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Effects of GeneXpert MTB/RIF Testing and GxAlert eHealth Platforms on MDR-TB Diagnosis
and Linkage to Care in Sofala Province, Mozambique

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Abstract

Effects of GeneXpert MTB/RIF Testing and GxAlert eHealth Platforms on MDR-TB Diagnosis and Linkage to Care in Sofala Province, Mozambique.

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Introduction: Mozambique ranks as one of the 22 highest tuberculosis (TB) burden countries in the world but has one of the lowest TB case detection rates of only 39%. To improve Multi-Drug Resistant TB (MDR-TB) case detection rates and linkage to care, we installed three GeneXpert MTB/RIF machines in Sofala Province starting in 2012 and installed an eHealth platform called GxAlert in 2014.

Methods: We conducted a retrospective clinical review using routine clinical data from GeneXpert MTB/RIF assays (Xpert), and the TB treatment and laboratory registries from 16 health facilities from March 2012-September 2015. Using multi-level logistic regression analyses, we conducted pre-post and time-series analyses of GxAlert to see if an innovative SMS notification system to key Ministry of Health (MoH) personnel of rifampin resistant (RR) patients would improve linkage to care.

Results: A total of 22,543 Xpert tests were recorded and 17,024 (75.5%) did not detect TB, 2,841 (12.6%) detected TB without rifampin resistance (RR), 2,256 (10%) were invalid, had no result, or had errors, 249 (8.3%) patients were diagnosed with RR-TB, and 173 (0.76%) detected TB and were RR indeterminate. 139 (55.8%) RR-TB study subjects were started on MDR-TB treatment. Across the 46-month period there was an increase in 0.66 (95% Confidence Interval [CI]: 0.32, 0.99; $p < 0.001$) MDR patients diagnosed every 6 months, and 0.21 (CI: 0.07, 0.35; $p = .003$) patients started on MDR-TB treatment. Using a simple pre-post analysis and a complex interrupted time-series analysis, there was no statistically significant change in the proportion of MDR-TB patients linked to care pre- versus post- GxAlert implementation (95% CI Confidence

Interval [CI]: 0.75, 2.0; p-value 0.41), (Odds Ratio [OR]: 0.83; CI: 0.30, 2.3); p=0.72), respectfully.

Conclusion: The introduction of three Xpert machines in Sofala Province led to an increase in the total number of RR-TB patients being diagnosed and started on treatment over a 4 year period from 2012-2015. Although the GxAlert platform did not show significant differences in linkage to care, it led to other positive benefits including rapidly assessing Xpert data using any computer with internet access, monitoring the performance of Xpert machines and cartridge capacity in real time, creation of summary reports, and formulating lists of patients with a positive test for MTB.

Introduction

In 2014, an estimated 9.6 million people developed active tuberculosis (TB) and 1.5 million died from this disease, making TB the leading infectious killer worldwide.¹ A growing number of cases of Multi-drug Resistant TB (MDR-TB) are occurring, with an estimated 480,000 new cases each year globally.¹ In particular, Mozambique ranks as one of the 22 highest TB burden countries in the world. In 2014, the World Health Organization (WHO) estimated an incidence of approximately 551/100,000 people – or 140,000 new cases of TB each year in Mozambique – and it is projected that 3.5% of these TB cases and 11% of re-treatment cases are MDR-TB.² Unfortunately, Mozambique's case detection rate, which is a crucial step in linking patients into care, for all forms of TB is only 39%, which is one of the lowest rates in the world.² To improve case detection rates for drug sensitive and rifampin resistant TB (RR-TB), Health Alliance International (HAI), a non-governmental organization affiliated with the University of Washington, in partnership with TB REACH and the Mozambican Ministry of Health National TB program (MoH-NTP), installed three GeneXpert machines in Sofala province in March 2012.^{3,4} Clinical studies have demonstrated that Xpert MTB/RF testing (Xpert), which is a rapid, automated, molecular test for Mycobacterium Tuberculosis and for rifampin resistance, is a strong marker for MDR-TB. Xpert is more sensitive and specific than a routine sputum smear and this platform has been endorsed by the WHO to be used in resource-limited settings.³⁻⁶ Preliminary studies from initial pilot testing of Xpert at MoH health facilities in Sofala and Manica provinces showed low linkages to care rates with 67% of drug sensitive TB patients and 47% with RR-TB started on appropriate treatment.⁷

Recognizing the numerous factors along the TB and MDR-TB care cascade that lead to low treatment initiation, several eHealth technologies have been implemented to improve linkage

to care, and improved monitoring and evaluation activities. Many studies in resource limited settings have shown improved linkage to care, medication adherence, and treatment initiation using eHealth technology.⁸⁻¹⁴ The MoH-NTP and HAI implemented an eHealth remote monitoring platform in 2014 using cloud-based technology to disseminate real-time Xpert test results called GxAlert in Sofala and Manica provinces. This platform has previously been described in detail.¹⁵ Briefly, GxAlert is a secure cloud-based platform that extracts data from Xpert machines in real time. It monitors Xpert machine performance and the number of Xpert cartridges at each Xpert facility, sends SMS messages to key TB personnel when a positive rifampin resistant or drug-sensitive TB test occurs, and creates instantaneous spreadsheets to monitor performance parameters.

The aims of the present study are: (1) to provide up-to-date descriptive data on MDR-TB diagnosis patterns including age, gender and culture results; (2) to analyze the effects of Xpert implementation on MDR-TB treatment initiation in Sofala Province from 2012-2015; and (3) to evaluate the impact of GxAlert on treatment initiation.

Methods

Study Design and Setting

A retrospective clinical review was utilized to collect data in this study. This study was conducted with the support of the United Office for Project Services TB REACH grant and was coordinated through the MoH-NTP, and the non-governmental organization, HAI. HAI has worked in Mozambique for over 25 years and has partnered with the MoH-NTP and the Central Laboratory Department to support the scale-up of Xpert testing, GxAlert, and LED microscopy. This study was implemented at three MoH facilities that had Xpert capability with the assistance

of HAI in Sofala Province (Beira Central Hospital; Ponta-Gea Health Center; Nhamatanda Rural Hospital) and at thirteen surrounding health centers, which referred sputum samples from presumptive TB and MDR-TB cases for testing at these three Xpert sites.

Selection of Study Subjects and Sample Size

Study subjects were selected from the GxAlert secure online database which is a composite test result database for all three Xpert sites. After GxAlert was installed, each site uploaded test results every time the Xpert computer was connected to the internet. Study subjects included all age groups who were identified as having RR-TB by Xpert between March 2012 and September 2015. The Xpert database identified 249 RR-TB study subjects which were used in this study.

Data Collection

Further laboratory and clinical data on the 249 study subjects were collected between October 2015 through February 2016 at the 16 health facilities which referred patients for Xpert testing across Sofala Province. Seven different registries were used in data collection: 1) GxAlert registry; 2) laboratory TB microscopy (BK) registry; 3) laboratory Xpert registry; 4) MoH-NTP drug-sensitive patient treatment registry; 5) MoH-NTP MDR-TB patient treatment registry; 6) the MoH-NTP MDR-TB electronic database of all patients started on treatment for Sofala Province; and 7) National Reference Laboratory registries for TB culture and drug sensitivity testing. Data were collected by three trained data collectors and were entered into password-protected Microsoft Excel sheets. Data collectors searched for study subjects in the laboratory TB microscopy registry using the date of the Xpert test to look at the preceding 4 weeks of registry entries (per Mozambique MoH protocol, all Xpert tests are supposed to first have a

smear microscopy prior to having a Xpert test ordered). If a subject's name was not found within this 4 week time frame, the study subject was considered to have not had a microscopy result recorded in the registry. Next, data collectors reviewed the MDR-TB and drug-sensitive TB patient registries at the corresponding 16 health facilities. Data collectors searched for a study subject from 2 weeks prior to the Xpert test date (in the event a clinician used clinical judgment to start a study subject on MDR-TB treatment prior to receiving an Xpert test) to 4 weeks after the Xpert test. This allowed study subjects a 4 week grace period to be linked into care after a positive Xpert test result. If a study subject was not found within this time frame, data collectors met with the MDR-TB clinical staff in the corresponding health facility to discuss the case. When study subjects were not known to the MDR-TB clinical team, data collectors coded the study subject as not initiated on MDR-TB treatment. However, if a patient study subject was known to the MDR-TB clinical staff but was transferred to an outside health facility, data collectors confirmed with the laboratory and MDR-TB registries that the study participant was enrolled into care. If a study subject was not found during these attempts, they were deemed to have not been initiated on MDR-TB treatment.

Data Analysis

Stata 14 (College Station, TX, USA) was used for all analyses, with a two-sided alpha value <0.05 considered statistically significant. We first conducted descriptive analysis of overall trends for rifampin resistant study subjects, including gender, age, diagnoses over time, and culture results. Next, a mixed-effects logistic regression model was built to control for clustering within the three Xpert sites, and modeled changes over time in the absolute number of patients diagnosed and initiating MDR treatment. Our pre/post-test for the effect of GxAlert was

conducted in two ways. First, a simple pre/post controlling for clustering compared the mean proportion initiating treatment pre-intervention to post-intervention. We also conducted a more complex interrupted time-series analysis which estimated the trend pre-intervention, the immediate shift in the proportion initiating treatment, and the post-intervention trend. Last, we compared our local database to that at the provincial level to determine what percentage of overall MDR-TB patients notified each year were a result of an Xpert test at one of the three Xpert sites from this project.

Ethics Statement

This study was approved by the University of Washington Institutional Review Board, the NIH reviewers for the University of Washington Center for AIDS Research, and the Comité Nacional de Bioética para a Saúde in Mozambique.

Results

Study Subject Characteristics

Of the 249 study subjects analyzed in the study, 94 (37.8%) were women, 114 (45.8%) were male, and the sex of 41 (16.5%) could not be verified due to missing data. In terms of age, 8 (4.3%) study subjects were under 20 years old, 127 (68.4%) study subjects were between the age of 20-40 years and 50 (19.3%) study subjects were over 40 years old. 64 (25.7%) study subjects did not have their ages recorded. All the study subjects resided in Sofala Province (**see Table 1**).

Number of MDR-TB Patients Diagnosed by Xpert and Initiated on MDR-TB Treatment

During this study period from March 2012 to September 2015 a total of 22,543 Xpert tests were run across the three sites. During this time, all sputum-smear negative samples were eligible for testing, as were all re-treatment cases, cases that were smear positive at 2 months, or patients that were suspected of having MDR-TB. Of these, 17,024 (75.5%) did not detect TB, 2,841 (12.6%) detected TB without RR, 173 (0.76%) detected TB and were RR indeterminate, and 2,256 (10%) were invalid, had no result, or had errors. A total of 249 patients were diagnosed with RR-TB, leading to an overall RR-TB rate of 8.3% of patients diagnosed with TB **(See Figure 1)**.

As demonstrated in Table 2 and Figure 2, a significant increase was seen in the absolute number of Provincial MDR-TB cases detected and started on treatment in Sofala from 2011 to 2015. Across the 46-month period there was an increase in 0.66 (95% Confidence Interval [CI]: 0.32, 0.99; $p < 0.001$) MDR patients diagnosed every 6 months, and 0.21 (CI: 0.07, 0.35; $p = .003$) patients started on MDR treatment. That is, the number of patients diagnosed increased faster than the number of patients started on MDR treatment. Additionally, according to the MoH MDR-TB electronic database (which is a composite of MDR-TB cases from Xpert results, culture and direct sensitivity testing results), the number of patients started on MDR-TB treatment increased from 16 in 2011 to 92 in 2015 **(see Figure 2)**. The absolute number of patients diagnosed with RR-TB directly from the three Xpert sites also increased from 33 patients in 2012 to 73 patients 2015 (despite missing 4th quarter data in 2015) **(see Table 2 and Figure 3)**. The proportion of patients who were started on MDR-TB therapy in Sofala province attributed to the implementation of Xpert testing also increased from 2012-2015 **(see Figure 3)**. In 2012, the proportion of the MDR-TB patients diagnosed by Xpert at one of these three sites

who were started on appropriate MDR-TB treatment was 61%. This increased to 90% and 95% in 2013 and 2014, respectfully, demonstrating the significant contribution of Xpert testing to increases in Provincial MDR-TB treatment initiation. In 2015, the percentage dropped to 42% as fourth quarter Xpert testing and treatment data were not obtained in this study.

Despite these increases in the absolute number of patients being diagnosed and initiated on MDR-TB therapy, only 139 (55.8%) of the total 249 RR-TB cases were linked into care and started on appropriate second line treatment (note: patients who were diagnosed with rifampin-resistance by Xpert, were considered by the NTP to have MDR-TB and per NTP protocol, were started on MDR-TB treatment until culture results became available). Although this overall linkage to care appears to be low, the linkage to care proportion actually increased from 42% (14/33) to 68% (58/85) from 2012 to 2014. The data from 2015 was incomplete as 4th quarter data was not able to be collected at the time of the study. In addition, we were not able to conclusively demonstrate what happened to the remaining 110 patients who we could not verify were started on appropriated therapy – some may have died, transferred care to another site that we were not able to visit, or were simply lost to follow up. No statistical significance was observed between gender and/or age and linkage to care (see **Table 1**).

Effects of GxAlert Implementation on Proportion Initiating Treatment

GxAlert was installed on three Xpert machines in Sofala province beginning in August 2014. Prior to GxAlert, 126 RR-TB Xpert tests were recorded (March 2012-July 2014) and 67 (53.2%) patients were started on appropriate treatment for MDR-TB. From August 2014-September 2015, after GxAlert was implemented, 123 patients were identified as having rifampin-resistant TB and 72 (58.5%) were initiated on appropriate treatment for MDR-TB (see

Table 3). In a simple pre-post analysis, there was no statistically significant change in the proportion of MDR-TB patients linked to care pre- versus post- GxAlert implementation (95% CI Confidence Interval [CI]: 0.75, 2.0; p-value 0.41); (see **Table 3**). In a more complex interrupted time-series analysis, there was also no immediate effect of the intervention on the odds of patient linkage to care (Odds Ratio [OR]: 0.83; CI: 0.30, 2.3); p=0.72) and no difference between trends over time pre- versus post-intervention implementation (p=0.33).

Culture Results

Of the 139 individuals who were initiated on MDR-TB treatment, 46 (33%) sputum samples were sent for culture while 21 (15.1%) sputum samples were recorded in the laboratory or NTP MDR-TB databases. Of these, 8 (38%) sputum samples did not have growth on culture. The 13 culture samples where resistance patterns were identified, all 13 (100%) had both isoniazid resistant and rifampin resistant suggesting that Xpert diagnosed RR is a good marker for MDR-TB in this population. Three of the 13 (23.1%) samples had Streptomycin resistance and 1 (7.7%) sample had ethambutol resistance (see **Table 4**). Second line drug sensitivity testing was not done on any of our patients, and only became available in Mozambique at the national reference laboratory in Maputo in mid-2015.

Discussion

The findings of this study demonstrate that the implementation of Xpert testing in Sofala province significantly increased the total number of rifampin resistant patients being diagnosed and started on second line treatment. The proportion of patients started on MDR-TB therapy attributed to the implementation of Xpert testing also increased from 2012-2014 from 60.8% to

95%, respectfully. This study also revealed the RR-TB rate to be 8.3% among patients with a positive test for MTB by Xpert. While the new algorithm for Xpert testing has changed (all pediatric, pregnant, diabetic, HIV positive, cancer, and other immunodeficient patients should be tested by Xpert as a first line test) the majority of patients tested by Xpert during this time-period were sputum smear negative, and of these 12.6% tested positive by Xpert for drug-sensitive TB. According to the MoH NTP databases, HIV, TB, and MDR-TB incidence rates are much higher in Southern Mozambique (Maputo Province, Gaza Province, Maputo City). While Sofala is located in central Mozambique, the overall MDR-TB treatment initiation rates are much higher than surrounding provinces (Inhambane, Zambezia, Tete) suggesting that there was a significant amount of previously undiagnosed MDR-TB.

While linkage to care rates improved from 2012 to 2014, this study highlights the continual gap in the linkage to care for RR-TB as only 55.8% of patients with RR-TB diagnosed by Xpert were started on appropriate MDR-TB treatment during this study time-period. The Ministry of Health in Mozambique has been observing low linkage to care rates for MDR-TB for a number of years. In hopes of improving treatment initiation rates, GxAlert was piloted in Sofala province in 2014 and was evaluated in the present study. Although GxAlert did not demonstrate a significant increase in linkage to care rates for RR-TB patients, the GxAlert platform did provide many positive benefits including rapidly assessing Xpert data using any computer with internet access, monitoring the performance of Xpert machines and cartridge capacity in real time, creation of summary reports, and formulating lists of patients with a positive test for MTB, along with their resistance results to rifampin. Further details of the benefits and limitations of GxAlert and the treatment care cascade for TB, TB/HIV and MDR-

TB patients in these provinces will be described in a subsequent research paper based on results with qualitative interviews of health care staff at these Xpert facilities and patient focus groups.

There were a number of limitations in our study that may have contributed to the non-significant increases to linkage to care. First, our sample size of 249 RR-TB patients represent an average of <2 patients with confirmed MDR-TB per month, per facility. A sample size of this magnitude makes distinguishing time trends from intervention effects difficult. In addition, as knowledge about Xpert testing spread to nearby communities, sites in this study reported processing more samples referred from distant health. This shift made tracking patients with a positive RR-TB Xpert result more challenging; while we were only able to visit 16 health centers, we expect that some patients were treated at other health facilities outside the catchment areas covered. Furthermore, at times we experienced difficulties with internet access which delayed the reporting of Xpert results. Problems with the modem, connectivity issues due to inconsistencies of cellular service, and availability of funds required for the modem, negatively affected the GxAlert platform. Lastly, our linkage to care analyses could have been improved by TB community health activists who could engage in community visits to search for patients; which are not currently available at most TB treatment centers in Mozambique. We hypothesize that SMS messages and the overall GxAlert platform could be more effective with community health workers and socioeconomic interventions.¹⁸ Despite these challenges and continued poor linkage to care rates, we note positive trends in both increased diagnoses and linkage to care rates over the entire study period (2012-2015).

Our analysis also found gaps in the evidence-based processes around culture and DST. Only 33% (46/139) of sputum samples were sent for culture or direct sensitivity testing. Of these, 46% (21/46) were recorded in the laboratory or NTP MDR-TB databases. In addition,

38% (8/21) of samples recorded in the registries had no growth. This may have been due to delays in sample transport and processing, patients being started on treatment prior to sputum collection, or false positive RR Xpert results.^{16,17} We encountered many challenges when attempting to collect culture and DST data. The reference laboratory in Sofala province, Beira Central Hospital, has not been able to consistently run direct sensitivity testing for nearly two years due to electrical instability, stock outs, high contamination rates, and equipment failure. Therefore, cultures were often sent to the capital city, Maputo, which is nearly 1500 km from Beira Central Hospital. Other challenges, which have been described in other e-health programs, include limited transportation for sputum cultures, limited cold chain for sputum samples (leading to high contamination rates), and absence of a reliable platform of reporting culture data from Maputo (or from any reference laboratory) to the health facilities.^{13,19}

While our findings suggest that GxAlert did not significantly increase linkage to care and treatment initiation rates, the Mozambican Ministry of Health National TB Program has specifically highlighted the added benefit of access to real-time information about patient level Xpert results, remotely monitoring Xpert machine performance, and cartridge consumption to inform real-time decision-making. The Ministry of Health is working to scale-up GxAlert to all operating Xpert machines in Mozambique, and asking for monthly and quarterly reports from each province generated by GxAlert documenting how many of patients with a RR test in this time period started treatment for MDR-TB and had cultures sent for first and second line DST.

Conclusion

Since the implementation of Xpert in Sofala province, there has been an increase in both the absolute number of patients diagnosed with rifampin resistance and started on MDR-TB

treatment. However, the number of patients being diagnosed is increasing faster than those started on MDR-TB treatment, highlighting the need to ensure all patients with RR are linked to care and started on MDR-TB treatment if we are to realize the full benefit of Xpert testing. Although the results of GxAlert did not significantly increase linkage to care and treatment initiation rates, it did highlight the many benefits this platform offers including real-time information about cartridge consumption, Xpert machine performance, patient level Xpert results. This study also highlights the challenges obtaining reliable and consistent MTB cultures and DST results – this is critical to not only confirm Isoniazid and Rifampin resistance, but to also test for second line drug sensitivities so that we can take advantage of the fact that Bedaquiline and Delamanid were recently approved for use in Mozambique, especially for patients with adverse events to aminoglycosides, or those with extensively drug-resistant (XDR) TB.

Table 1. Demographics of Study Participants and Treatment Initiation

Factor	Total N (%)	n (%) started on treatment	n (%) not started on treatment	Odds Ratio (95% CI)	P-value
TOTAL	249 (100)	139 (55.82)	110 (44.2)		
Gender					
Female	94 (37.8)	60 (63.8)	34 (36.2)	1.07 (0.61, 1.9)	0.82
Male	114 (45.8)	71 (62.3)	43 (37.7)	1 (reference)	
Missing	41 (16.5)	8 (19.5)	33 (80.5)	excluded	
Age					
<20	8 (4.3)	5 (62.5)	3 (37.5)	0.77 (0.17, 3.6)	0.74
20-29	70 (37.8)	45 (64.3)	25 (35.7)	0.83 (0.40, 1.7)	0.62
30-39	57 (30.8)	39 (68.4)	18 (31.6)	1 (reference)	
40-49	24 (13.0)	14 (58.3)	10 (41.7)	0.64 (0.24, 1.7)	0.39
50+	26 (14.1)	17 (65.4)	9 (34.6)	0.87 (0.33, 2.3)	0.78
Missing	64 (25.7)	19 (29.7)	45 (70.3)	0.22 (0.82, 0.58)	0.002

Table 2. The Number of Patients diagnosed by Xpert with Rifampin Resistance and Started on MDR-TB Treatment from Q1 2012 through Q4 2015.

Quarter	Number Rif Resistance Patients Detected	N (%) put on Treatment
Q1 2012*	1	0 (0.0)
Q2 2012	6	3 (50.0)
Q3 2012	11	5 (45.5)
Q4 2012	15	6 (40.0)
Q1 2013	11	6 (54.5)
Q2 2013	7	4 (57.1)
Q3 2013	15	8 (53.3)
Q4 2013	25	10 (40.0)
Q1 2014	18	13 (72.2)
Q2 2014	13	8 (61.5)
Q3 2014	21	12 (57.1)
Q4 2014	33	25 (75.8)
Q1 2015	31	17 (54.8)
Q2 2015	21	11 (52.4)
Q3 2015	20	11 (55.0)
Q4 2015*	1	0 (0.0)
TOTAL	249	139 (55.8)

* With the exception of 1 patient this study did not enroll patients in Q1 2012, or in Q4, 2015.

Table 3. Simple pre/post GxAlert for MDR-TB Patients Using a Multi-level Logistic Regression Model to Control for Clustering across the Three Sites.

Factor	Total N (%)	n (%) started on treatment	n (%) not started on treatment	Odds Ratio (95% CI)	P-value
TOTAL	249 (100)	139 (55.82)	110 (44.2)		
<u>GxAlert</u>					
Pre GxAlert (March 2012 – July 2014)	126	67 (53.2)	59 (46.8)	1 (reference)	
Post GxAlert (August 2014 – October 2015)	123	72 (58.5)	51 (41.5)	1.24 (0.75, 2.0)	0.41

Table 4. Relationship between Culture Results and Number Rif Resistance Patients Detected, along with Correlation between Xpert Testing and Culture Results

TB Culture	N (%)
Ordered (% of 249)	46 (18.47)
Not received (% of 46)	21 (45.7)
Received (% of 46)	13 (28.3)
Streptomycin Resistance (% of 13)	3 (23.1)
INH Resistance (% of 13)	13 (100.0)
Rifampin Resistance (% of 13)	13 (100.0)
Ethambutol Resistance (% of 13)	1 (7.7)
Received Negative (% of 46)	8 (17.4)
Streptomycin Resistance (% of 8)	0 (0.0)
INH Resistance (% of 8)	0 (0.0)
Rifampin Resistance (% of 8)	0 (0.0)
Ethambutol Resistance (% of 8)	0 (0.0)
Missing (% of 46)	4 (8.7)
Not ordered (% of 249)	104 (41.8)
Missing (% of 249)	99 (39.8)

Figure 1: Number of Xpert Tests from 2012-2015

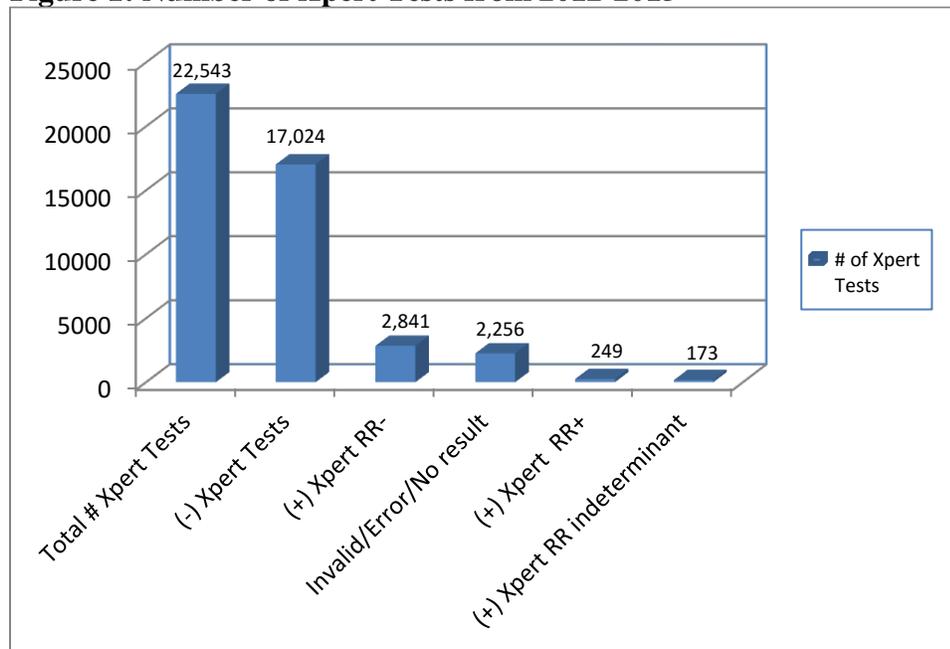


Figure 2. Number of MDR-TB Patients Started on Treatment over Time.

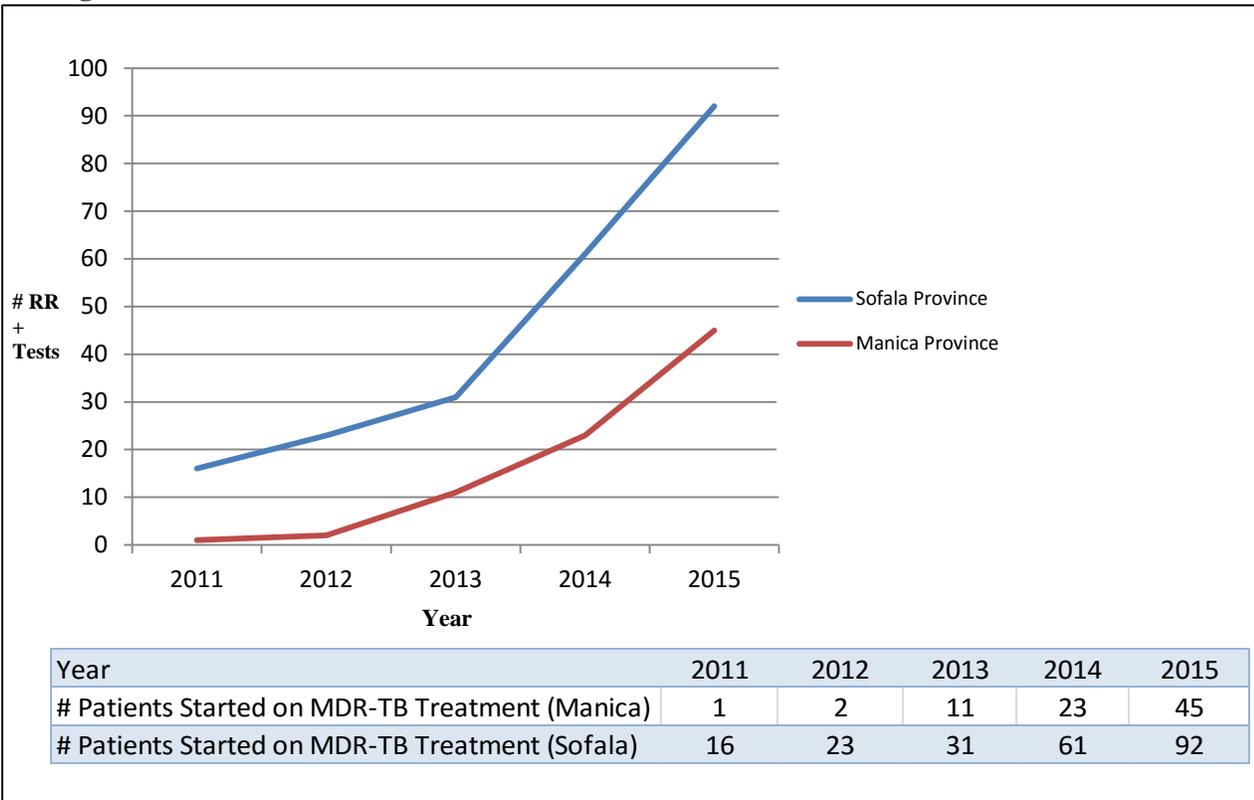
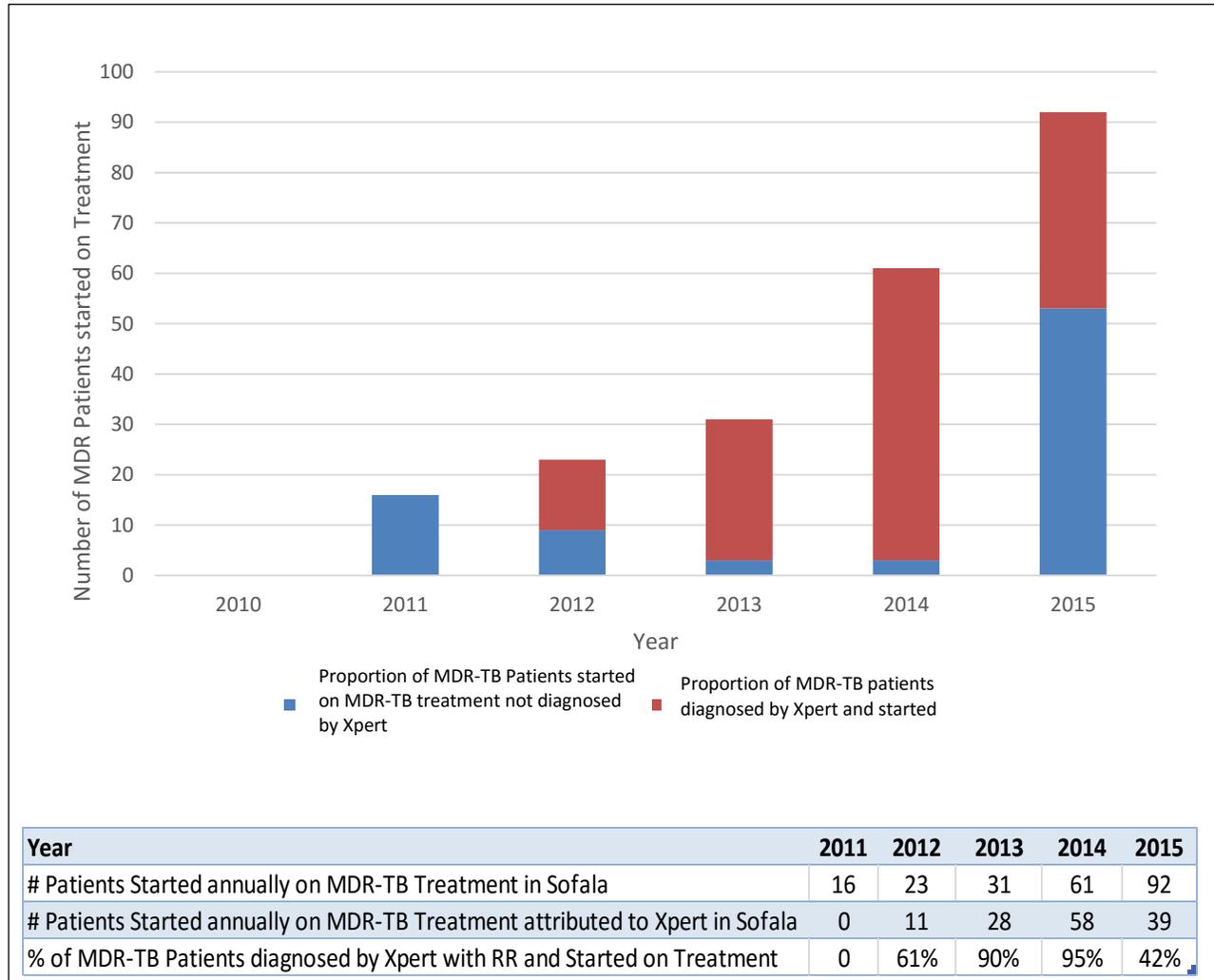


Figure 3. Annual number of MDR-TB Patients started on appropriate MDR-TB Treatment over Time and Proportion Attributable to Xpert Project -Sofala Province



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