FACTORS ASSOCIATED WITH THE UTILIZATION OF GENEXPERT IN THE DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS IN THE GREATER ACCRA REGION.

BY

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DECLARATION

I, Oghenekome Eboreime declare that this dissertation is the result of my own independent work aside specific references which have been duly acknowledged. I also declare that this dissertation has not been submitted wholly or partially for the award of any degree in any institution.

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ABSTRACT

Background

There has been a gap in the diagnosis of drug resistant tuberculosis, hence a new rapid diagnostic test; the geneXpert was introduced by the World Health Organization in 2010. The objective of this study was to identify factors that affect the utilization of the geneXpert intervention in the Greater Accra Region.

Methods

This was a mixed methods study. A qualitative approach was used to provide empirical explanations for the findings of the quantitative component which was cross-sectional.

Functional facilities administering geneXpert were enrolled into the study. Quantitative data on risk factors for drug-resistant tuberculosis and geneXpert testing were obtained from the tuberculosis registers on 386 cases of tuberculosis using a pre-tested data extraction tool. Ten health care workers were interviewed using a semi-structured in-depth interview guide. Quantitative and qualitative results were triangulated in line with study objectives.

Results

A total of 386 cases of tuberculosis were included in the study. Less than half of the total cases reviewed 89(23%) had a geneXpert test. The proportion of cases at risk of drug resistant tuberculosis who were tested with geneXpert was relatively low among the various risk categories. Risk factors for drug resistant tuberculosis had no influence on having a geneXpert test and cases of extra-pulmonary tuberculosis were less likely to have a geneXpert test compared to cases of pulmonary tuberculosis [AOR = 0.17 (95%CI = 0.06-0.51), p< 0.002].
In-depth interviews identified lack of skilled technicians to collect extra-pulmonary specimens, sputum collection in children, loss to follow up for testing, an inefficient test result communication system and cartridge supply management system, lack of refrigerators for temporary storage of specimen and equipment maintenance as factors affecting the utilization of geneXpert.

**Conclusion**

This study found the non-prioritization of patients at risk of drug resistant tuberculosis for geneXpert testing resulting from lack of adherence to standard guidelines a key factor affecting the utilization of geneXpert. Based on findings, making geneXpert guidelines available at health facilities as well as training of health workers on the guidelines is recommended to improve the uptake of geneXpert.
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CHAPTER ONE

1.0 INTRODUCTION:

1.1 Background

Globally tuberculosis is a leading cause of death now estimated to be about the same as deaths caused by HIV. In 2014 about 1.2 million deaths were caused by HIV, these included 0.4 million caused by tuberculosis in patients who were co-infected with HIV (WHO, 2015a). According to the World Health Organization (2015), the global burden of tuberculosis was estimated to be 9.6 million cases in the year 2014. Of these 5.4 million men, 3.2 million women and 1.0 million children were affected. Of the 9.6 million, there were only 6 million new cases reported (63% of the total estimate), indicating a significant rate of under-diagnosis (WHO, 2015). 5% of the global estimate of tuberculosis cases were found to be multi-drug resistant. 480 000 developed the disease in 2014 with 123 000 cases notified (WHO, 2015). 9.7% cases of multi-drug resistant tuberculosis also have extensively drug resistant tuberculosis and reported cases come from 105 countries (WHO, 2015b). Tuberculosis caused 1.5 million deaths of which over 95% were in low and middle income countries. 480 000 women; out of which 140 000 were HIV positive, 890 000 men and 140 000 children were affected. It is currently the fifth leading cause of death among women aged 15 to 44 years. Deaths caused by multi-drug resistant tuberculosis were estimated to be 190 000 in the 2014 (WHO, 2015b).

There has been an emerging resistance to the conventional medications used in the treatment of tuberculosis globally. This has been attributed partly to inappropriate administration of the anti-tuberculosis regimen, failure of patients to adhere strictly to therapy or even the use of substandard medications (Lange et al., 2014). Two major patterns of resistance exist; the Multi-Drug Resistant Tuberculosis (MDR-TB), which is resistance to at least two of the standard first-line medications.
(Isoniazid and Rifampicin) and the Extensively Drug Resistant Tuberculosis (XDR-TB) which is resistance to both the first line medications listed above as well as the second line medications (one of the fluoroquinolones and at least one of the injectables which include amikacin, kanamycin and capreomycin) (Skrahina et al., 2012).

The World Health Organization plans to end tuberculosis by the year 2035, hence it has in 2015 introduced the End TB strategy. This strategy targets that by the year 2035, there should be zero deaths, disease and suffering from tuberculosis. A reduction in deaths due to tuberculosis by 90% in 2030 and 95% in 2035 and a reduction in incidence rate by 80% in 2030 and 90% in 2035 (WHO, 2015c). One of the strategies put in place to achieving this goal is early diagnosis of tuberculosis, screening of contacts and all persons at risk of tuberculosis and drug resistant tuberculosis (WHO, 2015c). Also, part of the key component of the plan is the optimum roll out, implementation and use of new diagnostic tools with an increase in the number of patients diagnosed with new rapid diagnostic test greater than or equal to 90% as one of the set priority indicators to be achieved by all countries by the year 2025 (WHO, 2015c).

As part of the global plans to facilitate the diagnosis of drug resistant tuberculosis, the World Health Organization introduced the geneXpert in 2010. GeneXpert is a rapid diagnostic test that uses real time polymerase chain reaction. It is able to detect the DNA of the tuberculosis bacilli (mycobacterium tuberculosis) and at the same time detect resistance to rifampicin; one of the first line medications used in the treatment of tuberculosis. Resistance to rifampicin serves as a pointer to possible infection with drug resistant tuberculosis. The test procedure is simple to perform in that it is an automated process which operated by insertion of a disposable cartridge containing the sample unto the platform (Gotuzzo, 2011). Results are delivered by the machine within about two hours.
The World Health Organization has currently recommended that, all patients being managed for tuberculosis should also receive a geneXpert test to rule out the presence of drug resistant tuberculosis. So that in areas with resource constraints, patients with tuberculosis considered at risk of drug resistant tuberculosis based on certain risk factors must be identified and prioritized for geneXpert testing (WHO, 2014). These patients include all patients being managed for tuberculosis who are co-infected with HIV, still positive to sputum AAFB smear test at two or three months on treatment and cases of relapse. In addition patients in whom the diagnosis of tuberculosis and drug resistant tuberculosis may be challenging such as those who are negative to the sputum AAFB on initial presentation and cases of extra-pulmonary tuberculosis may also potentially have drug-resistant tuberculosis and are to receive a geneXpert test as recommended by the World Health Organization (Tadesse et al., 2015).

GeneXpert implementation may also be affected by some technical challenges, given that optimum functionality requires a laboratory with minimum standards such as a steady power supply, optimum temperature requirements, supply of disposable test cartridges and other considerations (Weyer et al., 2013).

The objective of this study is to determine to what extent the World Health Organization policy on geneXpert testing is being implemented as well as explore potential technical and process related factors that may affect the utilization of geneXpert in the Greater Accra region of Ghana.

1.2 Problem Statement:
There is a gap in the case detection and diagnosis of Drug Resistant Tuberculosis. The World Health Organization estimates that about 3.6 million cases of tuberculosis are missed each year by the health system and hence may not be appropriately managed. Only one in four cases of multi-drug resistant tuberculosis are detected (WHO, 2015c). Estimated case detection rate for all forms
of tuberculosis in 2014 was 33% in Ghana (World Bank, 2014). The World Health Organization introduced the geneXpert in order to improve case detection of drug resistant tuberculosis, however certain factors affect the implementation of this intervention in developing countries. They include but are not limited to process related factors such as identification and testing of patients at risk of Drug Resistant Tuberculosis, contact tracing and patient follow up as well as technical factors such as cartridge supply, temporary storage of specimen, equipment maintenance and power supply. It is important to note that the factors affecting the implementation of the intervention are context specific in terms of countries and regions, and there is paucity of data as to how this operates in Ghana.

1.3 Justification
This study would provide the data that could help improve the implementation of geneXpert in the diagnosis of drug resistant tuberculosis by detecting key areas that need improvement. This would lead to an overall health system strengthening in this area. Key lessons would also be learnt that may help improve rollout in other regions and facilities as well as inform policy. This would overall increase case detection of drug resistant tuberculosis which would impact on treatment, overall patient outcome and even the spread of the disease.

1.4 Study Objectives

1.4.1 General Objective:
To determine the factors affecting the utilization of geneXpert in the diagnosis of drug resistant tuberculosis in the Greater Accra region.
1.4.2 Specific Objectives:

1. To determine the proportion of patients at risk of drug resistant tuberculosis who are tested with geneXpert.
2. To determine if patients at risk of drug resistant tuberculosis and those who have been recommended for geneXpert testing according to WHO guidelines are more likely to get tested with geneXpert.
3. To identify technical factors affecting the utilization of geneXpert.
4. To identify process related factors affecting the utilization of geneXpert.

1.5 Conceptual Framework

The World Health Organization has recommended that all suspected cases of tuberculosis should receive a geneXpert test where resources permit. In resource constrained settings patients considered to be at risk of drug resistant tuberculosis be prioritized for testing (WHO, 2014). Appropriate utilization of geneXpert requires that these patients be specifically targeted for testing. Patients also need to be followed up after referral for geneXpert testing, both to ensure that they get tested and that they get reviewed with their results, contacts also need to be traced so that those at risk will be identified and tested. Facilities administering geneXpert should also receive referrals for geneXpert from other facilities not administering the test hence the need for an effective system to get patients from other facilities tested; a system for getting the samples to the laboratory and also communication of results. Several factors could affect these processes hence affecting the utilization of geneXpert. Technical factors such as power supply, equipment maintenance, cartridge supply and others which this study aims to identify may also affect utilization.
Figure 1: Conceptual Framework for Factors Affecting the Utilization of GeneXpert.
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Tuberculosis disease burden

Africa accounts for about 28% of the global tuberculosis burden, with a prevalence (281 per 100 000), being over twice that of the global average of 133 000 (WHO, 2015a). Multi-drug resistant tuberculosis accounted for between 32 000 to 49 000 of the prevalence (WHO, 2016a). Low and Middle Income Countries suffer a significant burden of tuberculosis including the resistant variants. In Ghana, the number of all forms of tuberculosis including drug resistant tuberculosis was about 14 999 in 2015 (GHS, 2015).

Families and communities have continued to suffer financial loss and hardship as a result of tuberculosis, this is despite the fact that most of the tuberculosis services are subsidized (Morishita et al., 2016). Tuberculosis is a disease affecting the world’s poorest population, hence resulting in catastrophic financial losses resulting from increased spending on medications, diagnostics and other services which exceeds household income (Madan et. al., 2015). On the average, greater than 50% of annual income loss can be attributed to tuberculosis, those affected by MDR-TB suffer the higher consequence (WHO, 2013). This estimate may vary by country and region, depending on health system factors such as the tuberculosis care scheme in operation and the availability and type of insurance cover. Individuals affected by tuberculosis also suffer stigmatization from family members and friends, as the disease is perceived to be a disease of the poor and dirty (Juniarti & Evans, 2011). This may have adverse consequences such as delay or failure to seek treatment, poor compliance with medications, development of resistance and also spread of the disease.
2.2 Efficacy of geneXpert

GeneXpert has been proven to be a very effective tool for diagnosis and case detection. A study conducted by Opota et al. (2016) compared the efficacy of the tool to the traditional smear microscopy examination using culture as the reference standard. The study found the sensitivity, specificity, positive and negative predictive value of geneXpert to be 91.5%, 99.4%, 98.5 % and 96.6 % respectively while that of smear microscopy was relatively lower being 64.7%, 94.2%, 82.1% and 86.6% respectively. GeneXpert also had an added advantage of being able to detect patients who were smear negative. Opota et al. (2016) also stated in their study, that 20 patients who were smear negative were detected by geneXpert. These categories of patients who are smear negative are usually not considered to be infective and hence not isolated, however of the 20 smear negative patients diagnosed by geneXpert, most were symptomatic, with 11% having pulmonary cavitation which is associated with a high risk of transmission. One patient was also found to have multi-drug resistant tuberculosis. Nakiyingi, Nankabirwa, & Lamorde (2013) also conducted a case review on a patient who was also smear negative and would have been a missed diagnosis as he had been managed in several health facilities for bacterial pneumonia until he was finally diagnosed using the geneXpert test under a research project. The efficacy of geneXpert in diagnosing tuberculosis and drug resistant tuberculosis has been demonstrated by several studies. A study in Dakar found the sensitivity and specificity of geneXpert in diagnosing extra-pulmonary tuberculosis to be higher than that of microscopy, being 94.74% and 97.95% respectively, compared to that of microscopy which was 43.86% and 98.36% respectively (Diallo et al., 2016). The efficacy of geneXpert in the diagnosis of tuberculosis affecting the lymph nodes including the diagnosis of drug resistance in this case has also been demonstrated by several studies hence has been recommended as first line diagnostic tool in such cases by the World Health Organization (Tadesse et al., 2015; Ghariani et al., 2015). Despite the promising potential this tool holds in
increasing the case detection rate, there is much still left unraveled concerning its being well adopted by health facilities in developing countries.

### 2.3 Risk factors for Drug-resistant Tuberculosis

One key factor in determining the utilization of geneXpert is the identification of patients at risk of drug resistant tuberculosis for geneXpert testing, among health care providers. This would be the case if there is strict adherence to standard diagnostic guidelines. Certain studies have been performed in various regions to identify groups who are at risk. Ignatyeva et al. (2015) carried out a study in the Baltic countries in Europe; Latvia, Lithuania and Estonia. These countries are considered as having the highest burden of drug resistant tuberculosis within Europe. The study found that younger age, male, history of contact with a patient with drug resistant tuberculosis were predisposing factors to primary drug resistant tuberculosis. Previous treatment for tuberculosis, and alcohol abuse were strongly associated with drug resistant tuberculosis while defaulters to therapy and treatment failure triggered the development of extensively drug resistant tuberculosis. In Estonia, the percentage of individuals found to be primary cases of multi-drug resistant tuberculosis was relatively high (about 85.2%) as these individuals had no history of prior treatment for tuberculosis and were presenting for the first time. This again highlights the need for the identification of risk groups so that they can be picked up even when they present for the first time to facilitate the appropriate line of treatment. In Latvia, the percentage was about 57.9% and 35.0% in Lithuania. The risk of drug resistant tuberculosis overall was found to be strongest in those who had been previously treated. Other risk factors identified were weight loss, presence of an underlying disease and patients who had a prolonged hospital admission. Long hospital stay facilitated nosocomial transmission of resistant variants and also increased the risk of superimposed infection. Malaysia is considered as having an intermediate burden of tuberculosis and a low burden of drug resistant tuberculosis however in a study conducted by Mohd Shariff,
Shah, & Kamaludin (2016), the risk factors identified for multi-drug resistant tuberculosis were similar; non-compliance with medications and previous treatment. Additional risk factors identified were smear positivity at the second and sixth month of treatment and region of residence. Individuals living in the suburban region were found to have a higher risk. As stated earlier the prevalence of tuberculosis is over twice the global average in Africa, with drug resistant tuberculosis accounting for a significant proportion of cases. A study on the risk factors for drug resistant tuberculosis in the Oromia region of Ethiopia by Mulisa et al. (2015) identified history of contact with a case of tuberculosis, alcohol use, HIV infection, diabetes, previous treatment for tuberculosis as well as occupational risk such as farming to be associated with drug resistant tuberculosis. They suggest that the association may be context specific. Treatment with second line anti-tuberculosis medications ideally should be reserved for patients with confirmed multi-drug resistant tuberculosis, however the study reported cases who were empirically treated with second line drugs to see for outcome, and identified such to be at a higher risk of drug resistant tuberculosis. As high as 40% of the cases of multi-drug resistant tuberculosis were women of child bearing age. This is significant because their children would also be at risk of the disease. While these factors could serve as a guide to identifying patients at risk of drug resistant tuberculosis, the authors advised caution with generalizability of the results as confounding factors such as the quality of anti-tuberculosis medications, poor drug compliance and drug malabsorption could not be controlled for. Also, only suspects of multi-drug resistant tuberculosis who could produce sputum were included in the study. The study area Oromia is mostly rural hence urban risk factors were not identified (Mulisa et al., 2015). There have been limited studies on the risk factors for drug resistant tuberculosis in Ghana, however a study conducted in South West Nigeria identified history of previous treatment for tuberculosis as the only risk factor significantly associated with multi-drug resistant tuberculosis. (Daniel & Osman, 2011).
2.4 Categories with challenges in the diagnosis of tuberculosis and resistance tuberculosis.

The diagnosis of tuberculosis can be quite challenging in some categories of individuals. These may be due to difficulty in producing sputum which is the specimen needed to run the test, as seen in children, sparse quantity of bacilli in the sputum produce or absence of bacilli in the sputum. In these scenarios diagnosis is difficult to make using the routine microscopy hence the need for other diagnostic methods to avoid the possibility of missed diagnosis. As highlighted earlier by Mulisa et al.(2015) children could be at risk of acquiring multi-drug resistant tuberculosis from their mothers hence there is the possibility of a child coming down with primary multi-drug resistant tuberculosis. The diagnosis of tuberculosis is quite challenging in children as they tend to present with less severe disease and non-specific symptoms that could mimic other respiratory diseases. Their chest radiographs also tend to appear misleading (Van Rie, 2013). The presence of HIV co-infection also complicates diagnosis, as the clinical and radiographic manifestations of other diseases caused by HIV immunosuppression tend to mimic the features of tuberculosis. (Zar et al., 2013). These children often times on hospital admission are often discharged without a definitive diagnosis while probably awaiting the results of a blood culture which may take several weeks. This wait further delays the institution of therapy. Sometimes in the absence of a microbiological diagnosis; when smear microscopy is unable to detect the bacilli to aid diagnosis, the clinicians go ahead to start patients on anti-tuberculosis drug treatment empirically. This has many draw backs such as difficulty in adherence to the regimen due to the pill count and unpleasant side-effects of the medications. It is also often difficult to administer medications to children especially younger children. This may predispose them further to resistance, as stated earlier, which is partly caused by lack of adherence to medications. In children, since collection of sputum spontaneously may pose a challenge, an induced sputum may be collected or even nasopharyngeal aspirate. GeneXpert is more sensitive in detecting tuberculosis in induced sputum than the routine
microscopy. It has the added advantage of being able to detect the bacilli in nasopharyngeal aspirates although with a lower sensitivity compared to induced sputum. (Zar et al., 2013). Zar and his colleagues in 2013 conducted a study to determine the diagnostic accuracy of geneXpert in children in a primary health care facility in South Africa. They took repeated samples of induced sputum and nasopharyngeal aspirates from children aged fifteen and below, who were suspects of tuberculosis, presenting at the primary care facility. These samples were tested using geneXpert and smear microscopy, and their sensitivities and specificities were determined using culture which is the gold standard as the reference standard. Of the 384 children tested, 5(1%) were positive by smear microscopy, 26 (7%) positive by geneXpert, 30 (8%) positive by culture. The sensitivity of geneXpert was found to be about five times more than that of smear microscopy. GeneXpert using induced sputum detected 16 out of 28 cases confirmed by culture, with a sensitivity of 57.1% (95% CI 39.1 – 73.5) and specificity of 98.9% (95% CI 96.9 – 99.6). For nasopharyngeal aspirate Xpert detected 11 of 28 culture confirmed cases, sensitivity of 39.3(95% CI 23.6 – 57.6) and specificity of 99.3%(95% CI 97.4 – 99.8). Although emphasis here is on the diagnosis of tuberculosis with geneXpert, one must bear in mind that geneXpert is able to diagnose resistance to rifampicin at the same time which indicates the presence of drug resistance which is the focus of this research. Considering the consequences of drug resistant tuberculosis, one missed case is extremely important as the disease not only poses a huge challenge in treatment, but the individual patient is at risk of transmitting the disease to others hence not only is it important to make a diagnosis, prompt identification of resistance is crucially important, which geneXpert is capable of doing. The authors stated that in a previous study, nurses rated induced sputum as being easy or very easy to collect. In the absence of induced sputum however, a nasopharyngeal aspirate serves as a feasible option. Zar and his colleagues also attempted to compare their findings with that documented by other studies that were done in children on hospital admission in South Africa,
Zambia, Uganda and Tanzania where the sensitivity of geneXpert in tuberculosis diagnosis in children was between 72 – 90% and also with a study done in Zambia that recorded a sensitivity of 90%. They stated that the children used in the latter study were however older and were able to produce sputum however the study recorded a sensitivity of 65% for gastric lavage for younger children which was similar to their findings for the induced sputum. A study by Verghese, Thomas, Michael, Rose, & Jeyaseelan (2016) on 286 children below the age of sixteen found geneXpert to be 78.9%, being able to detect 41 out of 52 culture confirmed cases. The World Health Organization has recommended the replacement of smear microscopy by geneXpert in cases of HIV co-infection, suspected multidrug resistant tuberculosis or in follow-up of patients in a low prevalence setting of multi-drug resistant tuberculosis, which includes children who meet these criteria (Zar et al., 2013). Where the referral is suboptimal, strategies would need to be put in place to improve the situation ultimately preventing or at least reducing the frequency of a missed diagnosis. This will contribute to bridging the existing gap in the case diagnosis of drug resistant tuberculosis. This would facilitate early treatment, while avoiding empirical treatment there by decreasing the probability of resistance.

Another category of patients of concern is those with extra-pulmonary tuberculosis such as tuberculosis of the bone, joint and lymph nodes. Gu et al. (2015) conducted a study to determine the sensitivity of geneXpert in detecting extra-pulmonary tuberculosis as compared to smear. The sensitivity of geneXpert was found to be 82% compared to that of smear microscopy which was only 26%. Specificities of the two were 100%. The diagnosis of bone and joint tuberculosis is quite challenging due to the limited number of bacilli found in the samples taken from those sites. The invasive procedures used to collect specimen and expertise requirement coupled with the long turn-around time of the regular assay used in the conventional diagnosis also constitute a challenge. Since the diagnostic capacity of geneXpert was comparable to that of the composite reference
standard for the diagnosis of extra-pulmonary tuberculosis, with the added advantage of detecting resistance to rifampicin, World Health Organization in 2013 recommended the use of geneXpert for the diagnosis of extra-pulmonary tuberculosis (Gu et al., 2015). In another study by Ghariani et al. (2015) the sensitivity and specificity of geneXpert in detecting tuberculosis of the lymph nodes were 91.5% and 70.4% respectively. The authors in their review stated that geneXpert may significantly improve the diagnosis of tuberculosis of the lymph nodes if properly implemented. Just to reiterate that in the application of geneXpert for the diagnosis of tuberculosis, drug resistant tuberculosis would also be detected if present since geneXpert is able to diagnose rifampicin resistance simultaneously.

In the earlier reviews, contact with a case of tuberculosis especially drug resistant tuberculosis was associated with an increased risk of tuberculosis with a probability of drug resistance. An active contact tracing with screening of household contacts will be beneficial in tuberculosis control. These household contacts would benefit from geneXpert screening. A study on 353 household contacts screened by Habte et al. (2016) found 41 presumptive cases of tuberculosis. Of the 41, 39 were screened with geneXpert, 14 were found to have tuberculosis with one being rifampicin resistant. Only five were detected by smear microscopy. GeneXpert is able to potentially increase the detection rate among contacts, however evidence on the extent to which these contacts are being traced, followed up and screened using geneXpert in this setting is limited.

### 2.5 World Health Organization criteria for geneXpert testing

Having discussed the categories of patients at risk of drug resistant tuberculosis and those likely to benefit from geneXpert test, it would be necessary to highlight the categories of patients recommended by the World Health Organization to receive geneXpert. The World Health
Organization has broadly categorized them into four groups; group A includes all adults and children considered to be at risk of drug resistant tuberculosis. In this group, geneXpert should be used as an initial diagnostic test rather than microscopy, culture or drug susceptibility testing (WHO, 2012). Countries in which the prevalence of rifampicin is high could decide to use geneXpert for all patients who are smear positive so that rifampicin resistance can be timely detected. Group B includes all adults and children living with HIV presenting with symptoms of tuberculosis such as poor weight gain in children, persistent cough, fever, night sweats and weight loss in both. Adults and children who are seriously ill and suspected to have tuberculosis irrespective of HIV status. Those in whom HIV status is unknown but present with clinical symptoms strongly suggestive of HIV in a high prevalence setting or individuals considered to be at risk of HIV. Here geneXpert should be used as an initial diagnostic test rather than the other available test previously mentioned (WHO, 2014). The policy also recommends that geneXpert be used as a follow-on to microscopy in adults not at risk of drug resistant tuberculosis or HIV associated tuberculosis since geneXpert has been proven to be more sensitive than microscopy. This would be helpful in detecting the disease in individuals who are smear negative however considering resource constraints in some settings it is not recommended as a rule but a possible beneficial and rational strategy in a setting where it is feasible (WHO, 2014). Next is group C who are individuals not at risk of drug resistant or HIV associated tuberculosis but suspected to have tuberculosis. It includes those whose HIV status is unknown or negative but presenting with symptoms of tuberculosis. They may be offered geneXpert as an initial diagnostic test, however in resource constraints, sputum smear microscopy may be conducted first, after which only those who are smear negative should be referred for geneXpert. This would reduce the frequency of a missed diagnosis (WHO, 2014). Children should also be prioritized given their peculiar diagnostic difficulties. Group D includes all individuals, adults and children suspected of having tuberculosis.
Here geneXpert should be used as an initial diagnostic test. This would lead to the detection of more cases, timely detection of resistance and shorten the time to the institution of therapy. This is only practicable where the resource capacity permits, however national programs may be limited by resource constraints hence the prioritization of specific categories for referral. (WHO, 2014). The test is also recommended for patients with extra-pulmonary tuberculosis where non-respiratory specimens such as lymph node tissue and cerebrospinal fluid may be collected (WHO, 2012). Given these guidelines, it would be necessary to assess what operates in the health facilities in the Greater Accra Region of Ghana. Do health workers follow the guidelines for geneXpert testing especially in resource constrained settings where all patients cannot be tested? Is there a significant proportion of individuals or target groups who are left out that could lead to a missed diagnosis? All these questions were addressed in this study.

2.6 Case Detection and a Better Diagnostic Tool

The overall aim of introducing geneXpert is to increase case diagnosis and reduce significantly or totally eliminate the event of missed diagnosis. Although geneXpert is a better diagnostic tool, the gains would not be realized if it is not strategically utilized. The introduction of a better diagnostic tool alone is not sufficient to increase case detection. There would have to be an overall health system strengthening and strategic planning. The case detection rate of tuberculosis in sub-Saharan Africa was estimated to be about 52% in 2014 by the World Health Organization. This is far from the target of 70% which was set in the year 2000 (Rudolf & Wejse, 2015). Two studies were compared by Rudolf & Wejse (2015) to assess how better testing may impact patient outcomes. They compared the XTEND; a cluster randomized trial on the effect of geneXpert on patient-relevant outcomes in a setting of routine implementation with TB-NEAT trial which also assessed the performance of geneXpert in a routine setting. They reported that in the XTEND trial there
was no observed difference in the two groups as regards mortality, proportion of patients started on treatment or loss to follow up, although the geneXpert group had a 50% higher rate of bacteriologically confirmed tuberculosis. The findings of the TB-NEAT trial were quite disappointing in that the health care staff had to make the decision on which patient to refer for geneXpert tuberculosis testing and this decision was suboptimal in that there was no change in the existing diagnostic pathway despite the introduction of geneXpert. This correlates with the finding of the XTEND trial above of no difference in the patient outcomes above in both random groups (one group with geneXpert implementation, the other no implementation of geneXpert). Rudolf and Wejse in 2015 stated that a pertinent lesson to note from these two studies is that no diagnostic technology no matter how sophisticated can overcome the gap in a weak health care system. The knowledge and practice of health care workers is a component of the health care system that in this context influences referral for testing and therefore the utilization of geneXpert. The authors stated that referral rates were often low due to the broad scope for tuberculosis case definition. Referral is also directly influenced by the index of suspicion among clinicians which is informed by their knowledge of the categories of patients to be referred for testing. They also stated that health care workers who received training for the implementation of Xpert had a lower threshold for referring patients than those who did not. They had a higher index of suspicion being more likely to refer apparently healthy tuberculosis patients for testing. In this setting it would be important to know to what extent the health care workers are being trained to deliver geneXpert and their knowledge on how the service should operate for example in terms of who they think should be referred for testing. They should also have a good referral algorithm in order to improve their sorting and decision of patients to be referred. Finally, geneXpert relies on regular power supply, constant supply of cartridges and other consumables. It is also largely donor-funded hence is mostly installed in centralized laboratories hence some health care facilities would have to refer
their patients to the centralized laboratories or send their samples for testing. These samples are supposed to be transported with a cold chain system. Health care workers should also be able to appropriately supervise the collection of the samples from the patients to ensure sample quality by giving out the right instruction to the patients. The laboratory staff should also be skilled in performing the test with some degree of supervision, to minimize the chances of inconsistent results which could delay diagnostic decision and treatment. All these factors affect the utilization of geneXpert, and evidence based information as to how this operates would be needed, so that where gaps are detected, appropriate policies can be formulated or interventions can be put in place to address such barriers.
CHAPTER THREE

3.0 METHODS

3.1 Study Site

The study was conducted in the Greater Accra region using four health facilities; the 37 Military Hospital, a tertiary facility, which primarily sub serves the military, but also receives patients from the entire region who are non-military personnel and three government facilities namely Ridge Hospital also a tertiary institution offering some specialized form of care, Amansama General Hospital and Tema General Hospital which are mainly secondary centers receiving patients from the primary facilities. These hospitals are the functional sites for geneXpert in the region. They were also selected for availability of quality data and other logistic reasons. The other two facilities implementing geneXpert in the region at the time of the study were excluded for lack of quality data and ethical clearance.

3.2 Study Design

This was a mixed methods study. A quantitative approach, using a cross-sectional study design was used to determine the proportion of patients at risk of Drug Resistant Tuberculosis who had a geneXpert test done and also to establish possible associations between known risk factors for drug resistant tuberculosis and having a geneXpert test. The qualitative approach was used to provide empirical explanations for the findings of the quantitative component. It was also considered more appropriate both in identifying and gaining a better understanding of the factors affecting the utilization of the geneXpert intervention which could not be explained quantitatively. The study employed phenomenology as the main strategy in the qualitative enquiry. This allowed participants to share their individual experiences working with geneXpert and also their perceived feelings about factors affecting the intervention.
3.3 Study Population
This study utilized all the total samples available at each of the health facility, since a large sample size was not anticipated, given that geneXpert was being implemented in only very few facilities in the region; the 37 Military Hospital and the Ridge Hospital had geneXpert implemented and fully functional in 2014, while geneXpert was implemented at about November 2016 in Tema General Hospital and Amansama General Hospital. All tuberculosis cases managed between January 2016 and May 2017 in 37 Military Hospital and Ridge Hospital, and all cases managed in Tema General Hospital and Amansama General Hospital between January 2017 and May 2017 were enrolled into the study. For the older facilities implementing geneXpert, complete data for 2014 and 2015 were unavailable at the time of the study.

3.4 Study Variables
3.4.1 Dependent variable: Tested for geneXpert.

3.4.2 Independent variables:

<table>
<thead>
<tr>
<th>VARIABLE NAME</th>
<th>VARIABLE TYPE</th>
<th>VALUES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis category</td>
<td>Categorical</td>
<td>Pulmonary positive, pulmonary negative,</td>
<td>According to physician diagnosis depending on the site affected; Lungs or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extra-pulmonary, smear not done.</td>
<td>other sites such as joints and lymph nodes.</td>
</tr>
<tr>
<td>Retroviral status</td>
<td>Categorical</td>
<td>Positive, negative</td>
<td>HIV test result</td>
</tr>
<tr>
<td>Initial Smear analysis</td>
<td>Categorical</td>
<td>Positive, negative</td>
<td>Sputum microscopy result at first presentation</td>
</tr>
<tr>
<td>Smear at two/three months</td>
<td>Categorical</td>
<td>Positive, negative</td>
<td>Sputum microscopy at two/three months</td>
</tr>
<tr>
<td>Case status</td>
<td>Categorical</td>
<td>Relapse, New, Other</td>
<td>Resurgence of symptoms after successful completion of therapy is a relapse,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>presenting for the first time is new.</td>
</tr>
</tbody>
</table>
Data were also collected on background variables such as age, gender, facility and year from which the case was selected.

3.5 Data Collection Tools

Data were collected using a data extraction tool and an in-depth interview guide. Tape recorders were used to record the interview sessions.

3.6 Data Collection

In all of the facilities, a total of 386 cases were enrolled, and data were collected on the risk factors for drug resistant tuberculosis and whether or not a case had geneXpert test done. Data were also collected on background variables such as age, gender, facility and year from which the case was selected. These information were obtained from the tuberculosis registers and entered into a microsoft excel form. A total of ten participants from the selected facilities were interviewed for the qualitative study; six nurses working in the tuberculosis clinic and four laboratory scientists working on geneXpert. In-depth interview covered areas such as experience working with geneXpert, tuberculosis patient management, selection of patients for geneXpert testing, patient compliance and also technical challenges working with geneXpert. A codebook was developed for the quantitative data entry. Nurses assigned to the tuberculosis clinic assisted in sorting out information from the registers. After the initial data entry, data was validated by independent research assistants who were initially taken through the codes and trained on data validation. In-depth interviews were audio taped and field notes were also taken.

3.7 Data Analysis

Quantitative data were imported into STATA 14 for cleaning and analysis. Pie charts were produced in STATA while bar chart was produced in microsoft excel.

Cases reviewed were described with respect to their distribution in terms of age, gender, facilities from which they were selected and other baseline characteristics. The total proportion of patients
at risk of drug resistant tuberculosis who were tested with geneXpert was determined by first summing up all the patients who had one risk factor in the absence of other risk factors and then dividing the number tested with geneXpert among this group by the total sum having one risk factor. The proportion of patients who had geneXpert test done among the various risk groups for drug resistant tuberculosis such as cases of relapse, retro-viral positive patients, sputum positive at two or three months of treatment and also those categories recommended for geneXpert testing according to the World Health Organization guidelines for testing, such as cases of extra-pulmonary tuberculosis was computed by dividing the number of cases who had a geneXpert test in each of the categories by the total number of cases in the respective categories. A chi square test and simple logistic regression reporting odds were done both to explore possible associations between baseline variables such as age category, gender and facility and the outcome variable which is getting tested for geneXpert and also possible associations between the independent variables; risk factors for drug resistant tuberculosis and getting tested with geneXpert. Multiple logistic regression analysis was done for variables which were statistically significant at p-values less than 0.05, controlling for possible confounders. All variables which were significant in the crude analysis were retained in the multivariate regression model. A regression diagnostics to assess collinearity between predictor variables was not performed since the pseudo R^2 of the multivariate regression model was low.

In-depth interviews were transcribed and imported into ATLAS.ti version 7 for analysis devoid of any identifying information. Unique identity codes were used to identify participants. Transcripts were read multiple times to gain a proper understanding; a codebook was developed based on the conceptual framework used in the study. Data were coded employing both a deductive approach; generating codes from the data, and also an inductive approach; coding data into priori codes. Categories were developed and themes identified. Memos containing a description of ideas
emerging from the categories and themes were written, constantly referring to the transcripts to ensure accuracy. These ideas were interpreted. Families representing specific groups were created based on facility and designation, and codes were also grouped into families and queries were run to compare between and within group similarities and differences.

3.8 Quality Control

1. Data validation was carried out by independent research assistants who were taken through the data codes and also trained on data validation.

2. Data validation commands were also in-put in designing the micro-soft excel form.

3.9 Ethical Consideration

Ethical clearance was obtained from the Ghana Health Service Ethical Review Board and from the 37 Military Hospital ethical review board. Cases used in the study were de-identified. Informed consent was also obtained from the participants in the in-depth interview; their anonymity was preserved and confidentiality taken into consideration. They were educated on the purpose and details of the study. They were also informed about their rights to withdraw from the study at any point in time and that their decision not to continue will be respected. No form of compensation was given to the participants. Data collected were stored on a pen drive password protected document and will be kept for a maximum of three years after which it will be destroyed. Only the principal investigator and the supervisor have access to the data. The study poses no potential hazards and will be beneficial in improving the delivery of the geneXpert intervention. The research was funded by the World Health Organization Tropical Diseases Research (ORID/TDR/11/2016-2017/006).
3.10 Pilot Study

Data collection tools were pretested at Ridge Hospital using twenty cases at the tuberculosis clinic.
CHAPTER FOUR

4.0 RESULT

In this chapter the study findings are presented. The chapter highlights results of the quantitative analysis which includes the baseline characteristics of study participants, the risk factors for drug resistant tuberculosis, proportion of patients at risk of drug resistant tuberculosis who get tested with geneXpert, association between the participant base line characteristics and getting tested with geneXpert and also association between the risk factors for drug resistant tuberculosis and getting tested with geneXpert. It also provides a descriptive account of the qualitative in-depth interviews.
4.1 Quantitative analysis

Table 1: Baseline Characteristics of cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 20</td>
<td>71</td>
<td>18.4</td>
</tr>
<tr>
<td>21 – 40</td>
<td>152</td>
<td>39.5</td>
</tr>
<tr>
<td>41 – 60</td>
<td>128</td>
<td>33.3</td>
</tr>
<tr>
<td>61 – 80</td>
<td>34</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>228</td>
<td>59.1</td>
</tr>
<tr>
<td>Female</td>
<td>158</td>
<td>40.9</td>
</tr>
<tr>
<td><strong>Facility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 Military Hospital</td>
<td>250</td>
<td>64.8</td>
</tr>
<tr>
<td>Ridge Hospital</td>
<td>75</td>
<td>19.4</td>
</tr>
<tr>
<td>Amansama General Hospital</td>
<td>33</td>
<td>8.6</td>
</tr>
<tr>
<td>Tema General Hospital</td>
<td>28</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Year Selected</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>262</td>
<td>67.9</td>
</tr>
<tr>
<td>2017</td>
<td>124</td>
<td>32.1</td>
</tr>
<tr>
<td><strong>Tested with GeneXpert</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested</td>
<td>89</td>
<td>23.1</td>
</tr>
<tr>
<td>Not Tested</td>
<td>297</td>
<td>76.9</td>
</tr>
</tbody>
</table>
4.1.1 Baseline Characteristics of cases

The baseline Characteristics of cases are presented in table 1.

A total of 386 cases seen were included in the analysis. Majority 250(64.8%) were from 37 Military Hospital, while 75(19.4%) were from Ridge Hospital, 33(8.6%) from Amansama General Hospital, and 28(7.3%) from Tema General Hospital. Majority of the cases 262(67.9%) were seen in 2016, while 124(32.1%) were seen in 2017. Out of the 386 cases, 228(59.1%) were males, while 158(40.9%) were females, with 71(18.4%) aged between 1 – 20 years, 152(39.5%) between 21 - 40 years, 128(33.3%) between 41 – 60 years and 34(8.8%) between 61 – 80 years of age. More than half of the cases 296(76.9%) were not tested with geneXpert, while 89(23%) were tested with geneXpert.
Table 2: Proportion of patients at risk of drug resistant tuberculosis who were tested with geneXpert

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Total Number with risk factors.</th>
<th>Total Number Tested With GeneXpert</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse Only</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Retro Viral Positive Only</td>
<td>107</td>
<td>29</td>
</tr>
<tr>
<td>Positive Smear at two/three Months Only</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total Number at risk</td>
<td>117</td>
<td>34</td>
</tr>
</tbody>
</table>

Out of the entire sample of 386 cases of tuberculosis reviewed, a total of 117 were found to be at risk of drug resistant tuberculosis; each of these 117 cases had only one risk factor for drug resistant tuberculosis. Table 2 shows each individual risk factor and the total number of cases having just that risk factor. Of the 117 cases at risk, only 34(29.1%) were tested with geneXpert.
Table 3: Risk factors for drug resistant tuberculosis, other categories of cases recommended by World Health Organization guidelines for testing and proportion tested with geneXpert

<table>
<thead>
<tr>
<th>Risk factors &amp; Other recommended categories</th>
<th>Total Number n = 386</th>
<th>Tested with geneXpert n(%)</th>
<th>Not tested with geneXpert n(%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New cases</td>
<td>363</td>
<td>79(21.8)</td>
<td>284(78.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Relapse*</td>
<td>7</td>
<td>5(71.4)</td>
<td>2(28.6)</td>
<td></td>
</tr>
<tr>
<td>Not Documented</td>
<td>16</td>
<td>5(31.3)</td>
<td>11(68.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Retro-Viral Status</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.136</td>
</tr>
<tr>
<td>Positive*</td>
<td>110</td>
<td>31(28.2)</td>
<td>79(71.8)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>275</td>
<td>58(21.1)</td>
<td>217(78.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial Smear Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.911</td>
</tr>
<tr>
<td>Positive</td>
<td>122</td>
<td>39(32)</td>
<td>83(68.0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>101</td>
<td>33(32.7)</td>
<td>68(67.3)</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>163</td>
<td>17(10.4)</td>
<td>146(89.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Smear at Two/Three Months</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.957</td>
</tr>
<tr>
<td>Positive*</td>
<td>6</td>
<td>2(33.3)</td>
<td>4(66.7)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>125</td>
<td>43(34.4)</td>
<td>82(65.6)</td>
<td></td>
</tr>
<tr>
<td>Not done</td>
<td>190</td>
<td>27(14.4)</td>
<td>163(85.8)</td>
<td></td>
</tr>
<tr>
<td>Not eligible for smear</td>
<td>65</td>
<td>17(26.2)</td>
<td>48(73.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Tuberculosis Category</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Pulmonary positive</td>
<td>176</td>
<td>58(33)</td>
<td>118(67.0)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary negative</td>
<td>119</td>
<td>23(19.3)</td>
<td>96(80.7)</td>
<td></td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>78</td>
<td>7(9.0)</td>
<td>71(91.0)</td>
<td></td>
</tr>
<tr>
<td>Smear not done</td>
<td>11</td>
<td>1(9.1)</td>
<td>10(90.9)</td>
<td></td>
</tr>
</tbody>
</table>

Note: *cases at risk of drug resistant tuberculosis (these had one or more risk factors, that is could have the risk factor in that category, in addition to any other risk factor). Guidelines recommend the testing of patients at risk of drug resistant tuberculosis in addition to cases for whom initial smear analysis is negative and cases of extra-pulmonary tuberculosis (WHO, 2014).
4.1.3 Risk factors for drug resistant tuberculosis, other categories of cases recommended for geneXpert testing and proportion tested with geneXpert.

Table 3 shows the proportion of patients in the different risk groups who were tested with geneXpert as well as the proportion tested among the categories recommended for testing according to the guidelines.

Of the 7 cases of relapse, 5(71.4%) had geneXpert test done for them. Out of the 110 cases who were HIV positive, only 31(28.2%) had geneXpert test done, of the 6 patients who were still smear positive at two/three months on treatment, only 2(33.3%) got tested with geneXpert. A total of 78(20.2%) patients had extra-pulmonary tuberculosis, out of which only 7(9%) had geneXpert test. Out of the 101 cases who were sputum negative on initial smear analysis, only 33(32.7%) had geneXpert test. Smear not done is a category representing children who could not produce sputum for smear analysis, in the sample, there were 11(2.9%) ages ranging between 1 and 3 years. Only one got tested with geneXpert.

Result of chi square test for associations between the risk factors for drug resistant tuberculosis, other recommended categories and getting tested with geneXpert was significant for only case status and tuberculosis category, (chi2(1) = 9.65, p < 0.002) and (chi2(3) = 20.50, p < 0.0001) respectively. Not documented, not done and not eligible were coded as missing values in the analysis.
Figure 2: Two/three Months follow up AAFB screening for sputum positive cases on initial AAFB screening.

Of all 122 cases who were sputum positive on initial screening in the entire sample, 80 had a follow up screening at two/three months, out of which 6(4.9%) were still sputum positive, and 74(60.7%) were sputum negative. As many as 17(13.9%) who were eligible for this screening were not screened and 25(20.5%) tagged in the figure above as ‘not applicable’ were not eligible for this screening at the time of the study.
Of 101 cases that were sputum negative, 44 actually had pulmonary tuberculosis. The rest were cases of extra-pulmonary tuberculosis.

Of the 44 cases of sputum-negative pulmonary tuberculosis, 22(50%) had a follow up sputum AAFB at two/three months and were found to still be negative. As high as 20(45.5%) had no follow up sputum AAFB done while only two were not eligible for this screening as at the time of this study.
Figure 4: Distribution of HIV Positivity rate by Tuberculosis Case Categories

This figure highlights the percentage of those who are HIV positive among the various tuberculosis case categories. Of note is that as high as 23.1% of cases of extra-pulmonary tuberculosis are HIV positive.
Table 4: Association between baseline characteristics of cases and getting tested with geneXpert

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tested n (%)</th>
<th>Not Tested n (%)</th>
<th>P-value (Chi sq)</th>
<th>cOR (95% CI)</th>
<th>P-value (Logistic regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age Category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-20</td>
<td>9(12.7)</td>
<td>62(87.3)</td>
<td>0.129</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>21-40</td>
<td>38(25)</td>
<td>114(75)</td>
<td>2.30(1.04-5.06)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>41-60</td>
<td>32(25)</td>
<td>96(75)</td>
<td>2.30(1.02-5.12)</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>61-80</td>
<td>10(29.4)</td>
<td>24(70.6)</td>
<td>2.87(1.04-7.93)</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37(23.4)</td>
<td>121(76.6)</td>
<td>0.889</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52(22.8)</td>
<td>176(77.2)</td>
<td>0.97(0.64-1.67)</td>
<td>0.889</td>
<td></td>
</tr>
<tr>
<td><strong>Facility</strong></td>
<td></td>
<td></td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 Military</td>
<td>40(16)</td>
<td>210(84)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridge</td>
<td>29(38.7)</td>
<td>46(61.3)</td>
<td>3.31(1.86-5.88)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Amansama</td>
<td>7(21.2)</td>
<td>26(78.8)</td>
<td>1.41(0.57-3.47)</td>
<td>0.451</td>
<td></td>
</tr>
<tr>
<td>Tema</td>
<td>13(46.4)</td>
<td>15(53.6)</td>
<td>4.55(2.01-10.29)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Year Selected</strong></td>
<td></td>
<td></td>
<td>0.097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>54(20.6)</td>
<td>208(79.4)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2017</td>
<td>35(28.2)</td>
<td>89(71.8)</td>
<td>1.5(0.93-2.48)</td>
<td>0.098</td>
<td></td>
</tr>
</tbody>
</table>

Note: cOR = Crude odds ratio, CI = Confidence interval
4.1.4 Association between baseline characteristics of cases and getting tested with geneXpert

Table 4 shows the association between the baseline characteristics of cases and getting tested with geneXpert.

The proportion of females who got tested with geneXpert did not differ significantly from the proportion of males who got tested with geneXpert, chi square test showed no association between gender and getting tested with geneXpert (Chi2 (1) = 0.02, p < 0.8889). Logistic regression also showed no association between these two variables [COR = 0.97, 95% CI (0.6-1.6) p<0.889]

While a Chi square test showed no significant association between age category and getting tested with geneXpert (chi2 (3) = 5.67, p< 0.129), logistic regression analysis showed a weak association. The odds of getting tested with geneXpert was 2.30 times as high in cases within the age category of 21-40 years compared to cases within the age category of 1-20 years[COR = 2.30(CI = 1.04 – 5.06), p< 0.039)]. The odds of getting tested with geneXpert was also 2.30 times as high in cases within the age category of 41-60 years compared to cases within the age category of 1-20 years[COR = 2.30(95%CI = 1.02-5.12), p< 0.043)]. The odds of getting tested with geneXpert was 2.87 times as high in cases within the age category of 61-80 years compared to cases within the age category of 1-20years [COR = 2.87(95%CI = 1.04-7.93),p<0.042].

There is also an association between facility and getting tested with geneXpert. The odds of getting tested with geneXpert was 3.31 times as high in cases from Ridge hospital compared to cases from the 37 Military Hospital [COR = 3.31(95%CI = 1.86-5.88), p<0.0001]. The odds of getting tested with geneXpert was also found to be 4.55 times as high in cases from Tema General Hospital compared to cases from the 37 Military Hospital [COR =4.55(95%CI =2.01-10.29),p<0.0001].
There is no association between the year from which the cases were selected and getting tested with geneXpert (COR=1.5 (95% CI = 0.93-2.48), p<0.098)
Table 5: Association between risk factors for drug resistant tuberculosis, other categories recommended for testing and getting tested with geneXpert

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>cOR(95% CI)</th>
<th>P Value</th>
<th>AOR(95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td>0.199</td>
</tr>
<tr>
<td>Relapse</td>
<td>8.99(1.71-47.2)*</td>
<td>0.009</td>
<td>4.41(0.76-25.7)</td>
<td>0.099</td>
</tr>
<tr>
<td><strong>Retro Viral Status</strong></td>
<td></td>
<td>0.137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.47(0.88-2.43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Smear Analysis</strong></td>
<td></td>
<td>0.911</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.97(0.55-1.70)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smear at Two/Three Months</strong></td>
<td></td>
<td>0.957</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.95(0.17-5.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tuberculosis Category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Positive</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary Negative</td>
<td>0.49(0.28-0.85)*</td>
<td>0.011</td>
<td>0.63(0.35-1.14)</td>
<td>0.133</td>
</tr>
<tr>
<td>Extra Pulmonary</td>
<td>0.20(0.09-0.46)*</td>
<td>0.0001</td>
<td>0.17(0.06-0.51)*</td>
<td>0.002</td>
</tr>
<tr>
<td>Smear not done</td>
<td>0.20(0.03-1.62)</td>
<td>0.133</td>
<td>0.36(0.04-3.63)</td>
<td>0.392</td>
</tr>
<tr>
<td><strong>Facility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 Military Hospital</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridge</td>
<td>3.30(1.86-5.88)*</td>
<td>0.0001</td>
<td>3.18(1.66-6.07)*</td>
<td>0.0001</td>
</tr>
<tr>
<td>Amansama</td>
<td>1.41(0.57-3.47)</td>
<td>0.451</td>
<td>1.02(0.39-2.70)</td>
<td>0.967</td>
</tr>
<tr>
<td>Tema</td>
<td>4.55(2.10-10.29)*</td>
<td>0.0001</td>
<td>5.31(2.18-12.95)*</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Age Category</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-20</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-40</td>
<td>2.30(1.04-5.06)*</td>
<td>0.039</td>
<td>2.13(0.92-5.95)</td>
<td>0.075</td>
</tr>
<tr>
<td>41-60</td>
<td>2.30(1.02-5.14)*</td>
<td>0.043</td>
<td>2.16(0.83-5.63)</td>
<td>0.115</td>
</tr>
<tr>
<td>61-80</td>
<td>2.87(1.03-7.93)*</td>
<td>0.042</td>
<td>3.19(0.98-10.40)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

Note: cOR = Crude odds ratio, AOR = Adjusted odds ratio, CI = Confidence interval, *statistically significant.
4.1.5 Association between risk factors for drug resistant tuberculosis, other categories recommended for testing and getting tested with geneXpert.

Table 5 shows the association between the risk factors for drug resistant tuberculosis and getting tested with geneXpert.

Results of the analysis showed that the odds of getting tested with geneXpert was 8.99 times as high in cases of relapse compared to new cases [COR = 8.99(95%CI = 1.71 -47.2),\(p< 0.009\)], however on adjusting for age category, facility, and tuberculosis category, this association was found not to be statistically significant [AOR = 4.41(95%CI = 0.76-25.7),\(p< 0.099\)]

There was no association between retro-viral status and having a geneXpert test. [COR =1.47(95%CI = 0.88 – 2.43), \(p< 0.137\)]

There was also no association between initial smear analysis and having a geneXpert test [COR= 0.97(95%CI =0.55-1.70), \(p<0.911\)] and also between smear analysis at two to three months on treatment and getting tested with geneXpert [COR = 0.95 (95%CI = 0.17-5.42), \(p< 0.957\)]

Crude analysis showed that compared to cases who were pulmonary positive, cases who were pulmonary negative were 51% less likely to get tested with geneXpert [COR= 0.49(95%CI = 0.28-0.85), \(p< 0.011\)], those who had extra-pulmonary tuberculosis were also 80% less likely to have a geneXpert test [COR= 0.20 (95%CI = 0.09 – 0.46),\(p< 0.0001\)] while there was no significant difference in the odds of having a geneXpert test done between cases who were pulmonary positive and cases classified as smear not done [COR= 0.20 (95%CI = 0.03-1.62),\(p< 0.133\)]. On adjusting for age category, case status and facility, the odds of having a geneXpert test was found to be significantly different only between cases who were pulmonary positive and cases of extra-pulmonary tuberculosis, cases of extra-pulmonary tuberculosis were 83% less likely to have a geneXpert test compared to cases who were pulmonary positive [AOR= 0.17 (95%CI = 0.06-0.51),
There was no difference in the likelihood of having a geneXpert test done between the pulmonary positive cases and pulmonary negative cases \( \text{AOR} = 0.63(95\% \text{CI} = 0.35-1.14), p < 0.133 \) and also between the pulmonary positive cases and those classified as smear not done \( \text{AOR} = 0.36(95\% \text{CI} = 0.04-3.63), p < 0.392 \).

The analysis also showed that after adjusting for case status, age category and tuberculosis category, cases obtained from Ridge and Tema general hospital were more likely to have a geneXpert test done compared to cases obtained from the 37 Military Hospital. The odds of having a geneXpert test done was found to be 3.18 times as high in cases obtained from Ridge Hospital compared to cases obtained from the 37 Military Hospital \( \text{AOR} = 3.18(95\% \text{CI} = 1.66-6.07), p < 0.0001 \). The odds of having a geneXpert test done was found to be 5.31 times as high in cases obtained from Tema general Hospital compared to cases obtained from the 37 Military Hospital \( \text{AOR} = 5.31(95\% \text{CI} = 2.18-12.95), p < 0.0001 \). Adjusting for case status, tuberculosis category and facility showed no association between age category and getting tested with geneXpert, all p-values were greater than 0.05. No regression diagnostics was performed to assess collinearity between predictor variables since pseudo R\(^2\) was low [0.14] and most of the variables were not significant.
4.2 Qualitative analysis
A total of ten people selected from each of the facilities were interviewed. A description of the in-depth interview participants is presented in table 6.

Table 6: In-depth Interview Participants

<table>
<thead>
<tr>
<th>Facility</th>
<th>Professional Background</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 Military Hospital</td>
<td>Nurse</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Laboratory Scientist</td>
<td>1</td>
</tr>
<tr>
<td>Tema General Hospital</td>
<td>Laboratory Scientist</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nurse</td>
<td>1</td>
</tr>
<tr>
<td>Ridge Hospital</td>
<td>Nurse</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laboratory Scientist</td>
<td>1</td>
</tr>
<tr>
<td>Amansama General Hospital</td>
<td>Nurse</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Laboratory Scientist</td>
<td>1</td>
</tr>
</tbody>
</table>

4.2.1 Process related challenges affecting the utilization of geneXpert

General findings from the study revealed that facilities generally lacked adequate resources to test every patient suspected to have tuberculosis with geneXpert as recommended by the geneXpert implementation policy. In addition, priority testing with geneXpert for some of the patients at risk of drug resistant tuberculosis particularly people living with HIV as one of the process related factors affecting the utilization of geneXpert. There was poor compliance with testing guidelines, focus of screening patients presenting to the tuberculosis clinics was mainly on the diagnosis of tuberculosis with less concern about drug resistant tuberculosis, and hence the choice of screening tool was informed mainly by other factors rather than risk factors for drug resistant tuberculosis. Some respondents reported that HIV positive patients were not tested with geneXpert if they have already been diagnosed with tuberculosis. Some also reported that at times they use AAFB for screening patients who were HIV positive particularly for the initial screening. In addition all
respondents reported that they did not have access to a written guideline specifically for geneXpert testing. These findings are evident from quotes by respondents like;

“No I don’t test the HIV patients again with geneXpert, if they are already positive, I don’t have to do the geneXpert again. They are already TB positive, so why do I do the geneXpert again” (Nurse, Amansama General Hospital)

“GeneXpert is mainly done at the emergency level to make quick diagnosis. It is not done if AAFB has already been done” (Nurse, 37 Military Hospital)

“With the HIV patients, what actually happens is, for their initial screening process, we use the AAFB”. (Laboratory Scientist, Amansama General Hospital)

Obtaining specimens from patients with extra-pulmonary tuberculosis was also a challenge to testing with geneXpert identified by the study. A respondent from only one of the facilities reported the availability of a specialist designated to collect samples such as synovial fluid aspirate for geneXpert testing, respondents in all other facilities reported the absence of a technician to collect such specimen. Collection of specimen from children was also a challenge. Respondents reported the use of Mantoux test for children a good number of times, they stated that at those times, either gastric aspirate or lavage was unsuccessful or could not be performed at the moment. They also reported that the collection of gastric aspirates and also performing gastric lavage to obtain specimen was the duty of the pediatricians. Of the six nurses interviewed, only two reported proficiency in obtaining gastric aspirates.

Dispatch of test results was another factor identified. Some of the respondents reported that patients either waited to pick up their test results or were asked to go and come back the next day. Occasionally results were picked up by health workers depending on urgency level. Respondents reported that some of the patients who are asked to go and come back later never come back to pick up their results. They reported that although the facilities make effort to trace such patients especially the positive ones, there are usually still others who cannot be traced hence a back log of unclaimed results. This is evident in quotes like;
“Yes yes yes, there are some cases where nobody comes for the results” (Laboratory scientist, Amansama General Hospital).

“The patients, I just don’t really know, some don’t see the essence of what we are doing for them, they think we are just joking, but when we have done it and we realize it is positive, we alert the nurses so that if the patient is delaying they can actually track them, but when it is a negative case and they are not coming, we don’t really bother them” (Laboratory scientist, Amansama General Hospital).

“We have had a positive case before, this year, he came to screen o, we took his contact number and contact address, he was positive. The following day, we called this client and the phone was switched off for a week, when the phone came on he said he was in Togo. Till date he has not come back” (Nurse, Amansama General Hospital).

“Yes we have a whole lot of results lying down there” (Laboratory scientist, Ridge Hospital).

“The results is there, it is there, the lab man would work on it and the results will be there. So if they don’t come and pick it doesn’t affect the work, the result is there” (Laboratory scientist, Ridge Hospital).

“Oh yea, I have a whole lot of results there. When you call them, some of their lines don’t go through, some pick up and they will tell you they will come and that is all” (Laboratory scientist, Tema General Hospital).

Loss to follow up was another important factor identified. Respondents reported that when some patients are sent for the test, for some reasons such as fear of stigmatization, some do not show up for the test at all. Others who show up at the laboratory, experiencing difficulty in producing sputum for the test who are advised to go back with a container and come back later when they are able to produce end up not coming back for the test:

“Oh yes, we have had many, they always tell you they will come back but they never come back. They will trace them, they will promise to come and still lie to you, ahh but patients are stubborn. They are just stubborn, there are few that they are financially handicapped because of money, they are not able to come, but some, they are just stubborn, I just don’t know.” (Laboratory scientist, Amansama General Hospital).

“You write the sputum test for them, they go, they come back and say the sputum is not coming, so I would go home and bring it back, and they never come back. Others too take the container, they don’t end up at the lab. They go home” (Nurse, Amansama General Hospital).

“You call them and they tell you that they will come and they don’t come and there is nothing you can do” (Laboratory scientist, Ridge Hospital).
“They even send some with request, they don’t even come at all, they will be resisting, they won’t come, they are afraid, they think you are going to tell them they have this and that’” (Laboratory scientist, Tema General Hospital).

4.2.2 Technical challenges

Only two respondents from one facility reported availability of test cartridge as a challenge, one stating that they have to go to a facility to collect test cartridges of which the quantity they are able to obtain is most times insufficient. All other respondents reported an adequate supply of test cartridge.

Two respondents in one of the facilities reported a breakdown of the equipment about twice since it was installed, taking as long as two weeks to fix. Respondents reported how this affected testing:

“there are certain measures that cannot be met, for example, we have the geneXpert machine here but a time comes whereby it can go for maintenance, its not working, it has spoilt, so when it happens like that, clients need to be screened, so we fall on AAFB. You have implemented geneXpert for all, but if machine is not working then it means nobody will be tested with it.” (Nurse, Ridge Hospital).

“We were at the regional hospital and so samples were coming. Work load on the machine, some time I remember and even the latter part of last year, we had a tough time getting results. For two weeks we were not running, and at a point, it was the UPS on two occasions that was last year.”(Nurse, Ridge Hospital).

In addition only respondents from one of the two facilities that have been administering geneXpert for more than a year reported that regular maintenance checks were carried out on the equipment on a weekly and monthly basis, apart from yearly calibration. The newer facilities have not had any maintenance checks done since the equipment was installed.

Some respondents also reported the availability of refrigerators for the temporary storage of specimen as a challenge. They reported that samples coming from distant places sometimes come in late and have to be stored temporarily awaiting analysis, however a refrigerator for storage of such specimen was lacking.
4.2.3 Enabling Factors

Effective collaboration between the tuberculosis and HIV clinic was identified as one of the positive factors. Respondents reported that patients being managed for HIV were frequently assessed for symptoms of tuberculosis and referred to the tuberculosis clinic for co-management:

“Every person who is HIV positive, because of the immune-suppression is a candidate for TB, because TB is an opportunistic infection, so we make sure that all patients that are our clients and tested positive to HIV are also screened for TB as well” (Nurse, Ridge Hospital).

Although loss to follow up was a challenge, respondents reported attempts by the facilities in tracing patients who were lost to follow up by the use of phone calls and home visits which was helpful in recovering some but not all the patients who were lost to follow up.

All respondents reported a regular power supply with back up hospital generators and the use of stabilizers and UPS for occasions of temporary power outages which was not common.
5.0 DISCUSSION

5.1 Proportion tested with geneXpert and risk factors for drug resistant tuberculosis.

Findings generally show that less than half of the patients being managed in the tuberculosis clinics in these facilities actually get a geneXpert test done; only 89 out of the 386 cases reviewed had a geneXpert test which is just about 23% of the total number of cases. This clearly indicates that the World Health Organization policy of getting every patient having or suspected to have tuberculosis tested with geneXpert has not been fully implemented in these settings. Furthermore, in this kind of setting where available resources may not permit the screening of every patient, policy recommends that patients at risk of drug resistant tuberculosis be prioritized for geneXpert testing. The study shows that this is not the case in this setting. Generally, total proportion of patients at risk of drug resistant tuberculosis who were tested with geneXpert was low, of the 117 considered to be at risk, conditioned on having one of the risk factor, only 34(29.05%) were tested with geneXpert. Among the various risk groups for drug resistant tuberculosis also, proportion screened with geneXpert was generally low with further analysis showing no difference in the likelihood of getting tested with geneXpert comparing cases at risk of drug resistant tuberculosis with cases considered not at risk.

These findings may be explained by factors such as resource constrain and poor adherence to testing guidelines as evidenced by the accounts given by the interview respondents. A study conducted in Botswana to assess adherence to national guidelines in diagnosing smear negative pulmonary tuberculosis in HIV positive patients by clinicians showed poor adherence; treatment was already instituted in 47% of patients without results of a sputum smear analysis, other approaches to accurately diagnose pulmonary tuberculosis were employed in only about 2.1% of cases and all clinicians who participated in the survey only requested for the standard three sputum smear results occasionally (Tafuma, Burnett, & Huis in ’t Veld, 2014). If this trend continues,
health workers would fail to prioritize these risk groups for geneXpert testing as well as other investigations and other special services they ought to receive. This may lead to poorer patient outcomes. Ukwaja & Oshi et al (2016) attempted to identify determinants of unsuccessful tuberculosis outcome in a rural setting in Nigeria. They found the odds of unsuccessful treatment outcome to be higher among cases of HIV/TB co-infection, smear negative tuberculosis patients and patients with extra-pulmonary tuberculosis. They concluded that these high risk group be targeted for closer monitoring and tuberculosis health services. A study conducted in Ethiopia obtained similar results; sputum negativity on initial AAFB screening, HIV positivity and sputum positivity at two months on treatment were independently associated with a higher risk of unsuccessful treatment. The authors also recommended particular attention to the follow up of these categories of cases. (Amante & Ahemed, 2015)

5.2 Process related factors
5.2.1 Sputum AAFB screening to detect patients at risk of drug resistant tuberculosis

Another important finding of this study is a gap in detection of patients at risk of drug resistant tuberculosis via sputum AAFB screening. Once patients with pulmonary tuberculosis are on anti-tuberculosis treatment, the current World Health Organization management guidelines for tuberculosis recommends that they should have another AAFB screening at about two to three months on treatment which marks the end of the intensive phase therapy (World Health Organization, 2010). The sputum analysis at this time is expected to be negative if indeed the patient is responding to treatment, more so when the patient was actually sputum positive on initial screening. A positive two/three month’s sputum smear result raises a suspicion of drug resistant tuberculosis which should warrant further investigations using geneXpert followed by a drug susceptibility testing. Findings of this study revealed that as high as 13.9% of cases who were sputum positive on initial AAFB screening did not have a follow up sputum analysis at two/three
months while for cases with pulmonary tuberculosis who were sputum negative, 45.5% of them had no sputum AAFB done at two/three months. The implication of this is that this small group of cases who are still sputum positive two to three months on treatment will not be detected and hence not even considered for further investigations with modalities like geneXpert which would aid in the diagnosis of drug resistant tuberculosis. These individuals would miss an opportunity for early treatment modification to more sensitive second line medications, hence they are likely to be on an ineffective regimen for a very long time which would impact on their overall outcome (Ukwaja et al., 2016). They may also all together add to the growing number of missed cases of drug resistant tuberculosis being more likely to die in the course of receiving an ineffective treatment regimen.

5.2.2 Specimen collection from patients with extra-pulmonary tuberculosis and children.

Patients with extra-pulmonary tuberculosis were less likely to benefit from the geneXpert intervention. Results showed that the odds of getting a geneXpert test was 80% lower in patients with extra-pulmonary tuberculosis compared to patients with pulmonary tuberculosis. Only 7(9%) out of the 78 cases of extra-pulmonary tuberculosis were tested with geneXpert. Responses from the in-depth interview suggested that this was most likely attributable to the lack of trained technicians to collect extra-pulmonary specimens for geneXpert testing. Only one of the facilities had very recently employed a technician to collect extra-pulmonary specimens, all other facilities had none. Neglecting this group of patients would likely lead to missing a significant number of cases of drug resistant tuberculosis. The study noted that as high as 23.1% of the cases of extra-pulmonary tuberculosis were HIV positive, placing them at an even higher risk of drug resistant tuberculosis. Another group affected by difficulty in obtaining specimen for testing is those classified as ‘smear not done’, these include children too young to produce sputum spontaneously,
hence requiring gastric aspirate. Of the 11 cases belonging to this category, only one had a geneXpert test which was not encouraging.

5.2.3 Policy and practical implementation

Although there is a policy in place for geneXpert testing, we see how the challenges discussed so far have affected actual implementation thereby affecting the overall utilization of the intervention. We see that policy does not always translate to practice, actual implementation of a policy tends to be affected by several other factors which if not properly addressed may lead to less gains. Marouane et al., (2016) analyzed the impact of geneXpert implementation on tuberculosis care in Malawi. They found very minimal contribution of geneXpert to the diagnosis of tuberculosis and overall tuberculosis care. Evidence from the study suggested that this was due to implementation challenges in specimen collection, empiric treatment and also poor linkage between in and outpatient setting. Empiric treatment as we saw in an earlier cited study resulted from poor adherence to standard guidelines (Tafuma et al., 2014), a challenge also identified in this study as discussed above. All these challenges overall lead to gaps in diagnosis, impacting patient management. Narasimooloo & Ross (2012) demonstrated in their study how delay in diagnosis of drug resistant tuberculosis has led to a significant delay in commencing treatment. Most of the patients who participated in their study both had symptoms of tuberculosis and were HIV positive. They recommended that workers be trained in the use of geneXpert and other investigative modalities such as line probe assay to ease this delay.

5.2.4 Loss to follow up

This study also identified loss to follow up as a significant challenge. This was seen in two dimensions; patients being referred for the test not presenting for the test and also some not showing up for their results. Result retrieval strategies was also a key challenge identified by a
study conducted in Nigeria (Mustapha et al., 2015). While the former would mean more missed cases with the accompanying consequences, the later may result in a gap between diagnosis and institution of therapy leading to poor patient outcomes and an increased risk of spread of the disease. Risk of infection becomes higher for delays in initiation of treatment beyond 30 days (Mwansa-Kambafwile, Maitshotlo, & Black, 2017). A study in South Africa demonstrated how despite the fact that geneXpert implementation has increased case detection, its contribution to reducing treatment gap is very minimal. Authors suggested a strategic linkage to treatment following the diagnosis of drug resistant tuberculosis (Cox et al., 2017). Loss to follow up resulting in treatment gap also affects other investigation modalities. Claassens et al., (2017) demonstrated how patients being diagnosed with smear positive tuberculosis were not started on treatment following diagnosis as a result of loss to follow up. They found that as high as 38% of cases documented as newly diagnosed patients where actually patients who presented in the past and were found to be smear positive but were not started on treatment because they were lost to follow up. Another study in South Africa demonstrated as high as 22.5% pre-treatment loss to follow up of patients being diagnosed with tuberculosis using either geneXpert or smear microscopy. The study found that of 271 patients who tested positive for tuberculosis, only 198(71.3%) were started on treatment, 61(22.5%) were lost to follow up hence not started on treatment (Mwansa-Kambafwile et al., 2017). Authors observed that availability of test results did not translate to a difference in the proportion of bacteriologically confirmed cases been started on treatment within 90 days. Among the programmatic challenges in geneXpert implementation identified by Chawla et al (2016) in Malawi were result-to-clinical decision and result-to-patient linkage.

So far the process related challenges affecting the utilization of geneXpert identified by this study have been discussed. Proper documentation and reporting of test outcomes, non-documentation of patients HIV status, poor integration of TB/HIV services at site level and low awareness of
geneXpert program and services by clinicians were key challenges identified by a similar study in Nigeria (Mustapha et al., 2015).

5.3 Technical factors
Finally this study identified poor organization in cartridge supply, lack of refrigerators for temporary storage of specimen, and equipment maintenance as technical challenges. While some facilities had an excess stock of cartridge, some had occasional shortage. The facilities that had excess were being supplied by a central system, while one of the facilities experiencing shortage had a system in which they go to a particular facility monthly to collect, of which they were given a fixed quantity irrespective of the number of cases they had. In occasions of shortage, patients in need of the geneXpert test would not receive it, as there would be no cartridge to run the test. Lack of refrigerators for temporary storage of specimen would mean that if for some reasons the samples received cannot be analyzed immediately, there would be no means of storage for analysis later. This may affect samples coming from distant places or at night. Poor maintenance of the geneXpert machine, just like every other machine would lead to a breakdown and hence unavailability of the machine for testing. A similar study conducted in Nigeria also identified inefficient geneXpert cartridge supply management system as a challenge. While frequent power interruption, sample transfer, long programmatic turnaround time were not challenges in this setting, they were key challenges in the study conducted in Nigeria (Mustapha et al., 2015).

5.4 Limitations
For the older facilities implementing geneXpert as far back as 2014, complete data for 2014 and 2015 were not available at the time of the study, hence data for only 2016 and 2017 were included in the quantitative analysis. Non-random selection of study sites may be considered a potential limitation, however this study utilized data from all functional sites for geneXpert for which data were available. This potentially has implications on generalizability to other settings, however lessons learnt from this study may guide implementation in other settings. Social desirability bias
is a potential limitation with respect to the qualitative component however findings of the qualitative and quantitative component of the study were triangulated and two different categories of health workers were interviewed. Confounders were controlled for in the multivariate analysis however there may still be some potential residual confounding.
CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion
This study identified non-adherence to standard guidelines as a key factor affecting the utilization of geneXpert. This has resulted in the non-prioritization of patients at risk of drug resistant tuberculosis for geneXpert testing given that available resources may not have permitted the testing of all patients and also screening of tuberculosis patients for drug resistant tuberculosis. Other key challenges identified were lack of skilled technicians to collect extra-pulmonary specimens, sputum collection in children, loss to follow up for testing, an inefficient test result communication system and cartridge supply management system, lack of refrigerators for temporary storage of specimen and equipment maintenance.

6.2 Recommendations
Addressing these challenges would improve overall implementation of the geneXpert program. The following recommendations may address these challenges to an extent:

- Guidelines concerning the program should be made available to all individual health care providers at the tuberculosis clinics, trainings on the guidelines should also be organized for all health care workers involved in geneXpert implementation.
- The geneXpert program should consider the training and deployment of technicians to collect extra-pulmonary specimens in administering facilities.
- Nurses should also be trained and designated to collect gastric aspirates and also perform gastric lavage for children.
• Health workers should be properly trained in patient counselling to minimize losses to follow up. Strategies should be put in place to improve patient follow up right from their index presentation to the facilities.

• The program should look into the cartridge supply chain. Amount of cartridge supplied should be adapted to the needs of the facilities.

• Facilities should have a system for a more regular maintenance checks to avoid system breakdown as well as addressing other technical challenges such as the provision of refrigerators to the laboratories.

• A more efficient system for the delivery of test result should be instituted. For example digital communication of test results between facilities may be more effective.
REFERENCES


http://www.who.int/tb/publications/UHC_SP_factsheet.pdf


http://doi.org/10.1017/CBO9781107415324.004


APPENDICES

Appendix 1: Informed consent form

Title: Factors Affecting the Utilization of GeneXpert in the Diagnosis of Drug Resistant Tuberculosis in Facilities Administering GeneXpert in the Greater Accra Region.

Principal investigator: Oghenekome Eboreime

Affiliated institution: School of Public Health, College of Health Sciences, University of Ghana

Address: School of Public Health, University of Ghana, Legon, Ghana.

E-mail address: kaykome1@gmail.com

Tel. No: 0268075948

General information about the research

The study seeks to determine the factors affecting the geneXpert delivery in facilities administering the test intervention. Respondents consisting of laboratory staff and nurses in the tuberculosis clinic will be enrolled in the study. Respondents will be asked to respond to questions on their knowledge about the intervention as well as test procedure related factors.

Possible risk and discomfort

It poses no potential risk to participants; the only concern is the participant’s time.
Permission

You have been selected to participate in this study. The objective of the study is to determine factors affecting the utilization of geneXpert in the diagnosis of drug resistant tuberculosis. Your consent is therefore required. However, you can may decide not to participate or withdraw from the study at any time without fear of stigmatization or harm. Your decision will be well respected.

Confidentiality

All information you provide in this study will be kept confidential. Identity numbers will be assigned to you; your names will not be documented and recorded interviews will be password protected to which only the researcher and supervisor will have access.

Benefits of participating

This study seeks to find out factors affecting the geneXpert intervention. Although there will no direct benefit for participating, the findings are expected to inform sound policy decisions and programs aimed at improving tuberculosis diagnosis.

Undertaken

I have read and understood the above information. I am satisfied and therefore consent to participating in this study.

……………………………….  ………………………………………………

University of Ghana  http://ugspace.ug.edu.gh
Code of participant                      Date and signature of participant

........................                  ..............................................................

Contact for additional information: In case of any concerns you can contact the Ethics Administrator, Ms. Hanna Frimpong GHS ERC on 0243235225 / 0507041223.
### Appendix 11: Data Extraction Tool

#### Data Extraction Tool

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type</th>
<th>Variable Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Id</td>
<td>Numeric</td>
<td>1,2,3………</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>Can take on any whole number</td>
</tr>
<tr>
<td>Gender</td>
<td>Categorical</td>
<td>Male, Female</td>
</tr>
<tr>
<td>Tuberculosis Category</td>
<td>Categorical</td>
<td>Pulmonary positive, Pulmonary Negative, Extra-pulmonary, Both</td>
</tr>
<tr>
<td>Retroviral Status</td>
<td>Categorical</td>
<td>Negative, Positive</td>
</tr>
<tr>
<td>Initial Sputum Analysis</td>
<td>Categorical</td>
<td>Negative, Positive</td>
</tr>
<tr>
<td>Sputum Analysis at 2/3 months</td>
<td>Categorical</td>
<td>Negative, Positive</td>
</tr>
<tr>
<td>Tuberculosis Case Type</td>
<td>Categorical</td>
<td>New, Relapse</td>
</tr>
<tr>
<td>Tuberculosis Symptom</td>
<td>Categorical</td>
<td>Cough, Cough, fever and weight loss, Others</td>
</tr>
<tr>
<td>Tested with GeneXpert</td>
<td>Categorical</td>
<td>Tested, Not tested</td>
</tr>
<tr>
<td>Date tested with GeneXpert</td>
<td>Date</td>
<td>Date</td>
</tr>
</tbody>
</table>

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Appendix 111: Codebook for Data Extraction tool

CODES FOR QUANTITATIVE DATA

ID – unique numbers 1 2 3 4 ...............................................................

Facility: 1 = Amasama

  2 = Ridge

  3 = 37-Military Hospital

  4 = Tema General Hospital

Age: Age at last birthday. Should be a whole number.

Gender: 0 = male

  1 = female

Tb_category: 1 = Pulmonary positive

  2 = pulmonary negative

  3 = extra_pulmonary

  4 = smear not done

New_relapse: 1 = New

  2 = relapse/treatment failure.

Initial_smear: 1 = positive

  2 = Negative
Smear_2_3: 1 = positive

2 = negative

RVS: 1 = positive

2 = negative

Tested_Xpert: 1 = tested

0 = not tested

Month_tested = numbers 1 to 12

Year_tested: 1 = 2016

2 = 2017

Chest_Xray: 1 = suggestive of TB

2 = not suggestive of TB

Represent:

99 = Not applicable

88 = not done

77 = not documented
Appendix IV In-depth Interview guide

IN-DEPTH INTERVIEW GUIDE

LABORATORY TECHNICIANS’ INTERVIEW

Introduction

(start at _____   end at _____)

Thank you for agreeing to participate in this interview. My name is Oghenekome Eboreime, an MPH student from the University of Ghana, Department of Epidemiology and Disease Control. I am conducting a study on utilization of geneXpert in the diagnosis of drug resistant tuberculosis. This study aims to explore factors that could affect the delivery of the geneXpert intervention.

The purpose of this interview with you today is to learn more about your experiences, challenges and recommendations related to the geneXpert intervention. The interview will last about 1 hour.

Please kindly read this consent form and respond accordingly. Do you have any questions?

Let me repeat that everything you tell me will be confidential. To protect your privacy, I won't connect your name with anything that you say.

At any time during our conversation, please feel free to let me know if you have any questions or if you would rather not answer any specific question. You can also stop the interview at any time for any reason.

Please remember that we want to know what you think and feel and that there are no right or wrong answers.

I will also seek your permission to audiotape this interview today, this is to help me not to miss out on our discussion points since I may not capture everything you say by writing?
Is it ok by you?

[Turn on recording equipment.]

BACKGROUND

I'd like to begin by asking you some questions about yourself and your current job.

Please introduce yourself.

Probe for…Position in [facility]; Major responsibilities in current position; How long have you been with [facility]?

Can you tell me a bit about your work and experience with geneXpert?

Probe for perception about the intervention

NURSES INTERVIEW

QUESTION 1

How does the management of tuberculosis patients work in this facility from the time the patient walks in?

Probes

Hospital procedures to get seen by the physician

Coordination of screening with sputum AAFB

Coordination of retro-viral screening for tuberculosis patients.

HIV/TB co-management
QUESTION 2

How does the referral for geneXpert work in this facility?

Probes

Who refers

Criteria for referral

Delay in referrals

Hospital procedures the patients have to follow to get tested with the geneXpert

Specimen collection

Patient follow up after referral

Contact tracing and screening

GeneXpert test result dispatch and patient review with result

QUESTION 3

What has been your experience receiving referrals for geneXpert test from other facilities, how does the process work?

Probes

Formal hospital arrangement

Specimen collection and transport

Result dispatch: probe for delay or non-retrieval of results.
QUESTION 4

What has been your experience in terms of patient’s compliance to get tested with geneXpert?

Probes

Test defaults

Facility measures to ensure patient compliance

QUESTION 5

What has been the challenges so far as well as the enabling factors with the geneXpert intervention?

QUESTION 6

How do you think the geneXpert intervention can be improved we do not want to be missing cases of tuberculosis especially DRTB?

LABORATORY STAFF INTERVIEW.

BACKGROUND

Please introduce yourself.

Probe for…Position in [facility]; Major responsibilities in current position; How long have you been with [facility]?

Can you tell me a bit about your work and experience with geneXpert?

Probe for perception about the intervention
QUESTION 1

How is patient screening for geneXpert coordinated?

Probes

Criteria for screening for geneXpert

Hospital procedures in getting AAFB done

QUESTION 2

What has been your experience receiving referrals for geneXpert test from other facilities, how does the process work?

Probes

Formal hospital arrangement

Specimen collection and transport

Result dispatch: Delay or non-retrieval of geneXpert test results.

QUESTION 3

What has been your experience so far regarding specimen quality?

Probes

Who collects the specimen

Time of collection

How specimen quality impacts the test performance and timing of results
QUESTION 4

What facilities are in place to ensure that the geneXpert test can be performed without hitches:

Probes

State of the equipment and servicing

Breakdown

Temporary storage of specimen; a proper functioning refrigerator.

Power supply

Test cartridge supply

QUESTION 5

What has been the challenges so far as well as the enabling factors with the geneXpert intervention?

QUESTION 6

How do you think the geneXpert intervention can be improved?