HIV/TB CO-INFECTION IN THE DEVELOPMENT OF DRUG RESISTANT TB AT
THREE MAJOR REFERRAL HOSPITALS IN SOUTHERN GHANA

BY:

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JULY, 2018
DECLARATION

I, Benjamin Sena Awuku-Fremont, hereby do declare that apart from references to work by other persons that have been duly cited, this dissertation is the product of my own research.

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(ACADEMIC SUPERVISOR)
DEDICATION

This work is dedicated to my parents, Mr & Mrs Denteh, my brother (Dickson), sister (Patience) for their motivation and commitment towards the achievement of my career goals.
ACKNOWLEDGEMENT

My sincerest gratitude goes to the Almighty God for His continuous guidance, blessings and protection, and for seeing me to the successful completion of yet another academic Programme.

I will also like to acknowledge the priceless contribution of my project supervisor, Dr Priscillia Nortey towards the success of my thesis. I am forever grateful for your wise counsel and guidance. May God continue to bless you and your family.

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Finally, my appreciation goes to my family.
ABSTRACT

Introduction: Tuberculosis (TB) remains an important cause of human suffering and death. The impact of Human immunodeficiency virus (HIV) on TB, drug resistant TB (DR-TB) and the implications for TB control, has been acknowledged as a major public health challenge. The influence of HIV/TB co-infection in the development of DR-TB has not yet been fully investigated in this part of the world.

Objective: The aim of this study was to determine the role of HIV/TB co-infection in the development of drug resistant TB at three major referral hospitals in Southern Ghana.

Methodology: A descriptive cross-sectional analysis of TB data at the Greater Accra Regional Hospital, the Korle-Bu Teaching Hospital and the Eastern Regional Hospital was conducted using databases of their TB Registry spanning the period of February 2013 to December 2017.

Results: A total of 9722 Tuberculosis (TB) patients diagnosed were reviewed. HIV prevalence was significantly high 30.0% ($p<0.001$). Drug resistant-TB prevalence was 101(1.0%). Previous TB treatment was associated with drug resistant-TB development ($p<0.001$). Drug resistance TB patients were more likely to have had previous TB treatment (AOR=348.61, CI=153.71-790.60). Patients with drug resistant TB had reduced odds of being HIV positive (AOR=0.69, CI=0.39-1.22). This was however and was not statistically significant ($p=0.215$).

Conclusion: At 1.0%, the prevalence of drug resistant-TB in the 3 study sites was low. There was no significant association between HIV infection and the development of TB drug resistance. However, there was a statistically significant association between previous TB treatment and TB drug resistance.

Keywords: Tuberculosis, Human Immunodeficiency Virus, Drug Resistance
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<tr>
<td>AOR</td>
<td>Adjusted Odds Ratio</td>
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<tr>
<td>ART</td>
<td>Anti-Retroviral Therapy/Treatment</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>COR</td>
<td>Crude Odds Ratio</td>
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<td>DR-TB</td>
<td>Drug-Resistant Tuberculosis</td>
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<td>DST</td>
<td>Drug Susceptibility Testing</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
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<tr>
<td>ERH</td>
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<td>MTB</td>
<td>Mycobacterium Tuberculosis</td>
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<td>NTR</td>
<td>National Tuberculosis Register</td>
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<td>Pre-XDR TB</td>
<td>Pre- extensively Drug Resistant Tuberculosis</td>
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DEFINITION OF KEY TERMS

Pulmonary Tuberculosis:
Mycobacterium Tuberculosis infection in the lungs

Extra-pulmonary Tuberculosis:
Mycobacterium Tuberculosis infection affecting other parts of the body

Rifampicin resistant-TB (RR-TB):
Resistance to anti-TB drug Rifampicin

Poly resistant-TB:
Resistance to at least two first-line anti-TB drugs but not to both rifampicin and isoniazid

Multi-drug-resistant tuberculosis (MDR-TB):
A form of tuberculosis (TB) infection which is resistant to treatment with at least two of
the most powerful first-line anti-TB drugs, namely isoniazid and rifampicin

Extensively drug resistant TB (XDR-TB):
MDR plus resistance to fluoroquinolones, and at least one second-line injectable drug
(aminoglycosides) (World Health Organization, 2014)

Pre-extensively drug-resistant TB (pre-XDR-TB):
MDR-TB having already acquired resistance to the quinolones or injectable
aminoglycosides (Gehre et al., 2016)
CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Tuberculosis (TB) is a global infectious disease that most often affects the lungs (pulmonary TB). The WHO in 2016, estimated that 2–3 billion people were infected with *M. tuberculosis* in 2015, however only a small proportion (5–15%) will go on to develop TB disease throughout their lifetime (World Health Organization, 2016b).

People infected with Human Immunodeficiency Virus have much higher probability of developing TB disease (HIV) (World Health Organization, 2016b). Worldwide, incidence of TB and HIV remains high; 10.4 million new TB of which 26% are in Africa and 1.8 million new HIV infections in 2015 (World Health Organization, 2016b).

In 2015, the incidence of TB was 160 per 100,000 (World Health Organization, 2017) and the prevalence of HIV in Ghana was 1.6% (290,000) (UNAIDS, 2017). TB and HIV caused 1.4 million and 1.0 million deaths respectively in 2015 globally (UNAIDS, 2017). In Ghana, TB case fatality ratio of 0.39 (World Health Organization, 2017) and the HIV death rate of 5.2% was recorded in 2015 (UNAIDS, 2017).

Tuberculosis drug resistance refers to the development of resistant TB strains to anti-TB medication. As a result, treatment of TB disease becomes ineffective. Among factors contributing to TB drug resistance, previous treatment for TB and HIV co-infection are key (Suchindran, Brouwer, & Van Rie, 2009). The very high mortality rates in HIV/TB co-infected
adults demonstrate that drug resistant TB can be devastating in HIV infected individuals. The co-
infection of drug resistant TB, especially multi-drug resistant-TB (MDR-TB), and HIV has been
described to be a “Perfect storm” (Wells et al., 2007). In Africa, the drug resistant TB (MDR-TB
and XDR-TB) epidemic have been driven mainly by the HIV epidemic (Andrews et al., 2007).

In the spreading of drug resistant-TB, HIV has been shown to have a significant role in fuelling
it by accelerating the progression from TB infection to TB disease (Berhan, Berhan, &
Yizengaw, 2013). However, findings on the associations of HIV infection and drug resistance
among patients with TB have been contradictory. Some studies found strongly increased risks for
drug resistant-TB (MDR TB) among patients co-infected with TB and HIV (Campos et al., 2003;
Mac-Arthur et al., 2001; Moro et al., 1998; Pozniak, 2003; Robert, Trystram, Truffot-Pernot, &
Jarlier, 2003), whereas other studies have found no increased risk (Espinal et al., 2001; Quy et
al., 2006).

This study sought to assess TB/HIV co-infection in the development of rifampicin/drug resistant
TB to provide comprehensive and up-to-date information on the burden and trend of TB drug
resistance in the Ghanaian context.

1.2 Problem Statement

The aim of Tuberculosis treatment is to achieve first time cure to prevent the occurrence of drug
resistant-TB (World Health Organization, 2011). Despite this, the global incidence of drug
resistant- TB continues to rise in spite of efforts to reverse the trend (World Health Organization,
2008b, 2013, 2014). Current incidence is 480,000 (MDR-TB) with an additional 100,000
rifampicin resistant-TB (RR-TB) burden (World Health Organization, 2016b). This trend also
occurs in the SSA region including Ghana. The development of drug resistant-TB increases treatment period, prolongs hospital stay, increase TB mortality and complicates the TB control programme as a whole. Besides the comparably low success rates of cure for drug resistant-TB patients (48%) and its association with worse prognosis (van Halsema et al. 2012), drug resistant-TB treatment can be very difficult and expensive and can last for over 2 years.

Drug resistant-TB (MDR-TB) prevalence in Ghana has been reported to be 13%, and this is higher compared to that of other West African Countries (Gehre et al., 2016). Mortality due to MDR-TB worldwide and in the SSA is high and also on the increase (World Health Organization, 2013, 2014).

In understanding the influence of HIV/TB co-infection on the development and transmission of drug resistant-TB strains, policies targeted at HIV/TB can be re-enforced, management strategies re-structure and further strengthening of collaboration between the National AIDS and TB Control Programmes to improve and sustain gains made in the control of the major diseases.

In Ghana, the paucity of data on the role of HIV/TB co-infection in the development of drug resistant-TB exists. The only study found in the literature to have looked at this in the local setting could not do this fully and therefore recommended further studies in this area (Gehre et al., 2016) and hence further suggests the need for this study.

1.3 Research Questions

1. What is the prevalence of HIV infection among TB patients?

2. What is the prevalence of drug resistant-TB in Southern Ghana?

3. What is the prevalence of HIV infection among drug resistant-TB patients?
4. What is the association between HIV co-infection and drug resistant-TB?

5. What is the prevalence of drug resistant TB among patients with previous TB treatment?

6. What is the association between previous TB treatment and drug resistant TB?
1.4 Conceptual Framework

Figure 1.1: Conceptual framework illustrating HIV co-infection and previous TB treatment in the development of drug-resistant TB.
1.5 Narrative of Conceptual Framework

The conceptual framework illustrated in Figure 1.1 above shows the relationship between TB infection and HIV infection and their impact on the development of rifampicin/drug resistant-TB strains.

Tuberculosis diagnosis may be confirmed bacteriologically through sputum microscopy for the presence of acid-fast bacilli, culture of the bacteria on a media and isolation or using molecular technique such as the Xpert MTB/RIF diagnostic tool. TB patients can be cured. However, they may relapse, lost to follow-up, have other treatments such as incomplete treatment or even have treatment failure. Such patients may later present for retreatment, and due to the previous exposure to these anti-TB drugs, they may develop drug resistant strains.

HIV infection leads to an immunosuppressive state for reactivation of opportunistic infections particularly TB. The interaction between TB and HIV, as shown above, is synergistic, and the resultant TB/HIV co-infection has been found to be associated with the development of anti-TB drug resistant strains and also the promotion of the transmission of these strains of TB. The relationship between HIV and TB infection as well as HIV is bidirectional. As a result, the pill burden associated with TB/HIV co-infection may lead to poor adherence and subsequent TB treatment failures, loss to follow-up, relapse further promoting the development of drug resistance.
1.6 Objectives

1.6.1 General

To determine the role of HIV co-infection in the development of drug resistant-TB at three major referral Hospitals in Southern Ghana from February 2013 to December 2017.

1.6.2 Specific

1. To determine the prevalence of TB drug resistance at these referral Hospitals from February 2013 to December 2017.

2. To estimate the prevalence of drug resistant TB among HIV/TB co-infected patients and patients with previous TB treatment.

3. To assess the association between HIV co-infection and drug resistant-TB.

4. To assess the association between previous TB treatment and drug resistant-TB.
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Tuberculosis (TB)

Tuberculosis (TB) is an infectious disease that is caused by the bacillus *Mycobacterium tuberculosis* (MTB). It typically affects the lungs (pulmonary TB), but other sites can also be affected (extra-pulmonary TB). The spread of the disease is from person to person through droplet nuclei by coughing. TB infection may be active, where the infected individual is ill with the disease and is capable of transmitting the disease or latent, in which case the infected person is a carrier of dormant forms of the bacterium and therefore cannot transmit the disease until re-activated. More than 30% of the world’s population has latent TB. About 2 billion people are estimated to be latently infected with tuberculosis (TB) Worldwide (World Health Organization, 2012). An estimated 2–3 billion people infected with *M. tuberculosis* will develop TB disease during their lifetime, and this is relatively a small proportion (5–15%) (World Health Organization, 2016b).

Tuberculosis (TB) incident cases have been estimated to be 9.3 million and 1.4 million deaths occurred in 2007, and this makes TB a major cause of morbidity and mortality in the world (Lukoye et al., 2011). This figure however increased by about 12% to 10.4 million incident cases of TB (range, 8.7 million to 12.2 million) equivalent to 142 cases per 100 000 population in 2015 (World Health Organization, 2016b). HIV is the leading cause of death from infectious disease worldwide with TB only in the second place (World Health Organization, 2012). In 2014, an estimated 1.5 million died due to TB (World Health Organization, 2014) and Tuberculosis (TB)
remains the leading cause of death from a single infectious disease globally (World Health Organization, 2008a).

In 2015, Asia accounted for 61% of global TB, and the WHO African Region recorded (26%) (World Health Organization, 2016b).

TB remains a major public health problem in Ghana, just like in other Sub-Saharan African countries. The national prevalence was estimated at 356 per 100,000 population and the incidence rate of 160 per 100,000 of the population in 2015 (World Health Organization, 2016b).

2.2 HIV and TB Co-Infection

The HIV epidemic is an important contributor to the rise in TB incidence worldwide, and HIV is the leading risk factor for the development of TB. TB is often the first indicator of human immunodeficiency virus infection (World Health Organization, 2008a). TB incidence rate is strongly affected by HIV (Suchindran et al., 2009) and HIV infection strongly increases the risk for tuberculosis infection. A third of people living with HIV were infected with TB worldwide in 2015 (World Health Organization, 2016b).

According to the WHO, HIV among TB patients is classified according to status. Three main status classifications exist: HIV positive when TB patients test positive or confirmed serologically to have the virus; HIV negative when patients test negative or confirmed serologically not to have the virus; and HIV status unknown when the status of the patient cannot be verified (World Health Organization, 2012). The WHO, therefore, recommends screening and documentation of HIV status among TB patients as an essential component of the TB care package. Studies have shown about 90% documentation of HIV status among TB cases
indicating that 9 out of 10 cases have documented HIV status in Ghana (Osei, Der, Owusu, Kofie, & Axame, 2017) and other parts of Africa (Tarekegne et al., 2016). WHO in 2015 globally estimated 55% documentation of HIV status among TB patients and that of the African Regions as 81% (World Health Organization, 2016b).

In 2015, the incident TB cases among people living with HIV was estimated at 11% (range, 9–14%) and there were an estimated 1.2 million TB/HIV co-infected people (World Health Organization, 2016b). In other studies, 7%–10% of patients with HIV infection each year have TB disease (Frieden, Sterling, Munsiff, Watt, & Dye, 2003). People living with HIV have 20 to 30 times increased risk to develop active TB disease. One in eight cases of TB occurs in HIV positive individuals (Venturini et al., 2014). Of the 11% estimate, 400,000 deaths occurred (World Health Organization, 2016b) compared to 430,000 deaths in 2012 (World Health Organization, 2012) and although there has been an improvement, HIV associated TB mortality remains high. The proportion of TB cases co-infected with HIV was highest in countries in the WHO African Region and exceeded 50% in parts of southern Africa (World Health Organization, 2016b).

The impact of the generalized HIV and tuberculosis epidemics has been borne by many sub-Saharan African countries which have strained health systems and overwhelmed populations in the region. In 2010 alone, a third of the approximately 2.3 million people who developed Tuberculosis was HIV positive and in Africa (World Health Organization, 2012). Overall, In 2015, 1.2 million new cases of HIV/TB co-infection were reported across the globe, and 32% of TB cases were estimated to be infected with HIV in this region. This accounts for 74% of TB cases among people living with HIV worldwide (World Health Organization, 2016b).
Across all age groups it has been reported in the sub-region that HIV infected patients are twice more than likely to die compared to HIV-negative patients, RR = 2.19 (95 % CI: 2.03–2.37) (Osman et al., 2015).

The impact of HIV on TB and vice versa and the implications for TB and HIV control have been recognized as a public health challenge in Ghana, as is the case in many other sub-Saharan African countries. Ghana has been categorized into the group of countries with a high burden of TB/HIV co-infection. According to the WHO in 2015, there were approximately 9900 incident cases of TB/HIV co-infected patients represented by a rate of 36 per 100,000 of the Ghanaian population (World Health Organization, 2016b).

TB/HIV co-infection prevalence varies among regions and countries, ranging from 2.9 to 72.3%, with a pooled prevalence of 23.5% reported (Gao J, Zheng P, 2013). Overall, the global prevalence of TB/HIV co-infection has been falling since 2008 (World Health Organization, 2016b). The global HIV sero-prevalence in TB patients estimated as 15% but much lower than the estimate from the African Region (36%) (World Health Organization, 2016b). HIV/TB co-infection rates of 18.9% and 19% have been reported in India and Brazil (Kamath, Sharma, Pattanshetty, Hegde, & Chandrasekaran, 2013; Prado et al., 2014).

Estimates in Ghana have shown that the influence of HIV on TB has been increasing since 1989 with about 14% of TB cases attributed to HIV/AIDS. The national average is 24% (World Health Organization, 2014). Studies have also shown that HIV prevalence among TB patients is approximately 25–30% and that as many as 50% of patients with a chronic cough could be HIV positive (Osei et al., 2017).
According to Osei et al. 2015, the overall prevalence of HIV/TB co-infection in a five-district study conducted in the Volta Region of Ghana was 18.2% (95% CI: 16.4–20.1) (Osei et al., 2017). The prevalence was significantly low among males (15.1%; 95% CI: 13.1–17.4) ($p < 0.001$) compared to females (24.1%; 95% CI: 20.8–27.7), and in the elderly $\geq$70 years (3.5%; 95% CI: 1.6–7.4) ($p < 0.001$) compared to children <15 years of age (27.0%; 95% CI: 18.2–38.1). Treatment success rate was lower among TB/HIV co-infected patients (77.0%; 95% CI: 71.7–81.7) compared to patients with only TB (90%; 95% CI: 88.1–91.5) (Osei et al., 2017) making TB/HIV co-infection a major public health concern considering its attendant TB drug resistance complications.

2.3 TB Drug Resistance

Tuberculosis drug resistance (DR-TB) indicates resistance to at least one of the anti-TB drugs which include isoniazid and rifampicin, fluoroquinolones, injectable drugs (amikacin, kanamycin and capreomycin and aminoglycosides) (World Health Organization, 2013). Resistance to these medications may be primary or acquired which has also been referred to as secondary resistance in another literature (Biadglegne, Sack, & Rodloff, 2014). Primary resistance to anti-TB drugs occurs when a patient is infected with wild-type Mycobacterium Tuberculosis that is resistant to anti- TB drugs (Urassa et al., 2008). Acquired resistance to anti-TB drugs occurs when a patient is infected with susceptible forms of MTB which become resistant during treatment (Urassa et al., 2008).

Globally in 2013, the World Health Organization reported an estimated of 3.6% and 20.2% primary and acquired multidrug-resistant tuberculosis (MDR-TB) among notified TB cases (World Health Organization, 2013). Data on anti-TB resistance indicate a median primary
resistance to at least one drug of 9.9%; 6.5% streptomycin resistance, 1.8% to rifampicin, 1.0% to ethambutol while primary MDR accounted for 1.4%. From 2002 to 2007 global WHO data covering 114 countries including Tanzania and 2 special administered regions of China has shown a global prevalence of primary drug resistant *M. tuberculosis* of between 0% in two Western European countries to 56.3% in Baku, Azerbaijan while prevalence of MDR-TB ranged from 0% to 19.4 in eight countries and in the Republic of Moldova and Baku, Azerbaijan, 22.3% (World Health Organization, 2008b). However, MDR-TB survey in three SSA countries demonstrated a prevalence of and 0.6–2.0% (Sanchez-Padilla et al., 2013).

In the past decade, WHO surveillance has shown a growing rate of resistance against TB drugs (World Health Organization, 2014). Whereas, in 2014, MDR-TB constituted 3.3% of new Tuberculosis (TB) cases, in 2015 an estimated 3.9% of new cases were found to be (MDR/RR-TB) (World Health Organization, 2016b).

Rifampicin resistant-TB (RR-TB) defined as resistance to rifampicin; Polydrug resistance is resistance of *M. tuberculosis* strain to two or more of the first-line drugs; multi-drug resistant tuberculosis (MDR-TB) is a form of tuberculosis infection which is resistant to treatment at least two of the most powerful first-line anti-TB drugs, namely isoniazid and rifampicin. In some cases a more severe drug resistance can develop: extensively drug resistant (XDR-TB), defined as MDR-TB plus resistance to fluoroquinolones, and at least one second-line injectable drug (amikacin, kanamycin and capreomycin) (World Health Organization, 2014). Another type of drug resistance to TB, pre- extensively drug-resistant (pre-XDR) has been described as MDR-TB having already acquired resistance to the fluoroquinolones or injectable aminoglycosides (Gehre et al., 2016).
From 2002 to 2007, global survey by WHO also showed that the highest prevalence of MDR-TB among newly diagnosed and previously treated TB cases was 22% and 60%, respectively (World Health Organization, 2008b). In 2006, the total incidence of MDR-TB cases estimated to have occurred worldwide was 489,139 (4.8%) of all TB cases (World Health Organization, 2008b). This reduced by 8% in 2012 (450,000) (World Health Organization, 2013) and saw an increase of 6.7% from the 2012 figure to 480,000 incident MDR-TB cases in 2013 (World Health Organization, 2014). In 2015, new cases of MDR-TB was estimated at 480 000 and an additional 100 000 people with RR-TB making them eligible for MDR-TB treatment (World Health Organization, 2016a). Although the 2015 incident cases remained same as that of 2013, there is an additional RR-TB burden (World Health Organization, 2016b).

Cases of DR-TB continue to rise. Whereas MDR-TB constituted 3.3% of new Tuberculosis (TB) cases in 2014, this figure rose to 3.9% in 2015 and 21% of previously treated TB cases were found to be (MDR/RR-TB) and most of these cases occur in South America, India, China, and the former Soviet Union and sub-Saharan Africa (World Health Organization, 2016a).

Across the world, of the 1.5 million TB deaths that occurred in 2013, About 210,000 were due to MDR-TB (World Health Organization, 2014); which is a significant increase when compared to the 170,000 deaths that occurred in 2012 out of the 1.3 million TB related (World Health Organization, 2013). A further increase in 2015 saw an estimated 250,000 MDR-TB deaths (World Health Organization, 2016a).

Africa has one of the highest proportions of MDR-TB and South Africa combined with other countries have over 80% of the estimated MDR-TB cases worldwide (World Health
Organization, 2013, 2016b). Data from several African countries (Malawi, Burundi, S. Africa, Central African Republic and Kenya) suggest that MDR-TB rate ranging from 1.4% to 11.6% and is of public health significance (Githui et al., 2004; Lin, Sattar, & Puckree, 2004; Sanders et al., 2006). According to report in sub-Saharan Africa, an estimate of any form of DR-TB (drug resistance-TB) prevalence is 12.6% (95% CI 10.6-15.0) while for MDR-TB, this was 1.5% (95% CI 1.0-2.3) (Lukoye et al., 2015). WHO estimates of MDR-TB in cases in Africa has been rated at 1.9% (Zignol et al., 2012). Among previously treated patients, there was 27.2% (95% CI 21.4-33.8) and 10.3% (95% CI 5.8-17.4%), respectively (Lukoye et al., 2015). In another study, a meta-analysis of data from 2007 to 2017 showed the prevalence of MDR-TB to be 2.1% (95% CI; 1.7±2.5%) (Musa et al., 2017).

In 2015, the WHO estimated the incidence of MDR/RR-TB in Ghana at 5.5 per 100,000 people. MDR-TB prevalence was also reported to be 13%, high in Ghana compared to other West African Countries (Gehre et al., 2016).

2.4 HIV/ TB co-Infection and the Development of TB Drug Resistance

Among factors associated with the emergence of multi-drug resistant tuberculosis (MDR-TB) are but not limited to inadequate treatment, irregular drug supply, inappropriate regimens and poor patient compliance, and their effects on the epidemiology of TB are intricate and multi-layered (Urassa et al., 2008). However, among factors contributing to TB drug resistance, HIV infection has emerged as a key risk factor (Jindani & Enarson, 2015; Ormerod, 2005; Suchindran et al., 2009).
Drug resistant-TB, especially MDR-TB can be disturbing in HIV infected individuals as revealed by the very high HIV positive adult mortality rates. The co-infection of DR-TB and HIV has been well described by Wells et al. as the “Perfect storm” (Wells et al., 2007). In Africa, the DR-TB epidemic has been driven mainly by the HIV epidemic (Andrews et al., 2007). This creates an environment where an individual has double pathology with further suppressed immunity, and each is hastening the disease progression of the other, development of drug resistant-TB strains and also fuelling transmission of these strains (Andrews et al., 2007; Berhan et al., 2013; Wells et al., 2007). Also, poly-pharmacy due to two sets of drugs increase pill burden further leading to poor adherence and poor TB treatment outcome. HIV has a significant role in stimulating the spread of drug-resistant TB by accelerating the progression from TB infection to TB disease as has been shown by studies (Berhan et al., 2013). The rise in numbers of patients with HIV/TB has also raised concern about the potential for increased transmission of drug resistant Mycobacterium tuberculosis strains (Gordin et al., 1996).

Reports suggesting that there is an association between HIV co-infection and TB drug resistance development or not have been conflicting. While some studies have found significantly increased risks for drug resistant-TB (MDR TB) among patients with TB/HIV co-infection (Campos et al., 2003; Mac-Arthur et al., 2001; Moro et al., 1998; Pozniak, 2003; Robert et al., 2003), other studies found no statistically increased risk (Espinal et al., 2001; Lukoye et al., 2011, 2015; Quy et al., 2006; Urassa et al., 2008).

According to a 2007 study, MDR-TB was significantly associated with HIV infection both before (COR=2.78, p = 0.033) and after adjustment by multivariate analysis for age, sex, and the continent of origin (AOR=3.43, p=0.015). Drug resistance rate was reported as 12.1%; isoniazid
resistance was reported in 6.6%, rifampicin resistance in 0.8%, and multidrug resistance in 0.7% (Haar, Cobelens, Kalisvaart, Have, & Gerven, 2007). MDR-TB was significantly more frequent among previously untreated patients with TB/HIV co-infected cases than among those with HIV negative status (Haar et al., 2007). The association between HIV infection and any rifampicin resistance was statistically significant (OR=4.12, CI=1.01–15.67, \( p<0.05 \)) (Haar et al., 2007).

In addition, near-significant associations with HIV infection was noted for resistance to isoniazid (OR=1.50, CI=0.99–2.26) and resistance to rifampicin (OR=2.35, CI=0.82–6.24) (Haar et al., 2007). In 2009, HIV infection was also found to be associated with MDR-TB (Suchindran et al., 2009) with much-increased rates of resistance also observed in TB/HIV co-infected patients (Espinal, 2003). Acquisition of mono-resistance to rifampicin has associated with HIV infection as well (Aaron et al., 2004; Haar et al., 2007). In institutional settings, HIV infection has also been associated with MDR-TB (Suchindran et al., 2009).

Most studies date from before the roll-out of antiretroviral therapy (ART) on the large-scale. Antiretroviral therapy strongly reduces mortality in co-infected patients. However, it may have some paradoxical effect to increase transmission of MDR-TB through prolonged survival of infectious MDR-TB patients (Ammassari, 2001).

Global DR-TB prevalence among HIV positive patients have ranged from 2.4-44.8% (Haar et al., 2007; Suchindran et al., 2009) whiles in the SSA region where studies in this area have been limited; it has been between 2.2-5.3% (Mac-Arthur et al., 2001).
2.5 Previous TB treatment and the Development of TB Drug Resistance

Previous TB treatment has also been characterized as a key contributor to TB drug resistance development (Jindani & Enarson, 2015; Ormerod, 2005; Suchindran et al., 2009) and WHO define previous TB treatment or re-treatment as anti-TB chemotherapy in a TB patient returning after default, retreated after treatment failure or relapse (World Health Organization, 2012).

In 2015, 21% of previously treated TB cases were found to be (MDR/RR-TB) (World Health Organization, 2016b). Among the 315 previously treated patients, drug resistance was reported in 21.6%; isoniazid resistance in 16.5%, rifampicin resistance in 6.0%, and multidrug resistance in 5.4% (Haar et al., 2007). Several studies have shown evidence of significant association between the development of TB drug resistance and previous treatment for TB (Gehre et al., 2016; Ormerod, 2005; Suchindran et al., 2009). Findings from neighbouring countries such as Nigeria (Ani, Idoko, Dalyop, & Pitmang, 2009; Daniel & Osman, 2011; Kehinde & Adebiyi, 2013; Lawson, Yassin, Abdurrahman, Parry, & Dacombe, R, 2011; Otu, Umoh, Habib, & Ansa, 2014) and Burkina Faso (Sangare L, Diande S, Ouedraogo G, 2011) have also found significant relationship between previous TB treatment and TB drug resistance.

2.6 Tuberculosis, HIV, and Drug Resistant-TB Diagnosis

Diagnosis of TB accurately and promptly leads to timely initiation of appropriate therapy to reduce transmission and mortality (Lienhardt et al., 2001). TB disease diagnoses include: the more than 100 years old Sputum smear microscopy in which sputum samples are microscopically examined for the presence of bacteria, and a single positive result is required for the diagnosis of a smear-positive pulmonary Tuberculosis; Rapid molecular tests-the WHO
currently recommends Xpert® MTB/RIF assay (Cepheid, Sunnyvale USA) as the only rapid test for diagnosis of TB and it was first recommended (in 2010) for diagnosis of pulmonary TB in adults. It has also been recommended for children and specific forms of extra-pulmonary TB from 2013. It has high accuracy and sensitivity (79.7–100%) compared to microscopy as well as the shorter diagnostic time of fewer than 2 hours (Boehme et al., 2010; Rie, Page-Shipp, Scott, Sanne, & Stevens, 2010; World Health Organization, 2011). Other methods include the Culture methods. These include the BD BACTEC mycobacteria growth indicator tube (MGIT) 960 system (Helb et al., 2010). These are the current reference standard and results can take up to 12 weeks (World Health Organization, 2011).

Globally, the use of rapid molecular tests is on the increase, and many countries are phasing out the use of smear microscopy for diagnostic purposes (although microscopy and culture remain necessary for treatment monitoring).

Diagnosis of drug resistant-TB, as well as HIV/TB, can be complex and costly. Diagnosis is by drug susceptibility testing (DST) performed against first and second line anti-TB drugs. In 2008, WHO first recommended rapid line probe assays (LPAs) for resistance testing to rifampicin and isoniazid (first-line LPAs). A rapid LPA that tests for resistance to fluoroquinolones and injectable anti-TB drugs (second-line LPA) was first recommended in May 2016. Culture-based methods currently are still the reference standard for drug susceptibility testing. Xpert MTB/RIF, which simultaneously tests for TB and resistance to rifampicin (the most effective first-line anti-TB drug), is in use in most regions including Ghana. Ghana introduced a rapid molecular test (Gene Xpert MTB/RIF) in February 2013 (Ghana Health Service, 2015).

In addition to all these newer TB diagnostic technologies, clinical suspicion and thorough screening of TB in HIV still plays a vital role.
2.7 Treatment of HIV/TB Co-Infection and Drug Resistant TB.

Tuberculosis disease is treatable and curable. Active, drug-sensitive TB disease is treated with a standard 6-month course (2 months-initiation phase and 4 months-continuation phase) of 4 antimicrobial drugs that are provided with information, supervision and support to ensure adherence and prevent the spread of disease. Majority of TB patients can be cured when drugs are provided and taken appropriately. Through TB diagnosis and treatment, an estimated 49 million lives were saved between 2000 and 2015 (World Health Organization, 2016b).

Treatment of TB/HIV co-infected patients requires the use of first-line (of which Rifampicin and Isoniazid are most potent) and second-line anti-TB drugs as well as antiretroviral (ARTs).

MDR-TB is treated with second-line drugs and is curable; however, options are limited requiring extensive therapy of 9 to 12 months and can take up to 2 years. In May 2016, WHO issued guidance that all cases of RR-TB, including those with MDR-TB are treated with a second-line MDR-TB treatment protocol (World Health Organization, 2016b). Patients with XDR-TB cannot use this regimen and need to be put on longer MDR-TB regimens to which one of the newer drugs (bedquiline and delamanid) may be added (World Health Organization, 2016b).
CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design

A descriptive cross-sectional analysis of TB patient data was carried out.

3.2 Study Site

The study was conducted from February 2013 to December 2017 in three major referral facilities in the Southern part of Ghana. These were the Korle-Bu Teaching Hospital (KBTH), the Greater Accra Regional Hospital-Ridge (GARH), both in Accra, the national capital and the Eastern Regional Hospital (ERH), Koforidua. Specific sites were the Chest Clinic and Fever’s (for HIV) Unit and their Laboratories at the Korle-Bu Teaching Hospital and the TB/HIV Clinics and Laboratories of the two Regional Hospitals. Laboratories in these facilities were sites where TB diagnosis and drug susceptibility testing were carried out upon request by a physician.

The Korle-Bu Teaching Hospital

This is a tertiary hospital located in the Ablekuma South Sub-Metro of Accra and serves as a referral site for patients predominantly in Southern Ghana. It houses the Chest Clinic which serves as the national centre for the management of respiratory diseases but predominantly TB, and it is the centre for the pooling of national data on TB. This facility operates in collaboration with the Fever’s Unit (a designated clinic for HIV/AIDS patients) also situated in the hospital.
Greater Accra Regional Hospital-Ridge

This is an ultra-modern 420-bed capacity secondary facility located in the Accra Metropolis of the Greater Accra region. It runs a 24-hour service serving as a regional hospital and has a catchment area with an estimated population of 4,283,322 inhabitants. However, its immediate catchment areas include suburbs such as Nima, Kanda, Osu, La, Accra New Town, Kotobaabi, Adabraka, Achimota, Airport Residential Area and Accra Central. It offers Out-patient services, Emergency services, specialized services, Laboratory and Radiological services. It serves as a referral centre for the management of TB and HIV cases across the region.

Eastern Regional Hospital (ERH), Koforidua

It is a public healthcare facility located in Koforidua, South Eastern part of Ghana. It is the regional hospital serving as the main referral site for a population of 2,194,508. It is a 400-bed capacity hospital that runs a 24-hour service. It also serves as a referral hospital for the management of TB and HIV cases.

3.3 Study Variables.

Dependent Variable

The dependent variable was TB Drug resistance.

Independent Variables

These included the patient status of bacteriologically confirmed TB case. It included HIV status, previous TB treatment and antiretroviral therapy (ART) initiation status. Other independent variables were age and sex. Details are outlined in Table 1 below.
**Table 3.1: Operational definition of variables**

**Operational definition of variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Operational Definitions</th>
<th>Indicator</th>
<th>Variable type</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dependent Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug resistant-TB</td>
<td>Documented TB patient with resistant to anti-drug susceptibility testing as (any of the following):</td>
<td>Presence of (any of the following):</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td></td>
<td>1. Rifampicin resistance-Resistance to only Rifampicin.</td>
<td>1. Rifampicin resistance only</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Poly resistant TB-resistance to two or more anti-TB drugs but not including both rifampicin and isoniazid.</td>
<td>2. Poly-resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. MDR-TB -Resistance to first-line anti-TB drugs including Isoniazid and Rifampicin.</td>
<td>3. MDR-TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Pre-XDR TB-MDR-TB already acquired resistance to the quinolones or injectable aminoglycosides.</td>
<td>4. Pre-XDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. XDR-TB-MDR plus resistance to fluoroquinolones, and at least one second-line injectable drug.</td>
<td>5. XDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Independent Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Age of patient in years</td>
<td>Age at last birth day</td>
<td>Continuous-discrete</td>
<td>Records review</td>
</tr>
<tr>
<td>Sex</td>
<td>Biological sex of patient</td>
<td>Male or Female</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td>Variables</td>
<td>Operational Definitions</td>
<td>Indicator</td>
<td>Variable type</td>
<td>Source of data</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Tuberculosis status</td>
<td>Bacteriologically confirmed TB via microscopy, culture or Xpert MTB/RIF diagnostic tool</td>
<td>Presence of (any of the following): 1. Microscopy positive TB 2. Xpert MTB/RIF positive TB 3. Culture positive TB</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td>Type of TB patient</td>
<td>Documented type of TB patient as (any of the following):</td>
<td>Presence of (any of the following): 1. Previously treated TB patient 2. Not previously treated TB patient (New)</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td>Type of previous TB treatment</td>
<td>Documented types of previous treatment as (any of the following):</td>
<td>Presence of (any of the following): 1. Relapse 2. Failure 3. Loss to follow-up/Default 4. Other previously treated</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td>HIV status</td>
<td>First Response or ELISA confirmed HIV status</td>
<td>Presence of (any of the following): 1. HIV positive 2. HIV negative 3. HIV status unknown</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
<tr>
<td>Anti-retroviral therapy (ART)</td>
<td>Documentation of initiation of ART in HIV positive TB patients</td>
<td>Presence of (any of the following): 1. Started 2. Not started</td>
<td>Categorical</td>
<td>Records review</td>
</tr>
</tbody>
</table>
3.4 Study Population

The study population was data on TB and HIV/TB co-infected patients captured by the Chest Clinic and Fever’s (for HIV) Unit and their respective Laboratories of the Korle-Bu Teaching Hospital and the TB/HIV Clinics and the Laboratories of the two Regional Hospitals from February 2013 to December 2017.

3.5 Inclusion Criteria

1. Record of client’s TB diagnosis of in the TB record book, MDR-TB record books, Gene Xpert record books, TB culture books, HIV record books of the Korle-Bu Teaching Hospital and the two Regional Hospitals.
3. Drug susceptibility/culture record on TB and HIV/TB co-infected patients must have been documented.
4. The TB record must have the client’s HIV status documented.

3.6 Exclusion Criteria

1. Suspect TB cases diagnosed clinically, smear/Xpert negative but treated for TB.
2. TB cases that were diagnosed at other facilities but sent to the KBTH or GARH for confirmatory test of DST/culture.
3.7 Sample Size Determination.

This was a census of all records meeting the inclusion criteria stated above. The sample size included all TB and HIV/TB co-infected patients whose data were captured by

1. The Chest Clinic and Fever’s (for HIV) Unit and their respective Laboratories of the Korle-Bu Teaching Hospital,

2. The TB/HIV Clinics and the Laboratories of the two Regional Hospitals from February 2013 to December 2017.

3.8 Data Collection Technique.

All microbiologically confirmed pulmonary and extra-pulmonary tuberculosis cases were eligible for the study. Data on TB and HIV/TB co-infected patients were retrospectively collected (using structured data Extraction Form as shown in Appendix A) from records captured by the Chest Clinic and Fever’s (for HIV) Unit and their respective Laboratories of the Korle-Bu Teaching Hospital, the HIV Clinics and their Laboratories of the two Regional Hospitals from February 2013 to December 2017.

Data on TB diagnosis, previous treatment, drug susceptibility profile and demographic characteristics such as age and sex were obtained. Data on drug susceptibility were obtained from the Chest Clinic-KBTH Laboratory, the Greater Accra Regional Hospital Laboratory and the Eastern Regional Hospital Laboratory respectively which performs drug-susceptibility testing (DST), Xpert MTB/RIF and cultures on M. tuberculosis isolated from patients in these facilities. Laboratory records were matched by a combination of name, registration number, date of birth/age, and sex as available for correctness. Records on HIV infection status recorded as a response option as HIV positive, HIV negative and HIV status unknown (refers to HIV status not
documented or documented as unknown) were retrieved from patient record books. These records on HIV status were matched with HIV status from the Fever’s Unit for the KBTH and ART clinics of the two Regional Hospitals. A flow chart for the data collection is as shown in Figure 3.1 below.
Diagnosed TB cases in GARH, ERH and KBTH from February 2013-December 2017

All TB cases with incomplete data and unknown HIV status

Previous TB treatment

HIV +

DR
RR
MDR
PDR
O

No DR

HIV -

DR
RR
MDR
PDR
O

No DR

TB cases with HIV status known

New TB cases

HIV +

DR
RR
MDR
PDR

No DR

HIV -

DR
RR
MDR
PDR

No DR

Key: R = Treatment after relapse; F = Treatment after failure; D = treatment after default; O = other previous treatment; DR = drug resistant-TB; RR = rifampicin resistance; MDR = multi drug resistant-TB; PDR = poly resistant-TB; ART = antiretroviral therapy.

Figure 3.2: Flow chart for data collection for the study.
3.9 Training of Research Assistants

The research assistants, three were trained for three days prior to data collection on proper data collection and as well as on ethical issues.

3.10 Data Processing and Analysis

All data collected were entered into a spreadsheet (Excel) format, cleaned and exported into Stata. Data analysis was done using Microsoft Excel 2016 and Stata (Stata IC) version 14. Continuous variables were summarized with mean, mode and proportion. Categorical variables were summarized with frequency tables, bar graphs or pie charts.

For comparison of categorical variables and significance testing, Pearson’s chi-square ($\chi^2$) tests were used to determine whether an association exists between an exposure and the occurrence or otherwise of an outcome (drug resistant-TB). A $p$-value $<0.05$ was considered statistically significant. Crude and adjusted Odds ratios were calculated for the associations found. Univariate and multivariate analyses were conducted using logistic regression to find the strength of the associations between exposure variables and the outcome variable.

Multivariate analysis was conducted as several variables including HIV status and previous TB treatment have been found to be associated with the development of drug resistant TB strains (Aaron et al., 2004; Campos et al., 2003; Espinal, 2003; Haar et al., 2007; Mac-Arthur et al., 2001; Moro et al., 1998; Pozniak, 2003; Robert et al., 2003; Suchindran et al., 2009; Lukoye et al., 2015; Gehre et al., 2016; Haar et al., 2007; Ormerod, 2005; Suchindran et al., 2009).

The associations of any drug-resistant TB with HIV and anti-TB drug treatment history were analysed separately (any anti-TB drug resistant TB in HIV positives VS anti-TB drug resistant TB in HIV negatives; any anti-TB drug resistant TB in previously anti-TB treated VS any anti-
TB drug resistant TB in new TB cases). Variables (study site, TB site, type of TB patient and type of previous treatment) were adjusted for the odds of TB drug resistance among HIV positive patients and also adjusted (study site, TB site, type of TB patient and HIV status) for the odds of TB drug resistance among previously treated TB patients.

3.11 Quality Control

Data collected were carefully edited and cleaned. The data were double entered into the computer to check for any inconsistencies. Inconsistencies detected were promptly corrected to ensure good quality control. The data was collected together with three assistants between May and June 2018. Personal information and study data were treated privately and with confidentiality during data collection and analysis. Data were stored electronically and secured with alpha-numeric password protection.

3.12 Ethical Consideration

Ethical clearance was obtained from the Ethics Review Committee of Research and Development Unit of the Ghana Health Service through the School of Public Health, University of Ghana. Ethical approval number was GHS-ERC: 032/02/18.

Approval was also sought and obtained from Head of the National TB Control programme, Chest Clinic and Fever’s Unit of the KBTH and the Directors of the two regional Hospitals (Greater Accra and Eastern Regional Hospitals).
Confidentiality of data, electronic and hard copy was assured. Paper copies of personal data were stored in a secured location.
CHAPTER FOUR

4.0 RESULTS

4.1 Distribution of variables at the three study sites

Out of 11432 Tuberculosis cases recorded at the three study sites from February 2013 to December 2017, 9722 met the criteria for inclusion in this study as shown in Figure 4.1 below. HIV status was therefore known for 85.0% of all the TB cases captured. The Korle-Bu Teaching Hospital-Chest clinic (KBTH) had 2376 (24.4%), the Greater Accra Regional Hospital-Ridge (GARH) had 594 (6.1%), and the Eastern Regional Hospital-Koforidua (ERH) documented 6752 (69.5%). Data from the ERH was for the entire region and therefore accounts for skewing of proportions. Results obtained on the distribution of variables in this study are as shown in Table 4.1, Figure 4.2 and Figure 4.3 below.
Diagnosed TB cases in GARH, ERH and KBTH from February 2013-December 2017 = 11432

All TB cases with incomplete data and unknown HIV status = 1710

Previous TB treatment = 589

HIV+ = 146
  - DR = 18
  - RR = 11
  - MDR = 7
  - ART = 38

HIV- = 443
  - DR = 75
  - RR = 34
  - MDR = 36
  - ART = 257

TB cases with HIV status known = 9722

New TB cases = 9133

HIV+ = 2768
  - DR = 1
  - RR = 0
  - PDR = 0
  - ART = 257

HIV- = 6364
  - DR = 7
  - RR = 3
  - ART = 2511

Key: R = Treatment after relapse; F = Treatment after failure; D = treatment after default; O = other previous treatment; DR = drug resistant-TB;
RR = rifampicin resistance; MDR = multi drug resistant-TB; PDR = poly resistant-TB; ART = antiretroviral therapy.

Figure 4.1: Flow chart of data collected for the study.
### Table 4.1: Study distribution of all TB patients by Sex.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>Pearson chi square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=6211</td>
<td>N=3511</td>
<td>N=9722</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study site</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KBTH</td>
<td>1492(24.0)</td>
<td>884(25.2)</td>
<td>2376(24.4)</td>
<td>14.59</td>
<td>0.001</td>
</tr>
<tr>
<td>GARH</td>
<td>422(6.8)</td>
<td>172(4.9)</td>
<td>594(6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERH</td>
<td>4297(69.2)</td>
<td>2455(69.9)</td>
<td>6752(69.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1108(17.8)</td>
<td>671(19.1)</td>
<td>1779(18.3)</td>
<td>10.40</td>
<td>0.034</td>
</tr>
<tr>
<td>2014</td>
<td>1314(21.2)</td>
<td>760(21.6)</td>
<td>2074(21.3)</td>
<td></td>
<td></td>
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<tr>
<td>2015</td>
<td>1201(19.3)</td>
<td>684(19.5)</td>
<td>1885(19.4)</td>
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<tr>
<td>2016</td>
<td>1329(21.4)</td>
<td>659(18.8)</td>
<td>1988(20.4)</td>
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<tr>
<td>2017</td>
<td>1259(20.3)</td>
<td>737(21.0)</td>
<td>1996(20.5)</td>
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<td></td>
</tr>
<tr>
<td><strong>Age group</strong></td>
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<td>N=1068</td>
<td>N=3023</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>4(0.2)</td>
<td>0(0)</td>
<td>4(0.1)</td>
<td>96.02</td>
<td>0.000</td>
</tr>
<tr>
<td>5-14</td>
<td>28(1.4)</td>
<td>22(2.1)</td>
<td>50(1.7)</td>
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</tr>
<tr>
<td>15-24</td>
<td>215(11.0)</td>
<td>154(14.4)</td>
<td>369(12.2)</td>
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<td>25-34</td>
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<td>328(30.7)</td>
<td>680(22.5)</td>
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<tr>
<td>35-44</td>
<td>532(27.2)</td>
<td>237(22.2)</td>
<td>769(25.4)</td>
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<td>45-54</td>
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<td>55-64</td>
<td>236(12.1)</td>
<td>94(8.8)</td>
<td>330(10.9)</td>
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<td>65+</td>
<td>146(7.5)</td>
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<td>223(7.4)</td>
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<td>N=9722</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
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<tr>
<td><strong>Site of TB infection</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Extra P</td>
<td>812(13.1)</td>
<td>581(16.5)</td>
<td>1393(14.3)</td>
<td>24.08</td>
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</tr>
<tr>
<td>Pulmonary</td>
<td>5369(86.4)</td>
<td>2906(82.8)</td>
<td>8275(85.1)</td>
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</tr>
<tr>
<td>Both</td>
<td>30(0.5)</td>
<td>24(0.7)</td>
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<td><strong>Type of TB patient</strong></td>
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<tr>
<td>New</td>
<td>5787(93.2)</td>
<td>3346(95.3)</td>
<td>9133(93.9)</td>
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<tr>
<td>Previous treatment</td>
<td>424(6.8)</td>
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<td>589(6.1)</td>
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<td></td>
</tr>
<tr>
<td><strong>Type of previous treatment</strong></td>
<td>N=424</td>
<td>N=165</td>
<td>N=589</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>231(54.5)</td>
<td>74(44.8)</td>
<td>305(51.8)</td>
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<tr>
<td>Failure</td>
<td>87(20.5)</td>
<td>40(24.2)</td>
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<tr>
<td>Default</td>
<td>94(22.2)</td>
<td>43(26.1)</td>
<td>137(23.3)</td>
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<tr>
<td>Others</td>
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<td>20(3.4)</td>
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<td></td>
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<tr>
<td>Study characteristics</td>
<td>Male</td>
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</tr>
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<td>--------</td>
<td>-------</td>
<td>-------------------</td>
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<tr>
<td></td>
<td>N=6211</td>
<td>N=3511</td>
<td>N=9722</td>
<td>( \chi^2 ) p-value</td>
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</tr>
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<td>HIV status</td>
<td></td>
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<td>Negative</td>
<td>4809(77.4)</td>
<td>1998(56.9)</td>
<td>6807(70.0)</td>
<td>449.90 0.000</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1402(22.6)</td>
<td>1513(43.1)</td>
<td>2915(30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>N=1460</td>
<td>N=1509</td>
<td>N=2915</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not started</td>
<td>1254(85.9)</td>
<td>1366(90.5)</td>
<td>2620(89.8)</td>
<td>1.44 0.229</td>
<td></td>
</tr>
<tr>
<td>Started</td>
<td>152(14.1)</td>
<td>143(9.5)</td>
<td>295(10.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification of TB drug resistance</td>
<td>N=69</td>
<td>N=32</td>
<td>N=101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>31(44.9)</td>
<td>17(53.1)</td>
<td>48(47.5)</td>
<td>0.76 0.682</td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>34(49.3)</td>
<td>14(43.8)</td>
<td>48(47.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poly</td>
<td>4(5.8)</td>
<td>1(3.1)</td>
<td>5(5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of TB drug resistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquired</td>
<td>66(95.7)</td>
<td>28(87.5)</td>
<td>94(93.1)</td>
<td>2.25 0.133</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>3(4.3)</td>
<td>4(12.5)</td>
<td>7(6.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:** N=number; ART=antiretroviral therapy; Extra P=extra-pulmonary; R=rifampicin; MDR= MDR-TB; Poly= poly resistant TB.

In Table 4.1 above, the majority of the cases that were eligible for inclusion in this study were males, 6211 (63.9%). Data from the Eastern Regional Hospital, a regional data made up 69.5% of the cases retrieved. The highest number of cases was recorded in 2014, 2074 (21.3%). Out of the 9722 cases reviewed, data on age was available in 3023(31.1%) cases with a mean age of 41.1(SD=15.3) years and a modal age bracket of 35-44 years. Majority of the case were pulmonary cases (85.1%) \((p<0.001)\) when classified by site of TB infection. However, extra-pulmonary cases were much higher among the females (16.5%) compared to males (13.1%). Data according to the type of TB patient shows that the significant majority were new cases, 9133(93.9%) \((p<0.001)\). Among patients previously treated for TB, females were more (6.8%). As shown in the Table above, 1 in 2 who had been previously treated for TB had relapsed (51.8%).
The Prevalence of HIV among participants was significantly high at 30.0% \( (p<0.001) \). The prevalence of HIV among females (43.1%) is about twice that of males (22.6%) which reflects general HIV sex distribution in Ghana. A significant number of diagnosed TB cases co-infected with HIV were not initiated (89.8%) on anti-retroviral therapy (ART). The review shows that 101(1.0%) TB cases were resistant to TB drugs. These were 48(47.5%) Rifampicin resistant cases, 48(47.5%) MDRs and 5 (5.0%) Poly-resistant cases. There was no Pre-extensively (Pre-XDR) or Extensively drug resistant (XDR) case documented. TB drug resistance proportion among males (68.3%) was more than twice that of females (31.7%) and out of the 101 drug resistant TB cases noted, most 94(93.1%) were acquired.

\[ \text{Figure 4.2: Pattern of reported TB cases over the years.} \]

From the figure above, reported TB cases rose by about 10% from 1779 in 2013 to 2074 cases in 2014 and declined by 11% to 1885 cases in 2015 and with a steady rise over the next two years.
Figure 4.3: Auto correlation prediction of TB cases from 2018-2020.

Projecting into the next three years based on data obtained reviewed shows that cases of TB will decline in 2019 with a later rise in 2020.

4.2 HIV/TB Co-infection

Table 4.2: Distribution of all TB patients by HIV status.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>HIV Status</th>
<th>Study site</th>
<th>Year</th>
<th>N=6807 n(%)</th>
<th>N=2915 n(%)</th>
<th>N=9722 n(%)</th>
<th>( \chi^2 )</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV Status</td>
<td>KBTH</td>
<td>2013</td>
<td>1444(21.2)</td>
<td>932(32.0)</td>
<td>2376(24.4)</td>
<td>214.05</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GARH</td>
<td>2014</td>
<td>533(7.8)</td>
<td>61(2.1)</td>
<td>594(6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ERH</td>
<td>2015</td>
<td>4830(71.0)</td>
<td>1922(65.9)</td>
<td>6752(69.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2016</td>
<td>1385(20.3)</td>
<td>603(20.7)</td>
<td>1988(20.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2017</td>
<td>1441(21.2)</td>
<td>555(19.0)</td>
<td>1996(20.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study characteristics

|                  | HIV Status | Pearson chi-square |  
|------------------|------------|--------------------|---|
|                  | Negative   | Positive           | Total | χ²    | p-value  |
| **Age group**    |            |                    |       |       |          |
| 0-4              | N=2009     | N=1014             | N=3023| 127.08| 0.000    |
|                  | n(%)       | n(%)               | n(%)  |       |          |
|                  | 0(0)       | 4(0.4)             | 4(0.1)|       |          |
| 5-14             | 26(1.3)    | 24(2.4)            | 50(1.7)|       |          |
| 15-24            | 310(15.4)  | 59(5.8)            | 369(12.2)|       |          |
| 25-34            | 441(22.0)  | 239(23.6)          | 680(22.5)|       |          |
| 35-44            | 437(21.8)  | 332(32.7)          | 769(25.4)|       |          |
| 45-54            | 375(18.7)  | 223(22.0)          | 598(19.8)|       |          |
| 55-64            | 239(11.9)  | 91(9.0)            | 330(10.9)|       |          |
| 65+              | 181(9.0)   | 42(4.1)            | 223(7.4)|       |          |
| Missing data     | 4798       | 1901               | 6699  |       |          |
| **Site of TB infection** |            |                    |       |       |          |
| Extra P          | 821(12.1)  | 572(19.6)          | 1393(14.3)| 105.44| 0.000    |
| Pulmonary        | 5958(87.5) | 2317(79.5)         | 8275(85.1)|       |          |
| Both             | 28(0.4)    | 26(0.9)            | 54(0.6)|       |          |
| **Type of TB patient** |            |                    |       |       |          |
| New              | 6364(93.5) | 2769(95.0)         | 9133(93.9)| 8.06  | 0.005    |
| Previous treatment | 443(6.5) | 146(5.0)          | 589(6.1)|       |          |
| **Type of previous treatment** |            |                    |       |       |          |
| N=443            | N=146      | N=589              |       |       |          |
| n(%)             | n(%)       | n(%)               |       |       |          |
| Relapse          | 241(54.4)  | 64(43.8)           | 305(51.8)| 13.61 | 0.003    |
| Failure          | 101(22.8)  | 26(17.8)           | 127(21.6)|       |          |
| Default          | 88(19.9)   | 49(33.6)           | 137(23.3)|       |          |
| Others           | 13(2.9)    | 7(4.8)             | 20(3.4)|       |          |
| **Classification of TB drug resistance** |            |                    |       |       |          |
| N=82             | N=19       | N=101              |       |       |          |
| n(%)             | n(%)       | n(%)               |       |       |          |
| R                | 37(45.1)   | 11(57.9)           | 48(47.5)| 1.83  | 0.400    |
| MDR              | 40(48.8)   | 8(42.1)            | 48(47.5)|       |          |
| Poly             | 5(6.1)     | 0(0)               | 5(5.0)|       |          |
| **Type of TB drug resistance** |            |                    |       |       |          |
| Acquired         | 78(95.1)   | 16(84.2)           | 94(93.1)| 2.84  | 0.092    |
| Primary          | 4(4.9)     | 3(15.8)            | 7(6.9)|       |          |

**Key:** N=number of cases; Extra P=extra-pulmonary; R=rifampicin; MDR= MDR-TB; Poly= poly resistant TB.

Of the 2915 HIV positive cases, more than two-thirds (65.9%) occurred in cases captured at the Eastern regional hospital with a prevalence of 28.5%. the KBTH however, had the highest HIV
prevalence of 39.2%. HIV prevalence was noted to be 30.0% among the reviewed population with the highest proportion occurring in 2014, 656 (22.5%). A Major proportion of TB/ HIV co-infected cases 332(32.7%) were within the 53-44 age group. A significant proportion of the study population that were HIV positive were diagnosed in Pulmonary TB patients (79.5) with a statistically significant relationship between site of TB disease and HIV status ($p=0.000$). Newly diagnosed TB patients formed the majority of HIV positive cases (95.0%). HIV prevalence among previously treated TB patients was 24.9%. Relapsed (43.3%) and defaulted (33.6%) TB patients were the major contributors to HIV positivity among previously treated patients. Among drug resistant TB cases, HIV prevalence was 18.8%. Rifampicin and MDR in the TB population was 0.5% each. In Rifampicin resistant cases, HIV prevalence was 22.9% while Rifampicin resistance and MDR prevalence among HIV positive case was 0.4% and 0.3% respectively. Tuberculosis drug resistance among HIV cases was 0.7% and predominantly acquired (84.2%).
Figure 4.4: HIV prevalence among TB patients reported across the three study sites.

In the figure above, HIV infection rate of 30% was recorded among the TB patients.
Table 4.3: Logistic regression showing Association between TB drug resistance and study characteristics.

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>DR N=101</th>
<th>Pearson chi-square p-value</th>
<th>COR(95% CI) p-value</th>
<th>AOR(95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KBTH</td>
<td>27(26.7)</td>
<td></td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>GARH</td>
<td>30(29.7)</td>
<td>103.05 0.000</td>
<td>4.62(2.72-7.85)0.000</td>
<td>17.14(7.77-37.8)0.000</td>
</tr>
<tr>
<td>ERH</td>
<td>44(43.6)</td>
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<td>0.57(0.35-0.92)0.022</td>
<td>0.76(0.45-1.29)0.317</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5-14</td>
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<td>2.30(0.56-9.56)0.249</td>
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</tr>
<tr>
<td>15-24</td>
<td>12(11.9)</td>
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<td>1.22(0.45-3.29)0.700</td>
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<tr>
<td>25-34</td>
<td>22(21.8)</td>
<td>5.79 0.564</td>
<td>1.21(0.48-3.02)0.684</td>
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</tr>
<tr>
<td>35-44</td>
<td>21(20.8)</td>
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<td>1.02(0.40-2.55)0.974</td>
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<td>45-54</td>
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<td>1.25(0.49-3.15)0.635</td>
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<tr>
<td>55-64</td>
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<td>1.96(0.76-5.06)0.162</td>
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<td>65+</td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>69(68.3)</td>
<td>0.87 0.351</td>
<td>Ref</td>
<td>0.82(0.53-1.25)0.352</td>
</tr>
<tr>
<td>Female</td>
<td>32(31.7)</td>
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<td>TB site</td>
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</tr>
<tr>
<td>Extra P</td>
<td>4(4.0)</td>
<td>9.65 0.008</td>
<td>0.24(0.08-0.66)0.006</td>
<td>0.83(0.26-2.69)0.755</td>
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<tr>
<td>Pulmonary</td>
<td>97(96.0)</td>
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<td>Ref</td>
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<tr>
<td>Type of TB patient</td>
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</tr>
<tr>
<td>New</td>
<td>8(7.9)</td>
<td>1326.90 0.000</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Previous treatment</td>
<td>93(92.1)</td>
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<td>213.87(103.3-442.8)0.000</td>
<td>348.61(153.71-790.6)0.000</td>
</tr>
<tr>
<td>Type of previous treatment</td>
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</tr>
<tr>
<td>Relapse</td>
<td>32(34.4)</td>
<td></td>
<td>0.20(0.12-0.33)0.000</td>
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</tr>
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<td>Failure</td>
<td>47(50.5)</td>
<td>57.13 0.000</td>
<td>Ref</td>
<td>0.13(0.06-0.28)0.000</td>
</tr>
<tr>
<td>Default</td>
<td>10(10.8)</td>
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<td>0.43(0.13-1.34)0.147</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4(4.3)</td>
<td></td>
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</tr>
<tr>
<td>HIV status</td>
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<td></td>
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<tr>
<td>Negative</td>
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<td>6.07 0.014</td>
<td>Ref</td>
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<tr>
<td>Positive</td>
<td>19(18.8)</td>
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<td>ART</td>
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</tr>
<tr>
<td>Not started</td>
<td>8(42.1)</td>
<td>47.79 0.000</td>
<td>Ref</td>
<td>12.6(5.03-31.59)0.000</td>
</tr>
<tr>
<td>Started</td>
<td>11(57.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: N=number; ART=antiretroviral therapy; Extra P=extra-pulmonary; DR=drug resistant-TB;
COR=crude odds ratio; AOR=adjusted odds ratio; CI=confidence interval.
Review of 101 TB cases that were resistant to TB drugs showed Eastern region (43.6%) recording the highest proportion of the cases. TB drug resistance proportion among males (68.3%) was more than twice that of females (31.7%). Prevalence of drug resistance among new TB patients was 0.08% compared to 15.8% among previously treated TB patients.

Drug resistant TB cases had 18% reduced odds of being females (OR=0.82, CI=0.53-1.25). Again drug resistant TB patients had a 31% reduced odds of being HIV positive (AOR=0.69, CI=0.39-1.22), though this was not statistically significant (p=0.215). The Site of TB infection was not statistically significant with the development of TB drug resistance (p=0.755).

Previous TB treatment was associated with the development of drug resistant TB (p<0.001). Patients who had drug resistance TB were more than 348 times likely to have had previous TB treatment (AOR=348.61, CI=153.71-790.60).

Patients started on ARTs had 13 times the odds of developing TB drug resistance (OR=12.60, CI=5.03-31.59) and there was a significant association between starting ART and the development of drug resistant TB (p<0.001).
Figure 4.5: Prevalence of drug resistance by study site.

Across the three study sites, the Korle-Bu Teaching hospital saw the highest TB drug resistance prevalence, 1.1% which is above the general prevalence of the three sites altogether. The eastern regional hospital recorded the least prevalence of 0.7%.
The figure above shows an increasing trend in the TB drug resistance cases across the study period. A prevalence of 1.1% was recorded in 2013 and saw a decline to 0.3% in 2014 followed by a steady rise to 1.5% in 2017.

**Figure 4.6:** Pattern of DR-TB prevalence.

The figure above shows an increasing trend in the TB drug resistance cases across the study period. A prevalence of 1.1% was recorded in 2013 and saw a decline to 0.3% in 2014 followed by a steady rise to 1.5% in 2017.

**Figure 4.7:** Auto correlation prediction of overall Drug Resistance among TB patient from 2018-2020.
Projected prediction as in Figure 4.7 above shows that drug resistant TB case prevalence will continue to rise in the next three years with a decline in 2020.

**Figure 4.8:** Resistance patterns among TB patients across the study sites

The figure above shows TB mono-drug resistance to Rifampicin only (44.8%) as the most common form of resistance followed by resistance to Rifampicin and Isoniazid combination (21.6%). Resistance pattern containing Rifampicin and Isoniazid (MDR) accounts for 50.9%. 12.9% of all TB drug resistant cases were against all four medications susceptibility testing is conducted for.
Table 4.4: Auto correlation prediction of Drug Resistance pattern among TB patient from 2018-2020.

<table>
<thead>
<tr>
<th>Year</th>
<th>R</th>
<th>HR</th>
<th>HS</th>
<th>RS</th>
<th>HRE</th>
<th>HRS</th>
<th>RES</th>
<th>HES</th>
<th>HRSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>39</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
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**Key:** R=rifampicin; H= isoniazid; S= streptomycin; E=ethambutol.

Three years’ projection shows that resistance to Rifampicin will continue to dominate the pattern of TB drug resistance.
CHAPTER FIVE

5.0 DISCUSSION

5.1 HIV testing in TB patients and TB/HIV co-infection.

Co-infection of TB patients with HIV remains a challenge globally. The WHO therefore, recommends systematic screening for HIV among TB patients as an essential component of the TB care package. This study shows good adherence to this policy as 85% of the TB cases were documented to have known HIN status. This finding is similar to a report from the Volta region of Ghana (Osei et al., 2017) and other parts of Africa (Tarekegne et al., 2016). This 85.0% is higher than the WHO global estimate of 55.0% and 81% in the African sub-region in 2015 (World Health Organization, 2016b). This is significant and must be sustained and improved upon through continuous training and emphasis on proper documentation.

Analysis of the five-year TB data shows a 30.0% prevalence of HIV infection among TB patients. The HIV sero-prevalence in TB patients in this study is higher than the current global estimate of 15% but much lower than the estimate from the African Region (32-36%) (World Health Organization, 2016b). Another study reported a 2.9% -72.3% prevalence with a pooled prevalence of 23.5% (Gao J, Zheng P, 2013). In southern Africa, 50% prevalence has been reported (World Health Organization, 2016b). This HIV/TB co-infection prevalence of 30% is higher than findings from studies done in India (18.9%) and Brazil (19%) (Kamath et al., 2013; Prado et al., 2014).
In Ghana, this current HIV/TB co-infection rate also consistent with hospital studies done reporting a prevalence rate of 25-30% but higher than the national average of 24% (World Health Organization, 2014). In five districts of the Volta region of Ghana, a study reported that reported a 18.2% TB/HIV co-infection, lower than the 30% found in this current study (Osei et al., 2017). This difference could be attributed to disparities in general HIV prevalence rates in these regions. HIV rates in Greater Accra region and the Eastern region where this study was conducted has been among the highest in the country over the past five years compared to that of the Volta region.

In this study, the 43.1% prevalence of HIV among females is about twice that of males (22.6%). A similar finding has been reported in the Volta region (OR=1.79; 95% CI=1.38–2.31; \( p < 0.001 \) (Osei et al., 2017). The HIV prevalence of 43.1% and 22.6% among females an males is also consistent with global and sub-Saharan Africa studies (UNAIDS, 2017). This finding suggests that women continue to be the major sufferers with regards to TB/HIV co-infection.

**5.2 Tuberculosis drug resistance prevalence.**

In this study, the prevalence of drug resistance TB (DR-TB) was found to be 1.0%. The World Health Organization global report on overall resistance to any of the anti TB drug was noted to be 6.2% (World Health Organization, 2008b). In other global reports, a prevalence of 2.4-44.8% has been noted (Campos et al., 2003; Haar et al., 2007; Suchindran et al., 2009). Finding in this study is low compared to reported global prevalence and in some parts of the African region where the rate of 2.2-5.3% have been reported in the literature (Lukoye et al., 2011; Mac-Arthur et al., 2001). In Ghana, the current 1.0% observed DR-TB rate is also low compared to higher DR-TB prevalence of 13.0% reported (Gehre et al., 2016). The current level of DR-TB could indicate good TB control programs in these three study sites.
The rifampicin and MDR-TB in the TB population studied was found to be 0.5% each. This rate is low in contrast to the previously reported prevalence (Gehre et al., 2016). This current study has however shown evidence of an increasing trend in the prevalence of drug resistant-TB cases over the 5-year period in contrast to other studies (Musa et al., 2017). Global MDR-TB rate in 2015 accounted for 3.3% of all TB cases worldwide (World Health Organization, 2016b) and this is high compared to findings in this study. The 0.5% prevalence rate found in this study is also low compared to WHO estimates of MDR-TB prevalence of 1.9% in Africa (Zignol et al., 2012). In a Ugandan studies, MDR-TB rate was reported to be 2.3% (Lukoye et al., 2011). Data from several African countries (Malawi, Burundi, S. Africa, Central African Republic and kenya) have suggested MDR-TB rate ranging from 1.4% to 11.6% (Githui et al., 2004; Lin et al., 2004; Sanders et al., 2006). A 2013 meta-analysis of studies done in Africa reported a pooled prevalence of 1.5% (Lukoye et al., 2015). Another pooled prevalence of 2.1%, was demonstrated in cases of TB in SSA (Musa et al., 2017).

Multi drug resistant-TB survey in Western European and three SSA countries demonstrated a similar low prevalence of MDR-TB cases (prevalence range: 0.0-22.3 and 0.6–2.0) (Sanchez-Padilla et al., 2013; World Health Organization, 2008b). This current study’s findings are consistent with a systemic review in 2009 (Suchindran et al., 2009). In South Africa, levels of MDR-TB rate is high in comparison to other countries of SSA(World Health Organization, 2013), possibly fuelled by high nosocomial transmission rates in the context of very high rates of TB/HIV co-infection reported in this country.

There were no Pre-extensively (Pre-XDR) or Extensively drug resistant (XDR) case found in this study contrary to studies done suggesting the emerging threat of Pre-XDR (Gehre et al., 2016).
Any form of Tuberculosis drug resistance prevalence among HIV cases was 0.7%. This is low compared to global prevalence among HIV positive patients (World Health Organization, 2016b). Also Rifampicin resistance and MDR prevalence among HIV positive case was found to be 0.4% and 0.3% respectively and low compared MDR-TB reported to range from 2.4-44.8% (Haar et al., 2007; Suchindran et al., 2009) and in the SSA region it has been between 2.2-5.3% (Mac-Arthur et al., 2001).

The development of TB drug resistance complicates TB treatment due to a limited number of drugs available for TB treatment. Development of drug resistance in a TB patient also extends the treatment period and increases pill burden. The increased pill burden may lead to poor drug adherence, which lead to more and other forms of TB drug resistance, a cycle which makes controlling TB and its eventual eradication very difficult. It is there necessary that measures are put in place to mitigate against any form of TB drug resistance, no matter the rate since epidemic levels could curtail gains made so far.
5.3 HIV/TB co-infection and development of drug resistant-TB.

Although HIV infection has been established to play a significant role in the propagation of the TB epidemic globally, its role in the development of TB drug resistance has not been conclusive. In this study, HIV co-infected TB patients had a 69% reduced odds of being drug resistant TB compared to HIV negative TB patients (AOR=0.69, CI=0.39-1.22), though this was not statistically significant ($p=0.215$). This finding is consistent with other recent studies that found no significant association between development of drug resistant-TB and HIV co-infection (Espinal et al., 2001; Lukoye et al., 2011, 2015; Quy et al., 2006; Urassa et al., 2008). On the other hand, other studies have found significant association between HIV infection and the development of drug resistant TB (Aaron et al., 2004; Campos et al., 2003; Espinal, 2003; Haar et al., 2007; Mac-Arthur et al., 2001; Moro et al., 1998; Pozniak, 2003; Robert et al., 2003; Suchindran et al., 2009). This variation could be attributed to differences in the HIV prevalence rate and as a result, study areas with low HIV infection rate compared to TB reporting statistically significant associations between HIV infection and the development of TB drug resistance. However, in places where there are high levels of MDR-TB rates possibly fuelled by high nosocomial transmission rates in the context of very high rates of TB/HIV co-infection, such studies could potentially skew results.

Patients started on anti-retroviral therapy (ART) had 13 times increased odds of developing TB drug resistance (OR=12.60, CI=5.03-31.59). There was significant association between starting ART and development of drug resistant TB ($p<0.001$). Findings in this study are consistent with other studies (Ammassari, 2001). However, this is in contrast to other studies that did not find significant associations between any drug resistance or MDR-TB and ART among the HIV co-infected patients (Lukoye et al., 2011).
5.4 Previous TB treatment and development of drug resistant TB.

There was an increased presence of drug resistance-TB (15.8%) among previously treated TB patients in this study compared to treatment naïve (New) patients. A study by WHO from 2002 to 2007 documented an estimated 60% drug resistance prevalence among previously treated TB patients (World Health Organization, 2008b). This figure (60%) is almost four time the findings in this study (15.8%). Global drug resistance-TB average reported by WHO among previously treated TB patients was 20.2% (World Health Organization, 2010). According to Haar et al, 2007 drug resistance was reported in 21.6% previously treated patients (Haar et al., 2007). Although this current finding (15.8%) is high, it is low compared to reported global figures (60%, 20.2% and 21.6%) (World Health Organization, 2008b). In the Sub-Saharan African context, this finding is however consistent with WHO report of 0.1–40 % for Mali, Guinea-Bissau, Ghana and Burkina Faso. In a 2011 study in Uganda, 28.3% prevalence was noted in previously treated cases (Lukoye et al., 2011) and in 2015, a pooled data also reported TB drug resistance rate was 21% of previously treated TB cases, higher than found in this study (Lukoye et al., 2015).

Several studies have shown evidence of significant association between the development of TB drug resistance and previous treatment for TB (Gehre et al., 2016; Haar et al., 2007; Ormerod, 2005; Suchindran et al., 2009). Just like those other studies, this study found previous TB treatment to be significantly associated with the development of drug resistant TB both before ($p<0.001$) and after ($p<0.001$) adjustment by multivariate analysis. Patients who had drug resistance TB were more than 348 times likely to have had previous TB treatment (AOR=348.61, CI=153.71-790.60). Findings from neighbouring countries such as Nigeria (Ani et al., 2009; Daniel & Osman, 2011; Kehinde & Adebiyi, 2013; Lawson et al., 2011; Otu et al., 2014) and Burkina Faso (Sangare L, Diande S, Ouedraogo G, 2011) have also found significant relationship.
between previous TB treatment and TB drug resistance. A history of prior TB treatment remains an important risk factor for drug resistant-TB (Jindani & Enarson, 2015; Ormerod, 2005; Suchindran et al., 2009) as shown in this studies.

5.5 Limitations.

1. This study was limited by the occurrence of missing data from available record books due to poor documentation was a major limitation.
6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion.

At 85%, this study reveals that screening for HIV among TB patients at the three study sites is high. This indicates that more than 8 out of 10 cases. This could be attributed to adherence to policy on documentation of HIV status of all TB cases diagnosed. The prevalence of HIV infection among TB patients is high (30.0%) and twice global estimate and it is on the increase.

The prevalence of drug resistance TB was found to be low (1.0%) in the five years covered by this study. Rifampicin and MDR-TB in the TB population studied was also low and there were no Pre-extensively (Pre-XDR) or extensively drug resistant (XDR) case found in this study. Tuberculosis drug resistance prevalence among HIV cases was also low (0.7%). There was no statistically significant association between HIV status and the development of TB drug resistance ($p=0.215$).

Patients started on anti-retroviral therapy (ART) had increased odds of developing TB drug resistance (OR=12.60, Cl=5.03-31.59) and there was significant association between starting ART and development of drug resistant TB ($p<0.001$). Prevalence of drug resistance was high among previously treated TB patients (15.8%) and previously treated TB patients were more likely to develop drug resistance TB (AOR=348.61, CI=153.71-790.60) and this association was statistically significant ($p<0.001$). In patients who have been previously been treated for TB, the threshold for drug resistance should be lowered. Routine surveillance of resistance to anti-TB drugs will improve timely recognition of resistant TB cases.
This current study also depicts gaps in documentation on drug resistant-TB cases across the study sites.

6.2 Recommendation.

To the National TB Control Programme (NTCP):

1. The NTCP should assess the national prevalence of TB and establish the drug resistance pattern across the country.

2. Further studies should be conducted to determine factors contributing to the development of TB drug resistance.

3. It is also recommended that the National TB control programme maintain continuous drug resistant-TB surveillance through healthcare facilities using disease control officers.

To Health care facilities;

1. They should maintain and promote TB drug resistance surveillance activities.

2. Health care facilities should collaborate with the NTCP towards the control of TB drug resistance.
REFERENCES


https://doi.org/10.1186/s12889-015-1614-8


### APPENDICES

#### APPENDIX A

Sample of data extraction instrument.

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*Key:* Sex= male/female; HIV status= positive/negative/unknown; TB diagnosis= smear/xpert/culture; TB site= pulmonary/extrapulmonary/both; Type of patient= new/previously treated; type of previous treatment= relapse, failure/default/others; DST status= unknown/done; Drug sensitivity pattern= H/R/E/S/HR/HE/HS/ES/RS/HRE/HRS/RES/HES/HRSE; Classification of resistance= Rif only/Poly/MDR/XDR; Type of resistance= acquired/primary; CPT= septrin therapy started/not started; ART status= antiretroviral started/not started; Year= 2013/2014/2015/2016/2017.
APPENDIX B

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App 18/2/18
Your Ref. No.

Benjamin Saka Awuku-Fremont
University of Ghana
School of Public Health
Legon, Accra

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

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<td>GHS-ERC Decision</td>
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This approval requires the following from the Principal Investigator:

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol.

SIGNED: ..................................................
DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIR PERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra