV status, ART status and age were the only predictors of treatment success. HIV positive patients initiated on ART were more likely to achieve treatment success (risk ration (RR): 1·32, 95% confidence interval (CI): 1·08 – 1·62, p=0·007) than HIV positive patients not on ART. Furthermore, HIV negative patients had a significantly higher probability of treatment success (RR: 1·32, 95% CI: 1·06 – 1·64, p=0·013) when compared to HIV positive patients not on ART. Older patients had 4% higher chance of treatment success than younger patients (RR: 1·04, 95% CI: 1·01 – 1·06, p=0·003).

**DISCUSSION**

WHO recommends Xpert MTB/RIF assay for use as the initial test for individuals at risk of MDR-TB, on basis of data that shows it has similar accuracy as that of conventional culture and drug-susceptibility testing (DST) for rifampicin (RIF). The advantage of the Xpert MTB/RIF is that the assay provides results operationally within 24 hours rather than the weeks that use of liquid media, and months that solid media takes to provide a result [4, 5]. Large scale demonstration studies under research conditions have shown that Xpert MTB/RIF assay introduction is feasible in high-TB burden countries [6-12]. Rapid rollout and implementation of the MTB/RIF assay in South Africa provided a new rapid diagnostic test and increased referrals of patients suspected of having MDR-TB. Given the protracted nature of both MDR-TB treatment regimens and conventional DST, a greater opportunity for impact of the Xpert MTB/RIF assay was aniticipated. It is thus generally believed amongst physicians that early diagnosis of MDR-TB would be associated with less morbidity at presentation, and early initiation of treatment would lead to improved treatment outcomes. To our knowledge there have been no studies which have evaluated the impact of the Xpert MTB/RIF assay on clinical management and treatment outcomes.

This study is the first to evaluate the clinical impact of the use of the Xpert MTB/RIF assay on the management and treatment outcomes of South African patients with MDR-TB. Our data show several interesting findings. *First*, and most important, there were no significant differences in treatment success rates (per WHO definition of cumulative of “Cure” and “Treatment completed”) between MDR-TB patients in the pre-Xpert MTB/RIF period who were diagnosed using conventional microbiological methods and those who were diagnosed in the period where the Xpert MTB/RIF assay was used. *Second*, the median time to treatment initiation for MDR-TB was significantly reduced by 78% in the Xpert MTB/RIF group compared to the Conventional group. *Third*, use of Xpert MTB/RIF assay was not associated with reduction of baseline morbidity at presentation contrary to what is the current view amongst clinicians. *Fourth*, Patients on anti-retroviral therapy had higher treatment success rates.

We had postulated that early and rapid diagnosis would result in reduced baseline morbidity, positively affecting treatment outcomes. There are several plausible reasons for the unexpected findings of our study. *First*, morbidity was found to be greater in the Xpert MTB/RIF assay group; the increased disease at baseline negates any potential cumulative effect of reduced time to treatment initiation. The higher morbidity observed in the Xpert MTB/RIF arm may be related to the absence of any TB treatment between diagnosis and MDR-TB treatment initiation. In both groups the baseline chest radiograph is always performed at the time of MDR-TB treatment initiation. In the Xpert MTB/RIF assay group this is likely to be closer to the acute TB episode and the patient is less likely to have received any TB treatment while awaiting MDR-TB treatment. In contrast, a Conventional group patient usually continues first-line TB treatment for several months whilst awaiting MDR-TB treatment initiation. It is possible that even though the patient may be resistant to isoniazid and rifampicin, they could still be sensitive to the other first line drugs such as pyrazinamide and ethambutol, hence lowering the “baseline” radiograph score in this group. *Second*, severely ill may have died awaiting conventional DST results and MDR-TB treatment initiation. These patients therefore did not enter the Conventional group of our study, possibly introducing a selection bias and accounting for the lower morbidity and mortality reflected in this group. This is supported by programmatic data showing that approximately 50% of patients diagnosed with MDR-TB, in South Africa, in 2009 were not initiated on appropriate treatment.[16](#_ENREF_16) Gandhi *et al*. has additionally shown that mortality from MDR-TB and XDR-TB was high and often occurred within 30 days of sputum collection in a high HIV prevalence setting in KwaZulu-Natal.[17](#_ENREF_17) *Third*, although Xpert MTB/RIF assay is a revolutionary diagnostic tool, it does not alter the behaviors of patients who often delay seeking treatment, nor does it address poor medication adherence to protracted and toxic MDR-TB treatment regimens.[18](#_ENREF_18)

Interestingly, the proportion of patients that defaulted in the Xpert MTB/RIF assay group was significantly lower than those in the Conventional group. While, Theron et al found that Xpert MTB/RIF assay reduced dropout (culture-positive patients not started on TB treatment) in drug sensitive TB,[15](#_ENREF_15) it is unclear why patients were better retained in the Xpert group of our study. The fragile public health system has however been shown to be an impediment to those who try to seek medical care.[19](#_ENREF_19) It is possible that since patients in the Conventional group had to engage with health care system for lengthier periods of time, they may have become increasingly disillusioned with it, further exacerbating the challenge of treatment interruption. Successful MDR-TB treatment outcomes have previously been found to correlate with health systems performance.[20](#_ENREF_20)

Although successful treatment outcomes did not differ between the Conventional and Xpert MTB/RIF assay groups, “treatment completion” was significantly higher in the Conventional group compared to the Xpert MTB/RIF assay group with a trend reversal for patients considered cured. Since the difference between the definitions for “treatment completed” and “cure” is a lack of bacteriological evidence in the former,[9](#_ENREF_9),[10](#_ENREF_10) it may be that patients in the Xpert MTB/RIF assay group were more likely to produce sputum, due to increased baseline morbidity. In fact, stratification of the median morbidity at baseline, by treatment outcome, supports this argument and shows that in patients successfully treated, those in the Xpert MTB/RIF assay group exhibited significantly higher baseline morbidity than patients in the Conventional group. Patients were also 32% more likely to achieve MDR-TB treatment success if they were on ART or HIV negative compared to HIV positive patients not on ART. This is consistent with the findings of other studies documenting the role of HIV status and ART initiation in MDR-TB patients.[17](#_ENREF_17),[21](#_ENREF_21) Increasing age was found to be a predictor of treatment success. This finding likely reflects the more adherent nature of older patients.

The significant reduction in time to treatment initiation in our study is consistent with several others, within the context of both drug-resistant TB[22-24](#_ENREF_22) drug-sensitive TB,[2](#_ENREF_2),[15](#_ENREF_15),[25-27](#_ENREF_25) and has important public health implications as it significantly reduces disease transmission. Given that the rapid diagnostic nature of Xpert MTB/RIF assay is two hours, the delay, about three weeks in our study, is still considerable. This alludes to the myriad of underlying programmatic challenges in the implementation of Xpert MTB/RIF assay. We have previously noted the importance of scientific advances and health system strengthening as complementary processes.[28](#_ENREF_28) Indeed, a recent retrospective study in the Western Cape Province, showed that a combination of decentralized MDR-TB management and Xpert MTB/RIF assay implementation, reduced treatment delay, in patients with rifampicin resistant TB, to a median of just eight days. One of the potential factors contributing to the delay in treatment initiation in our study was the placement of Xpert MTB/RIF assay at a centralized laboratory rather than at the point-of-care. Numerous studies have demonstrated that point-of-care Xpert MTB/RIF assay testing significantly reduces the time to treatment initiation and often results in same day treatment initiation.[15](#_ENREF_15),[26](#_ENREF_26),[29](#_ENREF_29) While these studies were conducted within the realm of drug sensitive TB, further decentralization and use Xpert MTB/RIF assay near the point-of-care could potentially improve existing system delays for the treatment of MDR TB.[23](#_ENREF_23)

Our study has several limitations. Although the data were collected prospectively for both cohorts of patients, pre- and post- implementation of Xpert MTB/RIF assay, the study relied on routine, programmatic data collected by health workers and the data recording which may have had errors –however the errors would have been across both periods of study. The possible selection bias resulting in exclusion of terminally ill patients could have substantially reduced the impact of Xpert MTB/RIF assay. Our study was performed shortly after the implementation of Xpert MTB/RIF, in a specialized drug-resistant TB facility, during a period where there was limited decentralization and access to drug-resistant TB treatment, and substantial reliability on centralized care. There may have been subsequent improvements due to the expansion of decentralization, and healthcare workers becoming more familiar with the implementation algorithms of Xpert MTB/RIF. We also note the disproportionate sample size between the two groups, however this had no statistical impact. Finally, our study was conducted in a region with a high HIV burden and may therefore not be generalizable to other settings.

**CONCLUSIONS**

Whilst the Xpert MTB/RIF assay has revolutionized rapid TB diagnostics our study failed to show that Xpert MTB/RIF does not positively impacts on clinical treatment outcomes. Recent studies evaluating Xpert MTB/RIF assay under programmatic conditions have laso shown no effect on its use on morbidity or mortality in patients with drug-sensitive TB,[14](#_ENREF_14),[15](#_ENREF_15) Since rapid diagnosis and treatment initiation is critical to reducing period of infectiousness and for interrupting transmission, the Xpert MTB/RIF assay may also have a role in reducing the burden of disease and the public health impact of Xpert MTB/RIF assay requires evaluation The full potential of Xpert MTB/RIF assay and its role in under resourced fragile public health systems requires further definition if we are to maximize their impact.

**AUTHOR CONTRIBUTIONS**

Designed the Study: NP, ML and KN were involved in the conception and design. ML collected the data. NYZ performed the analysis. NP, SA and MOD designed the chest radiograph scoring system and scored the chest radiographs. All authors contributed to interpretation of data and writing of the manuscript.

**ACKNOWLEDGMENTS**

We acknowledge support from the South African Medical Research Council.N Padayatchi, N Naidu, N Yende-Zuma, K Naidoo are supported by the Centre for the AIDS Programme of Research in South Africa (CAPRISA). Research reported in this publication was supported by the South African Medical Research Council. The authors would like to acknowledge Garth Osburn, Prem Moodley and Kumeren Govender for their contributions.

**DECLARATION OF INTERESTS**

All authors declare no conflicts of interest.

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| **Research in context****Background:** The continuing spread of multi-drug resistant TB (MDR-TB) is of great public health concern. Less than 10% of the estimated half a million MDR-TB incident cases emerging worldwide in 2013 were detected and reported.[1](#_ENREF_1) Conventional microbiological diagnostic tools, delay early detection and delay appropriate treatment initiation, which in turn potentially fuels transmission, and increases morbidity and mortality.The advent of a PCR-based Xpert MTB/RIF assay, in 2010 represented a new breakthrough in TB diagnostics, simultaneously detecting both *Mycobacterium tuberculosis* (MTB) complex DNA and rifampicin resistance in just 2 hours.[2](#_ENREF_2) In December 2010, the World Health Organization (WHO) endorsed Xpert MTB/RIF for use in TB endemic settings, leading to rapid rollout globally. Since the roll-out, numerous studies from all continents have confirmed the accuracy and operational implementability of Xpert MTB/RIF [2](#_ENREF_2),[4-6](#_ENREF_4) when used as an initial test replacing smear microscopy and the MTB/RIF sensitivity is being used as an initial test replacing conventional DST, detecting 95% of rifampicin resistant TB cases with a specificity of 98%.[7](#_ENREF_7) **Unanswered questions regarding use and rollout of MTB/RIF Assay:** Current assumptions in clinical management of MDR-TB patients with a positive Xpert MTB/RIF assay result are that since they are diagnosed early they will be more rapidly initiated on MDR-TB treatment; present with less severe parenchymal lung disease and morbidity; and that these benefits would translate into improved treatment outcomes compared to patients with MDR-TB diagnosed with conventional microbiological methods. While the diagnostic advantages of Xpert MTB/RIF Assay over conventional microbiological methods are apparent, its clinical usefulness in improving treatment outcomes in patients with MDR-TB remains undefined. We thus conducted the study was to evaluate the clinical impact of the use of the Xpert MTB/RIF Assay in patients with MDR-TB.**Added value of this study:** This study is the first to evaluate the clinical impact of Xpert MTB/RIF assay implementation in patients with MDR-TB and shows despite the greater opportunity for impact (compared to drug-sensitive TB), Xpert MTB/RIF assay had no positive clinical impact. Although Xpert MTB/RIF assay considerably reduced the time to MDR-TB treatment initiation, the delay is still significant. Improved time to treatment initiation did not translate into clinical benefits; Xpert MTB/RIF assay implementation did not improve successful treatment outcomes nor did it reduce baseline tuberculosis-related morbidity. **Implications of all the available evidence:** In our study the Xpert MTB/RIF assay significantly reduced the time to commencement of MDR-TB treatment, but had no significant impact on treatment outcomes of patients with MDR-TB. The Xpert MTB/RIF assay has important public health advantages through its use to rapidly diagnose and find more cases of TB and by reducing the time to treatment initiation. Studies on the impact of Xpert MTB/RIF assay usage on community-driven MDR-TB transmission, However, it is unlikely that its full potential will be realized in a fragile health system with inadequate capacity to provide optimal patient care. Health systems strengthening and scientific advances need to be considered complementary processes. **Search strategy:** At the time of study conceptualization, no data was available in the context of the impact of MTB/RIF assay on drug-resistant tuberculosis. A PubMed literature search for studies published from 01 January 2010 to 30 June 2015 using the terms (multi-drug resistant tuberculosis OR drug-resistant tuberculosis) AND (Xpert OR Genexpert OR MTB/RIF) AND (clinical impact OR treatment outcomes) did not identify similar studies. In drug sensitive TB, the XTEND and TB-NEAT studied revealed that Xpert MTB/RIF assay implementation did not improve morbidity or mortality at six months, in drug-sensitive TB.  |

**LEGENDS TO FIGURES AND TABLES**

**FIGURES**

Figure 1. Flow diagram of participant enrolment in the two study groups

Figure 2: Comparison between the scores of two chest radiograph readers with a Bland-Altman diagram for Xpert (A) and Conventional (B) groups

**TABLES**

Table 1: Baseline demographic characteristics of patients

Table 2: Treatment outcomes of patients in the two study groups

Table 3a: Total baseline chest radiograph score per reader and Krippendorff’s (α) estimates

Table 3b: Median (IQR) chest radiograph scores for each reader stratified by treatment

 outcome

Table 4: Multivariate log binomial regression analysis of factors associated with MDR-TB

 treatment success

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**Figure 1.**

**Flow diagram of participant enrolment in the two cohorts**



DST: drug susceptibility test

R: rifampicin

H: isoniazid

 **Table 1.**

 **Baseline demographic characteristics of patients**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Conventional**  **Group (N=813)** | **Xpert MTB/RIF Group (N=108)** | **p-value** |
| Mean age (SD), years | 35·2±10·6 | 34·8±10·2 | 0·665 |
| Female, % (n) | 50·8 (413) | 58·3 (63) | 0·152 |
| HIV status, % (n) |  |  | 0·222 |
| Positive  | 70·8 (576) | 78·7 (85) |  |
| Negative | 26·1 (212) | 18·5 (20) |  |
| Unknown | 3·1 (25) | 2·8 (3) |  |
| ART status, % (n)\*\* |  |  | 0·284 |
| On ART | 75·2 (433) | 77·6 (66) |  |
| Not on ART | 21·7 (125) | 22·4 (19) |  |
| Unknown | 3·1 (18) | 0 |  |

\*\*only for known HIV positive patients

ART=anti-retroviral therapy

 **Table 2.**

 **Treatment outcomes of patients in the two study groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment outcome, %, (n)** | **Conventional Group (n=813)** | **Xpert MTB/RIF Group (n=108)** | **p-value** |
| **Treatment success** | 54·0 (439) | 56·5 (61) | 0·681 |
| **Treatment completed** | 19·6 (159) | 11·1 (12) | 0·035 |
| **Cure** | 34·4 (280) | 45·4 (49) | 0·032 |
| **Default** | 28·3 (230) | 18·5 (20) | 0·038 |
| **Treatment failure** | 3·6 (29) | 4·6 (5) | 0·584 |
| **Death** | 13·9 (113) | 19·4 (21)  | 0·415 |
| **Transferred out** | 0·2 (2) | 0·9 (1) | 0·312 |

**Table 3a.**

**Total baseline chest radiograph score per reader and Krippendorff’s (α) estimates**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Conventional group (n=78)** | **Xpert group****(n=69)** | **p-value** |  |
| Reader 1: Median total score (IQ) | 10 (6 - 13) | 13 (10 - 15) | <0·001 |  |
| Reader 2: Median total score (IQ) | 10 (6 - 12) | 12 (8 - 15) | 0·006 |  |
| Krippendorff’s (α) | 0·96 | 0·81 |  |  |
| 95% CI | 0·94 – 0.98 | 0·70 – 0·89 |  |

**Table 3b.**

**Median (IQR) chest radiograph scores for each reader stratified by treatment outcome**

|  |  |  |
| --- | --- | --- |
|  | **Reader 1** | **Reader 2** |
| **Treatment Outcome** | **Conventional group** | **Xpert MTB/RIF****group** | **p-value** | **Conventionall group** | **Xpert MTB/RIF group** | **p-value** |
| **Treatment success** | 10 (6-13) (n=62) | 13 (10-16) (n=52) | 0·0001 | 10 (6-12(n=62) | 12 (8-16) (n=52) | 0·020 |
| **Treatment completed**  | 7 (6-13)(n=20) | 12 (9-17) (n=12) | 0·019 | 7 (6-11)(n=20) | 11 (5-16) (n=12) | 0·339 |
| **Cure** | 10 (7-13)(n=42) | 13 (10-16) (n=40) | 0·003 | 10 (6-12) (n=42) | 13 (9-17) (n=40) | 0·054 |
| **Defaulted** | 9 (5-13)(n=14) | 12 (8-15)(n=13) | 0·113 | 10 (5-12) (n=14) | 11 (8-15) (n=13) | 0·197 |
| **Treatment failure** | 11 (5-17)(n=2) | 18(n=1) | - | 11 (5-17)(n=2) | 14(n=1) | - |
| **Death** | - | 11 (10-14)(n=3) | - | - | 11 (10-14)(n=3) | - |

**Figure 2.**

**Comparison between the scores of two chest radiograph readers with a Bland-Altman diagram for Xpert MTB/RIF assay (A) and Conventional (B) groups**



**Table 4.**

**Multivariate log binomial regression analysis of factors associated with MDR-TB treatment success**

|  |  |  |
| --- | --- | --- |
|  | **Univariate** | **Multivariate** |
|  | **RR** | **(95% CI)** | **p-value** | **RR** | **(95% CI)** | **p-value** |
| Conventional group | 1·0  |  |  | 1.0  |  |  |
| Xpert MTB/RIF group | 1·05 | 0·88 – 1·25 | 0.619 | 1.08 | 0.91 - 1.29 | 0.367 |
| HIV positive not on ART | 1·0  |  |  | 1.0  |  |  |
| HIV positive on ART | 1·33 | 1·08 – 1·62 | 0.006 | 1.32 | 1.08 - 1.62 | 0.007 |
| HIV negative | 1·30 | 1·04 – 1·62 | 0.019 | 1.32 | 1.06 - 1.64 | 0.013 |
| Male | 1·0  |  |  | 1.0  |  |  |
| Female  | 1·10 | 0·97 – 1·24 | 0.127 | 1.10 | 0.98 - 1.24 | 0.107 |
| Age (per 5 year increase) | 1·04 | 1·01 – 1·06 | 0.004 | 1.04 | 1.01 - 1.06 | 0.003 |