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FACTORS ASSOCIATED WITH MULTI-DRUG RESISTANT (MDR) TUBERCULOSIS AMONG SUSPECTED MDR-TB CASES IN EASTERN REGION, 2014 – 2018

BY

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DECLARATION

I, **Emmanuel Tettey Sally**, hereby declare that, apart from specific references which have been duly acknowledged, this dissertation is my own work produced from research under the supervision of Dr. Bismark Sarfo and that it has not been presented elsewhere in part or whole.

…… …….

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(Student)

……. ……

Dr. Bismark Sarfo DATE

(Academic Supervisor)

DEDICATION

To my wife Abigail, children (Emmanuel, Anusia and Bryan) and late parent (Mr. E. K. Sally & Madam Peace Okumka).

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I thank God for the opportunity and the abundant Grace offered me.

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ABSTRACT

Background: Tuberculosis (TB) is a global public health menace especially in developing countries where it contributes significantly to the top ten causes of mortality. In Eastern region, the TB burden remains high and priority. The increasing trend of anti-TB drug resistance is a great challenge. This study assessed the resistance pattern and factors associated with MDR-TB cases among suspected MDR-TB cases in Eastern region, from 2014 to 2018.

Methods: This study was conducted in the Eastern region of Ghana using medical records from 1st January 2014 to 31st December 2018. Variables studied were socio-demographic factors, clinical, anthropometric and laboratory characteristics. Medical records were entered into excel and imported into STATA version 15. Data were cleaned and analyzed using STATA statistical analysis. Frequencies, proportions and tables were generated. Pearson's Chi-square test was used to determine factors associated with MDR-TB cases and multiple logistic regression was used to determine the magnitude of association. A test of significance was set at 0.05.

Results: All forms of MDR-TB accounted for 9.3% (47/503, 95% CI: 6.9-12.2) of cases with 39.5% among new cases and 6.9% among previously treated cases. The overall resistance to at least any of the first line anti-TB drugs was 39% (196/503) with Rifampicin been the most resistant. HIV positive test results (aOR=3.80, 95% CI: 1.09-13.26), type of case (aOR=0.07, 95% CI: 0.05-0.24) and sputum smear positive results (aOR=12.88, 95% CI: 5.47-30.34) were significantly associated with MDR-TB.

Conclusion: One in every ten suspected MDR-TB case was confirmed MDR-TB. Burden of MDR-TB was high in newly infected cases. Factors associated with MDR-TB were HIV positive results, sputum smear positive results and type of case. Therefore, improving early case detection and treatment, building capacity of laboratory for Drug Susceptibility Testing (DST), strengthening TB infection control and prevention activities and complying to DOTS strategy are recommended to minimize the menace of MDR-TB.

Keywords: MDR-TB, Drug resistance, Tuberculosis

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ABBREVIATIONS/ACRONYMS

AIDS	-	Acquired Immune Deficiency Syndrome
BMI	-	Body Mass Index
DOTS	-	Directly Observed Treatment Short course
DST	-	Drug Susceptibility Testing
E	-	Ethambutol
H	-	Isoniazid
HIV	-	Human Immunodeficiency Virus
IPC	-	Infection Prevention and Control
IUATLD (UNION)	-	International Union Against Tuberculosis and Lung Diseases
MDR-TB	-	Multi-Drug Resistant Tuberculosis
MTB	-	*Mycobacterium tuberculosis*
MTB-RR	-	*Mycobacterium tuberculosis* – Rifampicin Resistant
NTM	-	Non-Tuberculous Mycobacteria
NTP	-	National TB control programme
R	-	Rifampicin
S	-	Streptomycin
TB	-	Tuberculosis
WHO	-	World Health Organization
XDR-TB	-	Extensive Drug-resistant tuberculosis
Z	-	Pyrazinamide”

DEFINITION OF TERMS

Body Mass Index: "Derived from anthropometric measures (weight and height) used widely in Nutrition. Also, a clinical indicator for determining the nutritional status in adults. WHO standard reference classifies individuals with BMI <16 as severely malnourished, 16 to 18.5 to be moderately malnourished and BMI >18.5 to <25 are classified as normal.

Drug-Susceptibility Testing (DST): An in vitro testing using either phenotypic methods to determine susceptibility or molecular techniques to detect resistance-conferring mutations to a specific medicine.

Extensive drug resistance (XDR): resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

First line TB drugs: These are medications used as the first choice for treating TB disease. They include; Isoniazid (H/Inh), Rifampicin (R/Rif), Pyrazinamide (Z/Pza) and Ethambutol (E/Emb).

Mono-resistance: resistance to one first-line anti-TB drug only

Multidrug resistance (MDR): resistance to at least both Isoniazid (H) and Rifampicin (R).

Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin.

Previously treated: Any anti-TB regimen received in the past for one month or more, whether first- or second-line. These are also referred to as retreatment cases that can further be classified by the outcome of their most recent course of treatment into four categories

namely relapse, treatment after failure, treatment after loss to follow-up and other previously treated.

Relapse: patients treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)

Treatment after failure: patients who have previously been treated for TB and their most recent course of treatment failed thus they had a positive sputum smear or culture result at month 5 or later during treatment.

Treatment after loss to follow-up: patients previously been treated for TB and were declared 'lost to follow-up' at the end of their most recent course of treatment.

Other previously treated: patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Rifampicin Resistance (RR-TB or MTB-RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR

Suspected MDR-TB: cases of treatment failure; cases with Gene Xpert results confirming MTB-RR; a patient from known high-risk group such as health workers, HIV/AIDS; a symptomatic patient who had a close contact with confirmed MDR-TB patient; a patient who remains smear positive after 2 months of treatment (new cases); or remains smear positive after 3 months of retreatment with first-line treatment (retreatment cases such as defaulter and relapse)

Treatment failure: A TB patient who whilst on treatment remained smear positive, become positive again for sputum smear or culture at month five and beyond whilst on treatment or after commencement of treatment.

Extra-pulmonary TB: Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. abdomen, genitourinary tract, joints and bones, lymph nodes, meninges, pleura, skin.

Pulmonary TB: Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

New case of TB: A patient who has never been treated for TB or has taken anti-TB drugs for less than one month."

CHAPTER ONE

INTRODUCTION

1.1: Background to the study

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* that most commonly affects the lungs (WHO, 2018b). It remains a major public health burden. Globally, TB is among the top 10 causes of mortality and the leading cause from a single infectious agent (above HIV/AIDS). It affects millions of people each year. Generally, 90% of people infected are adults with higher proportion recorded in males than females; approximately 2:1 (WHO, 2018a).

People affected with pulmonary TB are often infectious and can spread the disease via coughing, sneezing or talking since these acts expels TB causative agents into the air. Individuals who also breathe in the bacteria become infected with TB but will not necessarily become sick with the disease (WHO, 2018b). However, when the bacteria go on to overcome the body's immune system, the person then becomes ill with TB.

Someone infected with TB shows several symptoms based on the part of the body affected. For TB classified as pulmonary, critical symptoms include cough with production of sputum which could be bloody in extreme cases, chest pain and shortness of breath. Aside the critical ones, generic symptoms include sweating in the evening, fever especially in the evening, inability to eat well, overall tiredness and muscle pains. If the person is left untreated, this person can infect about 10 to 15 people every year (WHO, 2018b).

Diagnosis of TB are done mainly by clinical assessment, bacteriological and radiological investigation. The examination of a sputum smear by microscopy developed over more than 100 years is the simplest, cheapest and most direct way to detect the availability of TB bacteria which helps to confirm pulmonary TB infection usually within a day or two (WHO, 2018a). However, to evaluate actual drug susceptibility, there is the need to grow the detected bacteria in a standard laboratory which can last between 6 and 16 weeks. It is the possible way of identifying the drug-resistant types of TB. Culture-based results forms the current reference standard and require more advanced laboratory capacity. Another recent diagnostic test with much better accuracy than sputum smear microscopy is the rapid molecular test, which can provide results in 2 hours; the only rapid test currently recommended by WHO is the Xpert© MTB/RIF assay (Cepheid, USA) (Ghana NTP, 2012c; WHO, 2018a). Sometimes, X-ray can be used but this finding may only be indicative of TB but usually need confirmation by means of other tests.

Globally, over 10 million people were infected in 2017, more males were affected than women and children. All countries reported TB cases amongst all age groups. It affected about 90% of adults (aged ≥15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries. Averagely, 1.8 million deaths recorded are linked to TB, with most (95%) emanating from the countries where resources are known to be limited (WHO, 2017, 2018a).

The TB situation is threatened by the rise in drug resistant TB cases globally. Resistance to drugs occur at the molecular level when genes responsible for the specific form of drug

resistance of *Mycobacterium tuberculosis* develop a spontaneous mutation uncontrollably (Pascopella & Flood, 2016). WHO indicates that Multi-Drug Resistance (MDR) TB is considered as a case with resistance to at least both Isoniazid and Rifampicin, the most commonly used and potent medicines in the current recommended first-line treatment regimen. Different patterns of drug resistance come with several implications for treatment and management. For monitoring purposes, drug-resistant cases are classified in categories based on Drug Susceptibility Testing (DST) in clinical isolates confirmed to be *Mycobacterium tuberculosis.*

WHO considers Tuberculosis drug resistance (DR-TB) as resistance to any of the anti-TB drugs either the first line or the second line. This generally means resistance to at least one of the anti-TB drugs especially isoniazid and rifampicin, fluoroquinolones, injectable drugs (amikacin, kanamycin and capreomycin and aminoglycosides).

The process involved in resistance could be primary or secondary. In the primary resistance, the new patient gets infected with the active *Mycobacterium tuberculosis* which is a resistant strain to anti-TB medications. The latter is sometimes referred to as the acquired resistance. In this situation, patients first get infected with the sensitive form of bacillus for tuberculosis. It implies that available anti-TB medications can effectively cure them if treatment regimen is well adhered to as prescribed. Where the opportunity is abused and current medications are no longer able to treat such cases, the strains become resistant making it difficult to manage.

Globally, during the year 2017 about 160,684 cases were detected and notified as MDR/RR-TB. Almost 500,000 people were estimated to have developed MDR-TB with about half of these cases reported by China, India and the Russian Federation (World Health Organization, 2017). In developing countries, the burden of MDR-TB is high mostly amongst individuals who have received treatment for TB using anti-TB drugs before compared with TB cases who are new (Otchere et al., 2016). Immediate measures are required to widen geographical access, general performance, methods of diagnosing focusing on quality, opportunities for appropriate treatment and support for drug-resistant TB cases because of the threat they pose to society (WHO, 2018a).

Some solutions have been proposed to control drug-resistant TB, these include; ensuring that TB patients are cured the first time of infection, provision of easy and quality access to diagnosis, making sure that we adhere to infection prevention and control protocols especially within health facilities, and lastly ensuring the appropriate use of recommended second line drugs currently available for use (WHO, 2016b).

1.2: Problem statement

The multidrug resistant TB has become an issue of public health concern globally and the menace is considered to be multifactorial (Kyu et al., 2018; Pascopella & Flood, 2016). Its emergence in recent decades have complicated the overall TB control efforts. Case management get complex by economic and social costs that patients incur while seeking help and on treatment (Pascopella & Flood, 2016). The management of such cases is extremely toxic and requires longer duration (WHO, 2016b). Ghana have been identified

among the top countries with high burden of TB/HIV coinfection which requires urgent attention (Addo et al., 2018).

According to the 2018 WHO report on Tuberculosis, the prevalence of MDR-TB in Ghana is 1.5% and 17% among new and previously treated cases, respectively. The drug resistance distribution of TB is not well documented and known, and there is paucity of information regarding MDR-TB strains in a relatively high TB/HIV burden country like Ghana. Addo et al, in 2018 also reported MDR-TB burden to be 1.4% after the first national survey. A review of the 2017 annual TB report indicates that, Eastern region records about 1500 TB cases annually of which 10% remain suspected MDR-TB cases. According to the NTP and WHO guidelines, all suspected MDR-TB cases must get diagnostic services of Gene Xpert and DST for confirmation at approved facilities. The routine testing for resistance among these selected patients presents an opportunity to add to the body of knowledge on the topic. There is an increasing trend in confirmed MDR-TB cases from 4 cases in 2014 to about 20 cases in 2017 as institutional data shows (ERHD, 2018).

For effectiveness of the TB control program, managers and policy makers require answers to three main questions, thus what is the burden? What are the strains circulating and what are the associated factors? In this regard, the study seeks to answer these questions by estimating the burden, describing the drug-resistance distributions of *Mycobacterium tuberculosis* strains amongst MDR-TB suspected clients and assessing the factors associated with MDR-TB cases.

1.3: Justification

Increasing number of suspected cases of MDR-TB have been reported in the region especially since 2014. This general observation supports the global concern of how drug resistance is retarding the attainment of goals for the TB control program. Recently, there is a growing concern in the area of TB drug resistance, but as a region no conscious effort have been made to review local data regarding the pattern, burden and associated factors with MDR-TB cases. This study will help to bridge the gap in this field, contribute to national and global pool of evidence for policy direction. Eventually, client care, case management and preventive measures will be improved and more focused based on availability of local data for action.

1.4: Objectives of the study

1.4.1: General objective

- To determine factors associated with MDR-TB among suspected MDR-TB cases in Eastern region, 2014 – 2018

1.4.2: Specific objectives

1. To describe the drug resistance pattern of *Mycobacterium tuberculosis* to the first line TB drugs
2. To estimate the burden of MDR-TB among suspected MDR-TB cases
3. To determine the factors associated with MDR-TB cases among suspected MDR-TB cases

1.5: Conceptual framework: factors associated with MDR-TB

MDR-TB have become a great concern to global public health. WHO have indicated severally that to attain targets of TB control, every single case of drug resistance must be considered as an emergency for action. It has ensured that MDR-TB indicators are included in all TB control programs for routine monitoring by member countries (WHO, 2010). The conceptual framework in Figure 1shows briefly the factors that could be associated with MDR-TB cases with details in the literature review chapter. The main outcome of the dependent variable is MDR-TB. All cases of TB need critical attention, but the ones considered as suspected MDR-TB needs that urgency the more due to the threat to public health (Gandhi et al., 2010). One of the approaches in handling MDR-TB burden is early detection, which is based on clinicians ability to suspect using standardized case definition. In the TB case management, suspected MDR-TB cases are "patients who are cases of treatment failure; cases with Gene Xpert results confirming MTB-Rifampicin resistance, a symptomatic patient who had a close contact with confirmed MDR-TB patient; a patient from known high-risk group such as health workers and HIV/TB individuals; a patient who remains smear positive after 2 months of treatment (new cases); or remains smear positive after 3 months of retreatment with first-line treatment (retreatment cases such as defaulter and relapse)" (Ghana NTP, 2012a; WHO, 2014a). In this framework, they are broadly classified as treatment failure, previously treated and new MTB-Rifampicin resistant (MTB-RR). These have been identified as main contributors of MDR-TB emergence, with higher rates amongst cases of retreatment (Fuge & Ayanto, 2016; Mulu, Mekkonnen, Yimer, Admassu, & Abera, 2015; Tesfay et al., 2016). At individual level, some factors of

socio-demographic, anthropometric and patient clinical characteristics may be associated with MDR-TB cases.

Here, socio-demographic factors include sex, age and residence. It interrelates with clinical characters and anthropometric factors. In other studies, age was found to be associated with MDR-TB with other factors like educational status, marital status, residence, income and sex having no association (Guled et al., 2016) and living in the rural setting were found to be associated with MDR-TB cases. Contrary, in a systematic review by Asgedom et al, 2018, being a male has also been identified to be a predictor of MDR-TB in Ethiopia (Asgedom, Teweldemedhin, & Gebreyesus, 2018).

Clinical characteristics used in this framework focuses on disease classification, type of patient and HIV status. This in a dual arrow relates with anthropometric factors and directly to category of suspected MDR-TB. The clinical characteristics are key in the framework, and it is a kind of classification based on the status of individual patients. It is based on the type of TB infection whether pulmonary positive, pulmonary negative or extra-pulmonary tuberculosis. Patient is categorized based on whether he/she is taking anti TB drug for the first time (new), defaulted or failed in the previous treatment, or he was declared cured in the previous treatment and has the TB again (relapse). The treatment after defaulter, relapse, failure or other are generally referred to as retreatment (Ghana NTP, 2012b; WHO, 2014b). Some studies show that previous history of TB treatment, HIV infection status and history of TB contact were significantly associated with MDR-TB (Demile, Zenebu, Shewaye, Xia, & Guadie, 2018; Guled et al., 2016; Mulisa et al., 2015; Ullah et al., 2016)

Anthropometric factors in this framework can be found linking the socio-demographic and clinical characteristics. Weight and Body Mass Index have all been reported to influence the treatment outcomes of TB and MDR-TB. However, Body Mass Index was identified not to be significantly associated with MDR-TB (Demile et al., 2018). Generally, malnourished (patients with BMI <17.0) patients have poor ill health and prognosis compared to well-nourished (BMI >18.5) patients. Moderate to severe underweight is a risk factor for early TB death. Under-nutrition lowers individual's immunity leaving them more susceptible to opportunistic infections, MDR-TB and increase the risk of dying. A main reason why adequate nutrition is recommended amongst TB case management.

Socio-demographic factors:

Clinical characteristics:

HIV status

Anthropometric factors:

Treatment failure

Previously treated

New MTB-RR

Suspected MDR-TB

MDR-

Figure 1: Conceptual framework: Factors associated with MDR-TB cases

CHAPTER TWO

LITERATURE REVIEW

2.1: Tuberculosis

Tuberculosis, an infectious disease remains a global public health menace, over 10 million people were infected in 2017, more males were affected than women and children (WHO, 2018a). Every country reported TB cases amongst all age groups globally during 2017. It affected about 90% of adults (aged ≥15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries (WHO, 2018a). Averagely 1.8 million TB-related deaths, with the most (95%) of deaths reported from countries with resource challenges (WHO, 2017, 2018a). Sub-Saharan African contributes significantly to the global TB burden. The projected worldwide annual deaths attributed to TB is near to 2million people (WHO, 2018b). It is clear that management of TB has suffered significant obstacles in the past. Currently there are 2 monumental threats to global TB control; the HIV epidemic and the increasing prevalence of drug resistance (Seddon & Shingadia, 2014; WHO, 2018a).

Estimates from WHO in 2013 and 2014 for Ghana's burden of TB was 72 and 92 per 100,000 population, respectively. However, National prevalence survey conducted in 2014 showed much higher burden of the situation than estimated. It was 286 per 100,000, thus three times more than what WHO estimated. This implied that only 20% of these cases were notified to National Tuberculosis Control Programme. Several efforts are in place to reduce the very high death rate of 7.5 per 1000 persons by 35% by the end of 2020 (Ghana NTP, 2014a).

In 2017, Eastern region recorded a total of 1,586 incident cases of TB equivalent to 51/100,000. Total new cases of 1,488 accounted for 94% leaving 98 (6%) as previously treated. Nine out of twenty-six districts in the region contribute to about 57% of all TB cases reported. These high reporting were; Lower Manya Krobo, Denkyembour, East Akim, New Juaben, Birim North, Kwahu West, Nsawam-Adoagyiri, Suhum and Yilo Krobo (ERHD, 2018).

The burden of TB is not only about the suffering and hardship they endure as individuals, but to a large extent the family, community and nation. Although, in most countries the services of TB control programs are subsidized the direct and indirect financial cost is unbearable (Morishita, Yadav, Eang, Saint, & Nishikiori, 2016). Ukwaja et.al., performed studies using systematic review, whilst summarizing the state of economic impact and consequences of tuberculosis (TB) diagnosis and treatment for patients/households in Africa described it as catastrophic (Ukwaja, Modebe, Igwenyi, & Alobu, 2012). Most studies have established association between TB cases and poverty. A study in Bangladesh support individuals who are affected are mostly those within the lower brackets of socioeconomic status leading to a drain on household funds which is mostly insufficient to support medications, transportation, improved nutrition and diagnostics (Madan, Lönnroth, Laokri, & Squire, 2015).

Further analysis of the 2015 Global burden of disease by Kyu et al., suggest that strengthening health systems for prompt detection of tuberculosis and advances in the

quality of tuberculosis care, quick and accurate diagnosis, early initiation of treatment, regular follow-up visits should be made priorities in other to avert burden of TB. In some countries especially the Africa and Asia region the challenge of TB was far more than the current sociodemographic developmental stage, and this requires urgent action (Kyu et al., 2018).

In an attempt to handle the burden of TB "all Member States of WHO and the UN have committed to the TB goal, initially through their unanimous endorsement of WHO's End TB Strategy at the World Health Assembly in May 2014 and then their adoption of the UN Sustainable Development Goals (SDGs) in September 2015. Specific targets for 2030 set in the End TB Strategy are a 90% reduction in the absolute number of TB deaths and an 80% reduction in TB incidence (new cases per 100 000 population per year), compared with levels in 2015" (WHO, 2018a).

2.2: Antimicrobial resistance and public health

Antimicrobial Resistance (AMR) is the capacity of a microorganism, for example, microbes, infections, growths and a few parasites, to endure the deadly impacts of an antimicrobial, bringing about a circumstance where standard medicines wind up ineffectual and contaminations continue which may spread to other people (Eldholm & Balloux, 2016). The ramifications of the above wonder on worldwide wellbeing has prompted a few endeavors to battle and contain AMR both at the worldwide, local and national dimensions. The "One Health" idea was acquainted with impart the possibility that human wellbeing and creature wellbeing are related and bound to the strength of the biological systems in

which they exist (Ministry of Health, Ministry of Food and Agriculture, Ministry of Environment, Science, & Ministry of Fisheries and Aquaculture Development, 2017). Multifaceted, far reaching and incorporated procedures, as pushed by the WHO Global Action Plan and the Food and Agriculture Organization (FAO) Action Plan in line with the One Health approach, are critically required. WHO exhorts that nations pursue WHO, OIE, FAO proposals to actualize national activity designs including the human, nourishment, creature and the environment (WHO, 2018c).

The rise of protection from antimicrobials is a characteristic of natural event (Eldholm & Balloux, 2016). Anytime a potent antimicrobial agent is manufactured for control of specific diseases, these agents immediately begin to devise measures to counter their effects. Such obstruction might be either a trademark related with a whole species or gained through change or gene transfer. WHO have indicated that with expanding antimicrobial use and abuse throughout the years, protection from antimicrobial agent has developed in microbes (viruses, bacteria, fungi and protozoa) posing new challenges for both clinical management and control programmes.

AMR is an undeniably genuine risk to worldwide general wellbeing that requires activity over all communities and countries (WHO, 2018c). In line with this, Ghana launched its policy on use of Antimicrobials and resistance. Adding to this document was the National Action Plan; comprehensive one on Antimicrobial Resistance (AMR) for 2017 - 2021 in April 2018. The field testing for AMR and support to veterinary laboratories were also established (Ministry of Health et al., 2017).

2.3: Tuberculosis drug resistance

TB control programs globally have been hit with antimicrobial resistance. This is when isolates of *M. tuberculosis* gets resistant to one or more anti-TB drugs. Falzon et al., 2017 also contributes to the pull of knowledge that drug resistance of *Mycobacterium tuberculosis* develops by the selective growth of resistant mutants evolving in a wild population when exposed to enough drugs that can inhibit growth of sensitive organisms (Falzon et al., 2017).

There are a couple of special cases, yet these exemptions are not thought to contribute incredibly to the general weight of resistance. For example, isolates of *M. tuberculosis* from Madras (Chennai), India, have been found to have a higher normal dimension of protection from Para-Amino Salicylic corrosive (PAS) than isolates from patients in the United Kingdom (Dodd, Sismanidis, & Seddon, 2016). These categories are called the natural resistance. Falzon et al., argues that most bovine isolates are naturally resistant to PAS and pyrazinamide (PZA), and most Mycobacteria Other Than Tuberculosis (MOTT) are resistant to the standard anti tuberculosis drugs.

In fact, several studies have established that usage of a single drug, regardless of whether as a result of irregular drug supply, or poor drug quality, poor adherence to treatment, incorrect prescription, lowers the growth of bacilli susceptible to that drug but permits the multiplication of pre-existing drug-resistant mutants (Asante-Poku et al., 2016; Kam et al., 2002; Nachega & Chaisson, 2003). This can lead to development of acquired resistance.

These infected individuals can also infect some additional individuals, here they infect others with such resistant strains of bacillus leading new infections of drug resistant instantly for the first time. It is called primary resistance. These two terms acquired, and primary appear to be more conceptual hence the most commonly used terms in TB are "resistance among new cases" and "resistance among previously treated cases".

2.4: History of Tuberculosis Drug resistance

Protection from antimicrobial agents is an intrinsic feature for *M. tuberculosis*. Drug resistant TB was recognized few years after the identification and use of an effective anti-TB chemotherapy; as Pyle in 1947 described streptomycin resistance. The British Medical Research Council (MRC) in 1948 also supported this observation in a report published on Streptomycin therapy for pulmonary TB, which indicated that mortality was similar among treated and untreated patients. Subsequent investigations by MRC on treatment of Pulmonary TB with Streptomycin and Para-Amino-Salicylic Acid indicated majority who died had experienced relapsed linked to streptomycin-resistant strain. This is what influenced the principle of multiagent chemotherapy for TB which has proven to be effective in subsequent clinical trials (Marshall et al., 1950).

This resistance to anti-TB drugs continued to be noticed as a sporadic clinical problem during the 1960s, 1970s and 1980s, but there was less focus on the situation by researchers or public health officials. It became more pronounced and gained interest when in the early 1990s, multi-drug resistant TB emerged in the United States. At the time, several MDR-TB cases, defined as a disease caused by strains resistant to at least isoniazid and rifampicin

were identified as epidemics in the New York, New Jersey and Florida. The MRC reports that most of these cases were the result of micro epidemics with direct transmission among persons in hospital, jails and homeless shelters, especially among people with HIV infection. These forms of TB led to several deaths and required several commitment and resources of all forms from the government and stakeholders to reduce the burden in the United stated (Marshall et al., 1950).

In subsequent years, drug-resistant TB, especially MDR-TB, was identified as a potential catastrophic challenge to global public health. WHO reports that several outbreaks have been reported in former Soviet Union, and low levels of MDR-TB in countries with high rates of TB such as Peru, have resulted in large numbers of patients with the disease. The gradual spread of the disease led to the current global public health problem.

2.5: Tuberculosis drug resistance burden and pattern

Currently, MDR-TB is a global burden and has been reported everywhere in drug resistance surveys (WHO, 2018a). Although dense in some 'hot spots' (mostly in the former Soviet Union, China and India), it moves 'with individuals' who travel from one place to another. These people now account for the most of TB cases in some countries in which the disease burden has reduce to low levels (Blackman, Browning, Kogut, & Young, 2018). Albeit MDR-TB been a natural phenomenon, occurring in all wild-type populations of *M. tuberculosis*, its clinical significance originates in clinical mismanagement (Johnston, Shahidi, Sadatsafavi, & Fitzgerald, 2009). Other issues known to affect the burden and pattern is associated with the breakdown of routine services like collapse of

Soviet Union and the linked to economic and social crises; lack of standard protocol for TB case management like in China prior to the end of the 'Cultural Revolution'; influx of private sector that usually do apply standard case management especially in India (Enarson & Harries, 2013; Keshavjee & Farmer, 2012).

According to WHO's 2018 Global TB report, "30% (2.0 million) of the 6.6 million new and previously treated TB cases notified globally were reported to have been tested for resistance to rifampicin. Coverage was 24% for new TB patients and 70% for previously treated TB patients. Globally, 160 684 cases of multidrug-resistant TB and rifampicin-resistant TB (MDR/RR-TB) were notified in 2017 (up from 153 119 in 2016), and 139 114 cases were enrolled in treatment (up from 129 689 in 2016)" (WHO, 2018a)

Worldwide, the burden of drug-resistant TB was actually not well characterized until in recent times that it gained attention(Dye, 2006). A laboratory investigation is mandatory required in other to make definite confirmation of drug resistance. The traditional technique is to demonstrate that strains of *Mycobacterium tuberculosis* develop on culture media in the presence of at least one anti-TB medication, usually called the phenotypic testing. Currently, there are alternatives more sensitive and advanced techniques that can be employed at molecular level to detect resistance to certain drugs (Falzon et al., 2017; WHO, 2014a).

The variations of drug resistant patterns observe pose several implications for case management, resource mobilization, planning and control (Abate, Taye, Abseno, &

Biadgilign, 2012). For monitoring purposes, DST in clinical isolates confirmed to be *M. tuberculosis* are conducted to classify drug-resistant cases, these categories are NOT mutually exclusive (Enarson & Harries, 2013).

WHO, categorizes it broadly as "Mono-resistance: resistance to one first-line anti-TB drug only, Poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin, Multidrug resistance (MDR): resistance to at least both isoniazid and rifampicin, Extensive drug resistance (XDR): resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance and Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR" (Enarson & Harries, 2013; WHO, 2014a).

The first national survey of drug resistance in Ghana indicates that *M. tuberculosis* remains the leading MTBC species causing TB in Ghana. In this survey, 256/345 (74.2%) of the isolates examined were susceptible to all the first line drugs used for treatment with rate of resistance being 89/345 (25.8%). General drug resistance patterns were reported as 43/345 (12.5%), 6/345 (1.7%), 9/345 (2.6%) and 71/345 (20.6%) resistant to H, R, E and Z respectively. Multi-drug resistant (MDR) was 5/345 (1.4%) (Addo et al., 2018).

A study in Ethiopia showed higher prevalence of MDR-TB of 89 (39.4%), of which 73 (82.0%), 65 (73.0%) and 63 (70.8%) were additionally resistant to S, E and Z anti-TB

drugs, respectively. Amongst these MDR-TB cases, 52/89 (58.4%) were resistant for all first- line anti TB drugs thus H, R, Z and E. For any resistance, these were the pattern recorded H (49%), Z (42%), R (40%) and E (32%).

In the work of Mesfin et al., Rifampicin (R) drug was scored number three. Almost all these drug-resistant cases to Rifampicin when tested proved to be Isoniazid resistant as well, it therefore makes them classic for MDR-TB cases. They reported that supporting the present practice of TB programs to use Rifampicin resistance as a key indicator diagnosing MDR-TB and the consideration for starting second line anti-TB drugs (Mesfin et al., 2018).

2.6: Tuberculosis drug resistance diagnosis and surveillance

2.6.1: TB Drug resistance diagnosis

Detection and treatment of infected patients is the fundamental strategy for the control of TB. The clinical features of the disease are non-specific and requires more technical efforts in making diagnosis of drug resistance (WHO, 2016a). High proportions of individuals remain undiagnosed, this is what continuously increases the burden. The identification of acid-fast bacilli via Ziehl-Neelsen staining and direct microscopy is the most widely used approach for TB diagnosis, this offers no information on drug susceptibility and possess only moderate sensitivity. It therefore makes culture a requirement for the identification of *M. tuberculosis.*

Conclusive determination of drug resistant TB necessitates that "*Mycobacterium tuberculosis* agent be recognized and resistance against TB drugs decided. This should be possible by segregating the microorganisms by culture, recognizing it as having a place with the *M. tuberculosis* complex (MTBc), and conducting drug susceptibility testing (DST) using solid or liquid media or by performing a WHO- endorsed molecular test to detect TB DNA and mutations associated with resistance" (Falzon et al., 2017; WHO, 2014a).

Identifying drug-resistance promptly ensures appropriate treatment regimens for patients, and this has crucial effect on improved TB control. Several diagnostics exists, however approved methods by WHO include smear microscopy, culture and molecular testing. Using solid substrate, it takes averagely 3-8 weeks to grow and be able to identify *Mycobacterium tuberculosis* whereas same technique on a liquid substrate can produce results in about 1-3 weeks. If DST is to be done on the various MTB isolates, this will require extra 2-4 weeks on a solid media and 7-10 days in a liquid substrate. More time saving options can be done at Molecular level thus Xpert MTB/RIF and LPA. The later can produce results within 2 days whilst the Xpert MTB/RIF can even make results available in less than 2 hours (Falzon et al., 2017; WHO, 2014a). Table 1 below indicates the various TB diagnostic tests and DST methods and turnaround time.

Table 1: TB diagnostic tests and DST methods with their turnaround time

DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Smear microscopy	Conventional light microscopy – Ziehl-Neelsen	2 hours	Less sensitive than fluorescent/LED microscopy.
	Conventional fluorescence microscopy		Requires a quartz-halogen or high-pressure mercury vapour lamp. Sensitivity is improved over light microscopy, observation time is reduced. Expensive.
	Light emitting diode (LED) fluorescence microscopy		LED microscopes improve sensitivity by 10% over conventional light microscopy. Observation time is similar to conventional fluorescence microscopy. LED conversion kits for light microscopes are available.
Solid culture	Lowenstein–Jensen	3 weeks smear positive 4–8 weeks smear negative	Egg-based medium, inexpensive.
	Middlebrook and Cohn 7H10		Agar based medium. Less prone to contamination than Lowenstein–Jensen but more expensive.
Automated liquid culture		8 days smear positive 2–6 weeks smear negative	Liquid culture systems. Fully automated systems that use either fluorimetric or colourimetric detection.

Table 2: TB diagnostic tests and DST methods with their turnaround time, cont'd

DIAGNOSTIC PLATFORM	TEST NAME	TURNAROUND TIME	DESCRIPTION AND COMMENTS
Non-commercial WHO endorsed culture and DST techniques	Media-based microscopic observation drug susceptibility (MODS)	2–21 days direct 3–4 weeks indirect	MODS is a manual liquid technique that uses basic laboratory equipment (including an inverted microscope). Colonies are observed through the bottom of a sealed plastic container. Allows for H and R DST. MODS requires additional staff skills and a containment laboratory.
	Nitrate reductase assay (NRA)	6–9 days direct 7–11 weeks indirect	NRA is a colourimetric test using solid media. Allows for H and R DST. TB cells are cultured for 10 days and Greiss reagent is added, which indicates the presence of growing cells.
	Colourimetric redox indicator (CRI)	3–5 weeks	CRI is an indirect colourimetric test using liquid media. TB cell are cultured in the presence of a dye. Allows for H and R DST.
Molecular testing	Line probe assay (LPA)	1–2 day (direct on smear positive specimen only).	Two LPA have been developed to detect *M. tuberculosis* resistant to R and H either directly or indirectly. DNA targets are amplified by PCR and hybridized to immobilized oligonucleotide targets. Results are visualized colourimetrically. If it is a smear negative specimen, culture must be grown first.
	Xpert MTB/RIF	2 hours	A fully automated test working in a dedicated platform performing detection of MTB and R resistance, using real time PCR. Results are available in less than two hours.

Source: Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis

2.6.2: TB Drug resistance surveillance

"Drug-resistant TB today is a recognized significant public health threat with no country or region being spared (WHO, 2018a). Surveillance on the situation is therefore necessary to determine the burden and inform policy on prevailing agents in circulation. As alluded by Enarson, in 1994, the WHO, International Union Against Tuberculosis and Lung Disease (IUATLD) and other partners established a Global Project on Anti-TB Drug Resistance Surveillance with the objective of ascertaining the levels of resistance to first-line TB drugs (primarily isoniazid and rifampicin) in nationally representative populations using standardized methods" (Enarson & Harries, 2013).

In Madagascar, a national TB resistance survey was conducted between 2005 and 2007. Resistance among new cases was 6.5% and among previously treated cases it was 11.5%. Mono resistance among new cases was 5.8% and mainly to Isoniazid (3.7%). MDR to Isoniazid and Rifampicin was 0.2% (95%CI 0 – 0.5) and 3.4% (95%CI 0 –7.2) among new and previously treated cases respectively (Ramarokoto et al., 2010).

National survey conducted in Ghana reports that "among 410 samples, 345 positive cultures were obtained and identified as *Mycobacterium tuberculosis* complex (MTBC). Of the 345 isolates, 133 were further differentiated by GenoType MTBC as *M. tuberculosis*, 126 (94.7%) and *M. africanum* 7 (5.3%). The overall drug resistance patterns were as follows: 43/345 (12.5%), 6/345 (1.7%), 9/345 (2.6%) and 71/345 (20.6%) were resistant to H, R, E and S respectively and 5/345 (1.4%) were multi-drug resistant (MDR)" (Addo et al., 2018)

Japan conducted its nationwide drug resistance survey between 2007 and 2008. The frequencies of drug-resistant isolates from new cases were as follows: Isoniazid, 3.1%; Rifampicin, 0.7%; Streptomycin, 5.6%; Ethambutol, 1.3%; and 8.5% to any drug. Drug-resistant isolates from previously treated patients were as follows: Isoniazid, 12.3%; Rifampicin, 6.7%; Streptomycin, 12.3%; and Ethambutol, 2.6% (n = 852). The frequencies of multidrug-resistant isolates from new and previously treated patients were respectively 0.4% and 4.1%, with only one extensively drug-resistant case (Mitarai, 2015).

Other countries continuous to conduct nationwide surveys to understand the situation. However, WHO currently reports that globally, "there were an estimated 4.1% of new cases and 19% of previously treated cases with MDR/RR-TB in 2016 (World Health Organization, 2017). Drug resistance surveillance data show that an estimated 240 000 people died from MDR/RR-TB in 2016. In spite of increased testing, the number of MDR/RR-TB cases detected in 2016 only reached 153 000. In 2016, 8 000 patients with extensively drug-resistant TB (XDR-TB) were reported worldwide. To date, 123 countries have reported at least one XDR-TB case. On average, an estimated 6.2% of people with MDR-TB have XDR-TB" (WHO, 2017).

2.7: Factors associated with MDR-TB

The rise in drug-resistant *M. tuberculosis* has been linked to several reasons and factors which can be grouped under program management, health care providers and client's levels. WHO report on DR-TB in 2004 reported that in some countries, "management factors may include the lack of a standardized therapeutic regimen, poor programme implementation, compounded by frequent or prolonged shortages of drugs, inadequate resources and political instability or lack of political commitment". The use of unapproved and substandard anti-TB drugs mostly available over the counter is an additional concern. Moreover, when individual cases are not managed well, challenges in choosing the right medication regimen considering the right doses, diagnosed patients not adhering to the prescribed schedule have all been implicated in the emergence of drug resistant TB cases (Sharma & Mohan, 2004; WHO, 2004).

There are several contributions to support that multidrug-resistant TB menace is a multifactorial issue which is fueled by improper treatment of case management and holding, substance abuse, pregnancy, disbelief in diagnosis, relatively poor handling of supply and potency of medicines, and presence of the causative agent in circulation (Forson et al., 2018; Nachega & Chaisson, 2003; Pascopella & Flood, 2016; Tsega, Gedle, & Dilnessa, 2017; WHO, 2018a).

Studies conducted in other countries have showed that HIV infection, cigarette smoking, alcohol drinking, overpopulation, interruption of treatment, poor treatment follow up, and weak DOTS (Directly Observed Treatment Short-course) program are major risk factors

associated with MDR-TB infection (Boonsarngsuk, Mangkang, & Santanirand, 2018; Gandhi et al., 2010; Kimani, 2013; ShengFen, Yang, Yu, HuiWen, & YanLin, 2016; Villegas et al., 2016).

In Addis Ababa of Ethiopia, Mesfin and colleagues found that TB/HIV co-infection, frequent use of cigarette, excessive use of alcohol, hospital detention, and an evidence of periodic visits to health care centres were strongly associated with the development of MDR-TB. Also, for cases known to have history of previous treatment and individuals within the age category 25-43 years, a higher burden of MDR-TB observed was statistically significant (Mesfin et al., 2018).

In a study conducted in Malaysia, associated factors identified for multi-drug resistant tuberculosis were similar to other reported ones; non-compliance with medications and previous treatment. Others were smear positivity at the second and sixth month of treatment and region of residence. People living in the rural region were found to have a higher risk (Mohd Shariff, Shah, & Kamaludin, 2016). In some reports including the global Tuberculosis report 2018 by WHO, it is reported that the prevalence of tuberculosis is over twice the global average in Africa, with drug resistant tuberculosis accounting for a significant proportion of cases (WHO, 2018a).

A systematic review done in Ethiopia on Prevalence of Multidrug-Resistant Tuberculosis and associated factors by Asgedom et al., concurs that previous exposure to anti-tuberculosis treatment was the most commonly identified risk factor of MDR-TB (Asgedom et al., 2018).

In Somalia, a study by Guled et al., 2016 reported that the productive age group (21 – 40 years), previous TB treatment and sex (being a male) were significantly associated with MDR-TB (Guled et al., 2016). Cases of pulmonary tuberculosis that tested negative to sputum smear microscopy have always be considered virtually not infectious so seen to have less public health impact compared to their colleagues who test smear positive. However, in areas of Mexico, some studies found that the spread of resistant *M. tuberculosis* can greatly be influenced by cases declared as smear negative by sputum smear microscopy.

Generally, poverty and poor nutrition not only increase susceptibility but affects treatment outcome of patients. Most national TB control programs include nutritional support in the care and this have been identified to be very useful in the outcomes of patients. For example, in a Cambodian project which provided nutritional supplement showed significant improvement in treatment outcomes (Lutge, Lewin, Volmink, Friedman, & Lombard, 2013).

Additionally, low weight for height has been determined to be a major indicator for development of TB and MDR-TB. For instance, Lonnroth et al., 2010 in a systematic review to explore the reliability of low weight for height in the development of tuberculosis, six cohort studies that collected data on weight and height with outcome as development of active tuberculosis considered. The results indicated log-linear association between body mass index (BMI) less than 18.5kg/m2 and TB incidence in different areas

with varying levels of TB case-loads. They argued that, a unit reduction in BMI increases TB risk by almost 14% (Lönnroth, Williams, Cegielski, & Dye, 2010).

BMI below the normal range was identified to be key in the MDR-TB menace, a study by Shah et al., in India presents that majority thus 48 (96%) of MDR-TB patients had their BMI below 18.5 kg/m2 (Shah, Shah, & Dave, 2018). This indicated that most of the patients suffering from MDR-TB are malnourished, and diet plays a major role here. Malnutrition and TB are both problems of considerable magnitude in the developing countries like India but great opportunities of supplement exist for consideration in NTPs (Gupta, Gupta, Atreja, Verma, & Vishvkarma, 2009)

2.8: TB control in Ghana

Tuberculosis was documented before independence in Ghana. Colonial masters found the need to strategically address it as a challenge adequately before it escalates into a bigger problem uncontrollable in future. In mid-1954, efforts from government had peaked but there was still the need to support its activity. This led to the establishment of Ghana society for the prevention of Tuberculosis. During early part of 1960s, TB nurses surfaced in the system. These were nurses that had received special trainings from Israel on government sponsorship. Their services included outreach programs, screening and health education at the community level (Ghana National TB Programme, 2018).

Tb cases was noticed to be increasing in the country, at the time structures and systems were not clearly established to meet the challenge. Several efforts and commitments from

individuals and government helped in making a case for the burden of Tuberculosis in Ghana. This heightened the consensus and initiatives for a National Tuberculosis control Program (NTP) in 1993. NTP was to provide leadership for health sector response to fight tuberculosis in Ghana (Ghana National TB Programme, 2018).

Subsequently, the National TB control Program (NTP) was launched in 1994 and aims at reducing the transmission of the disease to a level it is no longer a major health problem. Danish International Development Agency (DANIDA) in recognition of efforts of Ghana to handle TB, jointly provided financial support for the program. The plan of work and activities were in line with the mainstream policy of the International Union Against TB and Lung Diseases (IUATLD/UNION) at the time. Planned implementation started in 1994 with series of intensified trainings, outreached and health promotional activities. It was around this same period that the country adopted the WHO DOTS (Directly Observed Treatment Short course) strategy, focused on the five key pillars of political commitment, diagnosis by sputum smear microscopy, standardized supervised treatment, uninterrupted drug supply and recording and reporting system. The DOTS strategy was rolled out in all hierarchy of the public health care system. By the year 2000, it was everywhere and WHO reported the country had successfully attained 100% coverage; what was required was to maintain the pace over time (Ghana National TB Programme, 2018; Ghana NTP, 2014b).

Currently, TB control is fully integrated into the health system. Ghana's health system is structured into a three-tiered system administratively, thus National, Regional and District levels but five-tiered regarding service delivery; National, Regional, District, Sub-district

and Community-based Health Planning and Services (CHPS) zones. NTP shares in the mission of Global Stop TB Partnerships. Its mission includes; ensure that every TB patient has access to TB treatment and care, stop transmission of TB, protect vulnerable populations from TB, reducing the social and economic toll that TB exerts on individuals, families, communities, and the nation (Ghana NTP, 2012b).

The attainment of such mandate over the years has not been easy. The main source of funding of NTPs activities is from the Global Fund, however, the Government of Ghana supports yearly as well. Sharing in the mission of Global Stop TB Partnership implies striving to achieve the three 90s; thus detecting 90% of people who need treatment and putting them on treatment, identifying 90% of cases from special populations such as vulnerable, underserved and at risk groups, and finally achieving at least 90% treatment success rate (Ghana NTP, 2012b).

Ghana in an attempt to strengthen efforts to curtail this unacceptably high prevalence and mortality rate and to contribute to achieving the global target of 90 (90) 90 by 2020, three strategic goals to reduce the 2013 prevalence by 20% by 2020, to reduce mortality rate by 35% of the 2012 death rate by 2020 and to end the TB epidemic in Ghana by 2035 without catastrophic cost due to TB-affected families.

Considering the burden of drug resistant TB cases in the country, several efforts are in place to promote early case detection and appropriate case management. These services are; trainings for health care professionals on updated policies, implementation of

intensified case finding using task shifting officers in hospitals, employment of Monitoring and Evaluation officers, establishment of MDR-TB case management teams, capacity building for laboratory personnel and availability of Gene Xpert machines, improving availability and supply of quality medications and advanced diagnostics services, etc.

CHAPTER THREE

METHODS

3.1: Study Design

A five-year retrospective (descriptive cross-sectional study) data review was conducted to describe the drug resistance pattern, burden and factors associated MDR-TB cases among all suspected MDR-TB cases registered from 1st January 2014 to 31st December 2018 in Eastern Region.

3.2: Study Area

The study was conducted in Eastern region of Ghana.

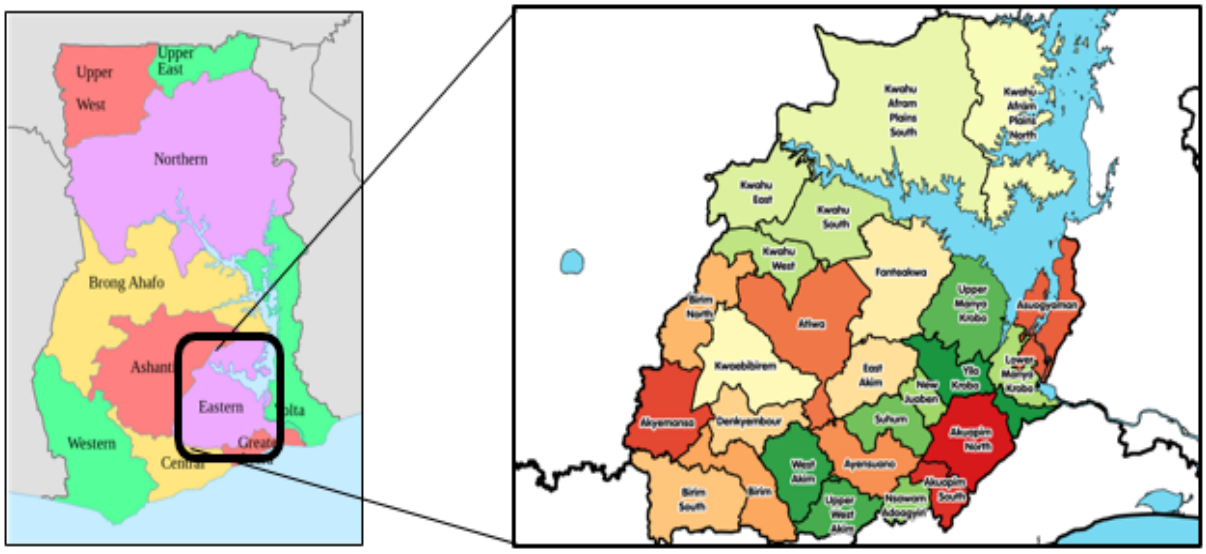

Figure 2: Map of Ghana highlighting Eastern region and its districts

3.2.1: Location and Size

"Historically, the Region was one of the three administrative areas of the then Gold Coast until independence. Eastern Region lies between latitudes 6 and 7 degrees North and

longitude 1.30 West 0.30 degrees East. It is the sixth largest region with a land area of 19,323 kilometers square, which is 8.1% of the land area of Ghana (Ghana Statistical Survey, 2005). It shares boundaries with five other regions: Greater Accra, Volta, and Brong Ahafo, Ashanti and Central regions. It has diverse topography, with forest and savannah vegetation.

3.2.3: Health Services

The region is divided into twenty-six (26) Municipals/districts, two hundred and six (206) sub-municipal/districts and one thousand one hundred and seventeen (1117) reporting health facilities dotted across. Almost all health facilities in the region are considered as DOTS centres for the management of TB cases. In every district there is at least one TB diagnostic centre. Currently, there are eighteen (18) Gene Xpert machines evenly distributed that support TB diagnosis within the region. This service started in the region at Atua Government hospital in Lower Manya Krobo district around 2013. The Regional hospital which is the main referral hospital is the only facility with DST, LPA and Culture services. All facilities that record suspected cases of MDR-TB mandatory process and transport appropriate samples to the regional hospital for further investigation. It is also the mandated centre for management of all confirmed MDR-TB cases within the region. Appendix 2 and 3 show the distribution of health facilities in the Municipality by types and the ownership, respectively."

3.3: Variables of the Study

The dependent variable of the study is the MDR-TB case which was categorized as MDR-TB case or Non MDR-TB case to enable the analysis using logistic regression and Chi square test. The independent variables included socio-demographic (age, sex, residence), anthropometric (weight, height, BMI) and clinical characteristics (disease classification, type of patient, HIV status, sputum smear results). This is presented in detail in Table 3.

Table 3: Variables table

Variable name	Variable type	Values/measurements
Dependent variable		
MDR-TB	Categorical	MDR-TB case Non MDR-TB case
Independent variables		
Age	Continuous	Completed age
Sex	Categorical	Male Female
Residence	Categorical	Rural Urban
District	Nominal	All 26 district codes
Weight (Kg)	Continuous	Real numbers
Height (m)	Continuous	Real numbers
BMI (kg/m^2)	Continuous	Real numbers
Disease Classification	Categorical	Pulmonary Extra-pulmonary
Type of patient	Categorical	New Re-treatment
HIV status	Categorical	Negative Positive Not Done
Sputum smear results	Categorical	Negative Positive Scanty
Category of MDR-TB suspect	Categorical	Treatment failure Previously treated New MTB-RR TB/HIV coinfection
Culture results	Categorical	No growth MTB Contaminated Suspected NTM
Drug susceptibility testing for Isoniazid (H) resistant	Categorical	No Yes
Drug susceptibility testing for Rifampicin (R) resistant	Categorical	No Yes
Drug susceptibility testing for Streptomycin (S) resistant	Categorical	No Yes
Drug susceptibility testing for Ethambutol (E) resistant	Categorical	No Yes
MDR-TB status	Categorical	Non MDR-TB case MDR-TB case

3.4: Sampling

Total sampling (census) was used.

3.4.1: Study Population

Records of all suspected MDR-TB cases that were investigated with samples to the referral centre, Eastern regional hospital within 1st January 2014 to 31st December 2018 was reviewed. The period was selected as a result of easy accessibility to records for use. It was difficult accessing records prior to 2014. Suspected MDR-TB are "patients who are cases of treatment failure; new cases with Gene Xpert results confirming MTB-Rifampicin resistance, a symptomatic patient who had a close contact with confirmed MDR-TB patient; a patient from known high-risk group such as health workers and HIV/TB coinfection; a patient who remains smear positive after 2 months of treatment (new cases); or remains smear positive after 3 months of retreatment with first-line treatment (retreatment cases such as defaulter and relapse)"

3.4.2: Sample size

No sample size was calculated for this study. This is because it included all suspected MDR-TB cases referred to the regional hospital in the region from 1st January 2014 to 31st December 2018.

3.5: Data collection Procedure

A specially designed data extraction sheet (Appendix 5) was used. Information on client's socio-demographic (age, sex, residence), anthropometric (weight, height, BMI) and clinical characteristics (disease classification, type of patient, HIV status, sputum smear results) were extracted from home verification forms, treatment cards, TB registers and Laboratory registers. All such cases were first identified from the regional hospital's main TB laboratory register and follow up made to the various districts and facilities where these cases were referred from. At the various districts, the detail records on other socio-demographic variables were retrieved.

3.6: Inclusion Criteria

- All suspected MDR-TB cases that were referred to the regional hospital for further investigation from 1st January 2014 to 31st December 2018
- Suspected MDR-TB cases recorded and reported within the region
- Suspected MDR-TB cases with socio-demographic and laboratory records available

3.7: Exclusion Criteria

- Suspected MDR-TB cases referred to the regional hospital from other regions
- Cases without socio-demographic and laboratory records (missing data)
- Suspected TB cases diagnosed clinically, smear/Xpert negative but treated for TB.

3.8: Data Collection Instrument

A checklist was developed for data collection (Appendix 5). It contained all the variables necessary for addressing the specific objectives and ultimately, the general objective of the study. Patients were not interviewed. The data collection tool compile data from TB home verification form, DOTS centres treatment cards, District Tuberculosis registers, Laboratory request forms, Tuberculosis laboratory register for sputum smear microscopy and XPERT MTB/RIF Test and Tuberculosis Culture and DST laboratory register.

3.9: Data processing, storage and security

The records of cases collected with the tool for this study was anonymized by using codes in place of participants identifiable variables (such as names, house numbers, etc) to maintain privacy and confidentiality. Hard copies of information collected was kept strictly under lock and key. These records were cleaned and computed into Microsoft Excel data entry sheet designed by the researcher which was then exported into Stata version 15 for analysis. All soft copies were kept on researcher's computer with password. Copies were backed up on a Western Digital (WD) external hard drive that is password protected. Same copies of the computed Excel and STATA database were stored in the researcher's email and dropbox cloud account. Hard copy records will be destroyed using environmentally friendly approach in the presence of a witness and photographic evidence after 5 years of study. The electronic versions will be permanently deleted from the researchers email and cloud accounts and the external hard drive used as backup will also be formatted.

3.10: Data Analysis

Data was entered and cleaned using Microsoft office excel and exported to STATA version 15 for analysis. Data completeness and consistency was checked by running frequencies of each variable.

Age, weight and height were collected as continuous variables, and these were transformed to generate new categorical variables. Age was transformed to age group which consisted of four age groups (≤14, 15-34, 35-64 and ≥65years). Weight of patients before treatment were transformed to weight category (30-39Kg, 40-54Kg and ≥55Kg). BMI was generated using weight (Kilograms) divided by height (meters) squared. This was then transformed to BMI status which consisted of three categories (underweight, Normal weight and overweight). These transformations were done to enable the researcher to determine associations between the independent variables and the outcome variable using Pearson's Chi square test. Tables were used to show the resistance pattern. Proportions in percentages were calculated for all first line drugs showing resistance to *Mycobacterium tuberculosis.* Bivariate analyses were carried out for all categorical variables and Pearson's Chi square test performed to determine association between the independent variables and the dependent variable. Where Pearson's Chi square test conditions were violated, appropriate Fisher's exact was estimated. The results were presented in a table comparing the proportions of the independent variables by the dependent variable. Variables that were found to be significantly associated with the outcome variable were put in multivariate logistic regression model to determine crude and adjusted odds ratios to quantify the strength of the observed association existing amongst associated factors and MDR-TB. After the univariate analysis, two models were generated with the first model containing

only the significant variables and second model with all the variables. Akaike Information Criterion (AIC) of the models were estimated to assess the fitness of the model relative to the other models. Multiple logistic regressions were modeled controlling for some possible confounders whilst assessing the effect of each variable on the likelihood of MDR-TB occurrence. A p-value of 0.05 was used as the cut-off point for statistical significance.

3.11: Quality control

- A research assistant who has good command over coding and data validation was engaged to independently cross check for accuracy, consistency and appropriateness.
- Data validation feature in Microsoft excel was used in designing the template to minimize possible errors at the data entry stage

3.12: Ethical Consideration

Ethical approval (ERC number GHS/ERC060/02/19) was obtained from the Ghana Health Service Ethical Review Committee before the commencement of the study. Permission was obtained from the Eastern Regional Director of Health Services, who then gave approval for the commencement of the study and use of data in the region. The study involved the use of data extraction tool to obtain information from patients TB registers, completed home verification forms, laboratory registers and treatment cards without the involvement of the patients.

On risk and benefits; there is no anticipated risk to any participant and for that matter no compensation package was provided.

To ensure confidentiality and maintain privacy, the records of cases collected with the tool for this study was anonymized by using unique codes in place of participants identifiable variables (such as names, house numbers, etc). These unique codes can only be linked to patient details by the researcher where necessary to avoid duplication of records.

The researcher has no conflict of interest in the study and all the costs involved in the study will be borne by the researcher.

3.13: Assumptions

The following assumptions were made in this study;

1. All care providers in the region used appropriate case definition to identify suspected MDR-TB cases
2. Adequate samples of suspected MDR-TB cases were transported to regional hospital for further actions
3. Screening and further laboratory investigations were conducted for all suspected cases

CHAPTER FOUR

RESULTS

4.1: General description

In Eastern region, a total of 682 clients were suspected as MDR-TB cases from 1st January 2014 to 31st December 2018. Culture results indicated 168 (24.6%) as "Negative or No growth", 4(0.6%) Non-Tuberculus Microbe, 7 (1.0%) contaminated and 503 (73.8%) positive for *Mycobacterium tuberculosis* bacillus. Only the five hundred and three (503) MTB cases with complete and accessible records were used for analysis. Of these, 308 (61.2%) were males, mean age 47.4± 16.3 years and 334 (66.4%) lived in urban communities as shown in Table 5. Over the 5-year period records reviewed, greater proportion, thus 32% were recorded in 2015. All suspected MDR-TB cases were pulmonary cases. Majority, (92.5%) of all suspected cases were cases of retreatment category. The HIV test was not done for about one out of every ten cases. Smear results were available for all cases analyzed with 64% indicated as negative. Relating to reasons why these cases were considered as MDR, history of previously treated accounted for about 70% of all cases. Except Kwahu North district, all the 25 remaining districts reported at least one case of suspected MDR-TB case during the period of review.

Table 4: Background characteristics of suspected MDR-TB cases in Eastern region, 2014 – 2018.

Variables	Number	Mean	Standard deviation (SD)	Minimum	Maximum
Age (years)	503	47	16	10	92
Weight (Kg)	503	52.1	10.5	20	82
Height (m)	503	1.6	0.1	1	1.9
BMI (Kg/m^2)	503	19.7	2.2	15.9	25.6

Table 5: Background characteristics of suspected MDR-TB cases in Eastern region, 2014 – 2018.

Variables	Number (n = 530)	Percent (%)
Sex		
Male	308	61.2
Female	195	38.8
Age group (years)		
≤14	4	0.8
15-34	113	22.5
35-64	299	59.4
≥64	87	17.3
Residence		
Rural	169	33.6
Urban	334	66.4
Year		
2014	87	17.3
2015	161	32.0
2016	90	17.9
2017	93	18.5
2018	72	14.3
Weight category (Kg)		
30-39	43	8.5
40-54	273	54.3
55+	187	37.2
BMI_status (Kg/m^2)		
Underweight	230	45.3
Normal weight	271	53.9
Overweight	2	0.4
Type of patient		
New	38	7.5
Retreatment	465	92.5
HIV status		
Negative	429	85.3
Positive	12	2.4
Not Done	62	12.3
Smear results		
Negative	321	63.8
Positive	161	32
Scanty	21	4.2
MDR-TB suspected category		
Treatment failure	107	21.3
Previously treated	351	69.8
New MTB-RR	33	6.6
TB/HIV	12	2.4

4.2: Drug resistance pattern of *Mycobacterium tuberculosis* drug resistant cases to the first line TB drugs

The study sought to describe the resistance pattern to TB drugs in the region. This is detailed in table 6 below. The pattern was considered as resistance to any of the first line drugs, mono resistance, multi-drug resistance and poly resistance. For any and mono resistance, Rifampicin recorded the most resistance of 35% (176/503) and 24.2% (122/503) respectively amongst all suspected cases. Half of all new cases were resistant to Rifampicin only as mono resistance.

Table 6: Drug resistance pattern to first line anti-TB drugs in Eastern region, 2014 – 2018

Drug Resistance Pattern	All suspected cases (n=503) Number (%)	Previously treated (n=465) Number(92.5%)	New cases (n=38) Number(7.5%)
Any Resistance	**196(39)**	**158(34)**	**38(100)**
H	58 (11.5)	43(9.2)	15(39.5)
R	176(34.9)	138(29.7)	38(100)
Z	44(8.7)	29(6.2)	15(39.5)
E	23(4.6)	18(3.9)	5(13.2)
Mono Resistance	**135(26.8)**	**115(24.7)**	**20(52.6)**
H only	4(0.8)	4(0.9)	0(0)
R only	122(24.2)	102(21.9)	20(52.6)
Z only	5(1.0)	5(1.1)	0(0)
E only	4(0.8)	4(0.9)	0(0)
Multi-Drug Resistance (MDR)	**47(9.3)**	**32(6.9)**	**15(39.5)**
H+R	18(3.6)	16(3.4)	2(5.3)
H+R+Z	16(3.2)	7(1.5)	9(23.7)
H+R+E	0(0)	0(0)	0(0)
H+R+Z+E	13(2.6)	9(1.9)	4(10.5)
Poly Resistance* (Non MDR)	**25(5.0)**	**18(3.9)**	**7(18.4)**
H+Z	4(0.8)	4(0.9)	0(0)
H+E	3(0.6)	3(0.6)	0(0)
R+Z	4(0.8)	2(0.4)	2(5.3)
R+E	1(0.2)	0(0)	1(2.6)
Z+E	0(0)	0(0)	0(0)
H+Z+E	13(2.6)	9(1.9)	4(10.5)

Isoniazid (H/Inh), Rifampicin (R/Rif), Pyrazinamide (Z/Pza) and Ethambutol (E/Emb).

From Table 6, all forms of MDR-TB accounted for 9.3% (47/503) of cases. No case was reported for the HRE category of MDR-TB cases. Of all MTB cases, poly resistance was 5% (25/503) with no case reported from the ZE category. The overall resistance to at least any of the first line anti-TB drugs is 39% (196/503).

4.3: Burden of MDR-TB among suspected MDR-TB cases

The records indicate a general burden of one MDR-TB in every ten suspected MDR-TB cases in the region during the period under review, 9.3% (95% CI: 6.9-12.2). Prevalence was higher in males compared to females. Proportion was 11.0% (95% CI:7.7-15.1) amongst individuals within the age group 35-64 years, which was the highest compared to other categories. The highest burden of 20.8% (15/72) was recorded in 2018. People in urban residence were most affected. MDR-TB burden was high, thus 41.7% (5/12 with 95% CI: 15.2-72.3) and 23% (37/161 with CI: 16.7-30.2) amongst cases that were HIV positive and sputum smear positive respectively. In table 7 below, the burden is displayed by other variables.

Table 7: Burden of MDR-TB amongst suspected cases in Eastern Region, 2014 – 2018.

Variables	Total Suspected	MDR-TB confirmed	Prevalence (%)	95% CI
Overall	503	47	9.3	6.9-12.2
Sex				
Male	308	33	10.7	7.5-14.7
Female	195	8	4.0	3.9-11.7
Age (years)				
≤14	4	0	0	-
15-34	113	10	8.8	4.3-15.7
35-64	299	33	11.0	7.7-15.1
≥65	87	4	4.6	1.3-11.3
Year				
2014	87	5	5.7	1.9-12.9
2015	161	6	3.7	1.4-7.9
2016	90	10	11.1	5.4-19.5
2017	93	11	11.8	6.0-20.2
2018	72	15	20.8	12.1-32
Residence				
Rural	169	14	8.2	4.6-13.5
Urban	334	33	9.9	6.9-13.6
Weight cat(Kg)				
30-39	43	3	7.0	1.4-19.1
40-54	273	29	10.6	7.2-14.9
55+	187	15	8.0	4.5-12.9
Type of patient				
New	38	15	39.5	24.0-56.6
Retreatment	465	32	6.9	4.7-9.6
HIV status				
Negative	429	36	8.4	5.9-11.4
Positive	12	5	41.7	15.2-72.3
Not Done	62	6	9.7	3.6-19.9
Smear results				
Negative	321	10	3.1	1.5-5.6
Positive	161	37	23	16.7-30.2
Scanty	21	0	0	-

4.4: Factors associated with MDR-TB among suspected MDR-TB cases

The study sought to determine factors associated with MDR-TB cases. These factors were categorized as socio-demographic (age, sex and residence), anthropometric (weight, height and BMI) and clinical (category of patient, sputum smear results and HIV status).

On socio-demographic factors, 10.7% (33/308) of all males were positive for MDR-TB which was higher compared to females. The mean age in years of clients with MDR-TB was 44.3±13.1 (95%CI: 40.4-48.2). No case was confirmed for four clients aged 14 years or less. Within the category 35-64 years, about 11% (33/299) were MDR-TB cases. This was the highest in the age categories. A proportion of 9.9% (33/334) of individuals resident in urban areas were indicated as MDR-TB positive cases. A Pearson's Chi-square test conducted to determine associations of the independent variables with MDR-TB showed no significance for all the socio-demographic factors, thus Sex, Age and Residence with p-values 0.18, 0.31 and 0.56 respectively. Univariate logistics regression for these variables and the dependent variables also showed no significant associations when odds ratios were calculated, and confidence intervals determined at 95%.

For the anthropometric factors, mean weight of MDR-TB cases in Kilograms was 51.3± 9.4(95% CI: 48.6-54.1). Clients within the weight category 40-54 Kg, 10.6% of them were positive for MDR-TB. From table 8, the mean BMI amongst the MDR-TB cases was 19.6±2.1 (95% CI: 19.0-20.3). No MDR-TB case was reported in the overweight category out of the two cases (Table 8). One in every ten case (21/230) of MDR-TB cases was recorded within the underweight category of cases. A Pearson's Chi-square test conducted

using significance level of 95% to indicate associations of the anthropometric factors with MDR-TB showed no significance for both, thus weight and BMI category with p-values 0.61 and 0.9 respectively. Details of these are displayed in Table 8.

Details of the last component of factors, clinical consisted of type of patient, HIV status and sputum smear results are all presented in Table 8. Fifteen (15) out of the 38 (39.5%) new cases were MDR-TB cases. For HIV status, proportion classified as MDR-TB was higher for those who were positive thus 41.7% (5/12). Similar observation was seen with sputum smear results as 23% (37/161) of all positive sputum results were declared MDR-TB cases.

To establish whether any of these factors were associated with the outcome variable, a Pearson's Chi-square test executed. All the three factors; type of patient, HIV status and Sputum smear results were significantly associated with MDR-TB; the p-values were <0.001, 0.005 and <0.001 respectively.

Univariate and multivariate logistic regression was done to determine the strength of association for the significant factors, thus type of patient, HIV status and Sputum smear results. Crude analysis showed that individuals with positive HIV test had 7.8 times odds of developing MDR-TB compared to HIV negative clients (crude OR=7.80, 95% CI: 2.35-25.82). Adjusting for age, sex, place of residence, weight and BMI, having an HIV positive results increases the odds of MDR-TB by 3.8 (adjusted OR=3.80, 95% CI: 1.09-13.26). In the same model and holding all other variables constant there was 12.9 increased odds if

an individual had a positive smear result (adjusted OR=12.88, 95% CI: 5.47-30.34). In Table 9, retreatment patients had 93% less odds of developing MDR-TB (adjusted OR= 0.07, 95% CI: 0.05-0.24) compared to new patients.

Table 8: Factors associated with MDR-TB cases in Eastern region, 2014 – 2018

Factors	MDR TB		χ^2	p-value
	No (%)	Yes (%)		
Sex			1.80	0.18
Male	275(89.3)	33(10.7)		
Female	181(92.8)	14(7.2)		
Age group (years)				0.31#
Mean ± SD (CI)	47.7±16.5(46.2-49.3)	44.3±13.1(40.4-48.2)		
≤14	4(100)	0(0)		
15-34	103(91.1)	10(8.9)		
35-64	266(89)	33(11)		
≥65	83(95.4)	4(4.60)		
Residence			0.34	0.56
Rural	155(91.7)	14(8.3)		
Urban	301(90.1)	33(9.0)		
Weight category (Kg)				0.619#
Mean ± SD (CI)	52.3±10.6(51.2-53.2)	51.3± 9.4(48.6-54.1)		
30-39	40(93)	3(7)		
40-54	244(89.4)	29(10.6)		
55+	172(92)	15(8)		
BMI_status (Kg/m^2)				0.901#
Mean ± SD (CI)	19.7±2.3(19.5-19.9)	19.6±2.1(19.0-20.3)		
Underweight	209(90.9)	21(9.1)		
Normal weight	245(90.4)	26(9.6)		
Overweight	2(100)	0(0)		
Type of patient				<0.001#*
New	23(60.5)	15(39.5)		
Retreatment	433(93.1)	32(6.9)		
HIV status				0.005#*
Negative	393(91.6)	36(8.4)		
Positive	7(58.3)	5(41.7)		
Not Done	56(90.3)	6(9.7)		
Smear results				<0.001#*
Negative	311(96.9)	10(3.1)		
Positive	124(77)	37(23)		
Scanty	21(100)	0(0)		

#Fisher's exact, *p-value < 0.05

Table 9: Multivariate logistic regression model of factors predicting MDR-TB in Eastern region, 2014 – 2018

"Variable	Univariate	Multivariate	
	Unadjusted OR (95%CI)	(significant variables) Adjusted OR (95%CI)	(All variables) Adjusted OR (95%CI)
Sex		-	
Male	1 (reference)		1 (reference)
Female	0.64(0.33-1.24)		0.65(0.28-1.52)
Age (years)	0.99(0.97-1.01)	-	0.98(0.96-1.01)
Residence		-	
Rural	1 (reference)		1 (reference)
Urban	1.21(0.63-2.33)		0.98(0.46-2.07)
Weight cat (Kg)		-	
30-39	1 (reference)		1 (reference)
40-54	1.58(0.46-5.45)		1.17(0.29-4.74)
55+	1.16(0.32-4.21)		1.01(0.24-4.61)
Type of patient			
New	1 (reference)	1 (reference)	1 (reference)
Retreatment	0.11(0.05-0.24)	0.067(0.02-0.17)	0.07(0.02-0.18)
HIV status			
Negative	1 (reference)	1 (reference)	1 (reference)
Positive	7.80(2.35-25.82)	3.80(1.09-13.26)	4.83(1.22-19.08)
Not Done	1.17(0.47-2.90)	0.78(0.26-2.36)	0.88(0.28-2.74)
Smear results			
Negative	1 (reference)	1 (reference)	1 (reference)
Positive	9.28(4.48-19.24)	12.88(5.47-30.34)	11.97(5.02-28.51)
Scanty	1.0	1.0	1.0
AUROC	-	0.87(0.83-0.90)	0.88(0.84-0.91)
AIC	-	235.08	242.6

OR= Odds Ratio, CI= Confidence Interval, AIC= Akaike Information Criterion, AUROC= Area Under Receiver Operating Characteristic"

CHAPTER FIVE

DISCUSSION

More males 308 (61.2%) were affected with TB out of all the records reviewed in Eastern region from 2014-2018. Same trends have been reported in several works in other settings. In Thailand, Chuchottawa et al., found a 65% male sex was affected (Chuchottaworn et al., 2015). Eyob et al., also identified about 58% males were affected with TB in Ethiopia (Mesfin et al., 2018). In 2013, the national TB control program authored an End-Term Comprehensive External review of Ghana National Tuberculosis Health Sector Strategic plan (2009-2013) which reports the overall male-female ratio to be 2:1. In Ghana, the first national survey to determine resistance to first line drugs conducted by Addo et al., also reported cases among 68% of males of all cases sampled (Addo et al., 2018).

It cannot be clearly explained why more males appear to be affected by TB than females but in Taiwan this has been linked to some behaviors such as smoking, drinking and poor nutrition which were more common in males than in females that could predispose males to developing active TB disease (Feng et al., 2012). Again, it could also be due to differences in the adherence behavior of males and females to anti-TB treatment. On the contrary, a study conducted in Addis Ababa, Ethiopia and China (Tao et al., 2017) found TB to be more prevalent among females (Getahun, Ameni, Medhin, & Biadgilign, 2013).

In this work, MDR-TB was reported amongst more individuals living in the urban areas compared to their counterparts in the rural settings though this was not statically significant. Similar findings were observed in studies in India where majority of MDR-TB

cases were urban residents. A work in Ghana also found that 67.4% of the cases lived in urban communities (Ansah, 2017). It was reported that patients who live in urban areas are more likely to develop drug-resistant TB due to slums/overcrowded area that favor for transmission of TB/MDR-TB (Parmar et al., 2018). Also, easy access to antibiotics without proper regulation in urban areas for self-management of cough related illness may contribute to the development and selection of drug resistant MTB strains.

More cases were reported in the 35-64 years category in this study. This age group embraces the productive age in the region and most likely that by their occupational requirement have to move to urban areas where exposure may be higher. The work did not find age to be statistically significant with MDR-TB. Other works also document higher proportions amongst same age brackets (Tesfay et al., 2016; Tsega et al., 2017)

This work reports general resistance to at least one of the first line anti-Tuberculosis drug(s) to be 39%. This rate could be due to the use of GeneXpert to detect new MTB-RR cases and also the fact that the study population focused on suspected MDR-TB cases. Comparable rate of 37% was reported amongst pulmonary TB patients by Singh et al., in Nepal (Maharjan, Singh, Khadka, & Aryal, 2017). They reported irregular supply of drugs, unavailability of drugs and delay in treatment as possible reasons for the high resistance rate. Contrary, higher rates of 58% and 72.9% have been reported in isolates from Addis Ababa (Adane, Ameni, Bekele, Abebe, & Aseffa, 2015; Tesfay et al., 2016). The variation could be due to the difference in proportion of retreatment sub-categories since most of the cases in that work were referral cases and most referral cases were treatment failure.

Resistance to rifampicin accounted for the greatest proportion, thus 34.9% in this study. It supports a finding in Addis Ababa where the proportion was reported as 33.3% for rifampicin resistance. The higher rates have been reported by several studies which is a worry to public health. Several adverse reactions such as nausea, vomiting, rashes, hepatitis, Gastro Intestinal Tract upset, flu-like symptoms, fever and jaundice have been reported with the use of Rifampicin. This could result in patient non-adherence and hence may lead to the selection of resistant strains (Mulu et al., 2017).

Isoniazid resistance of 11.5% (58/503) was the second highest recorded in this study over the period. In Ethiopia studies report resistance to Isoniazid to range between 1.9% - 21.4% (Maru, Mariam, Airgecho, Gadissa, & Aseffa, 2015). Much more higher rates of 52% (Hanif, Malik, & Dhingra, 2009) and 56% (Abate et al., 2012) were noticed in India and Addis Ababa respectively. The Eastern region study identified that all the cases resistant to isoniazid were also resistant to Rifampicin which makes them MDR-TB cases. This finding supports recent practice where TB programs in the developing countries use rifampicin resistance as a surrogate indicator for MDR-TB diagnosis warranting the initiation of second line anti-TB drugs. Isoniazid resistance is of public health importance since it is the pillar medicine recommended throughout the course of non-MDR-TB treatment. In developing countries like Ghana, it remains the preferred drug in chemoprophylaxis of TB for the management of latent TB infection. Therefore, loss of its effectiveness will be a big blow to TB control programs because of its usefulness in preventive and treatment functions.

For the period under review in eastern region, this study reports an MDR-TB burden of 9.3%. In Pakistan, a developing country, same rate was reported as prevalence of MDR-TB (Ullah et al., 2016). This rate is far higher than what was reported to be 1.4% for the first national survey conducted in Ghana (Addo et al., 2018). The reason could be the method and target populations used. In Ethiopia, prevalence of MDR-TB has been reported to be 54.6% (Tesfay et al., 2016). Like the case of Ghana, the burden of 54.6% was far more than Ethiopian's national prevalence survey which indicated the burden to be 12% (Federal democratic republic of Ethiopia Ministry of Health, 2011). These rates reported are still lower compared to a study conducted in Philippines which reports a rate of 76.4% (Gler et al., 2011).

This study used the three broad areas of factors; socio-demographic, anthropometric and clinical. Interestingly, only the clinical factors were observed to be significantly associated with MDR-TB. In this study considering whether a case was new or retreatment, indicated that rate of MDR amongst new cases was significantly higher as 39.5% were classified as MDR-TB. "Other works report the percentage of MDR-TB among previously treated cases was significantly higher (45.1%) compared to new TB cases (25%). They argue that previously treated cases are more likely to develop MDR–TB than new patients (Adane et al., 2015). A work in North East Ethiopia also reported that retreatment cases have 34.26 times more likely to develop MDR-TB than new treatment patients which was statistically significant (Tsega et al., 2017)". The variation of this study finding could be due to the target group used as suspected MDR-TB. The availability and use of GeneXpert services

that quickly determines new MTB presence and resistance to rifampicin for further action. This meant that if a new TB-case was classified as MTB with rifampicin resistance it is considered as suspected MDR-TB for action.

During, the first national survey conducted on resistance to first line anti-TB drugs, primary resistance was reported to be 22.0% (76/346) (Addo et al., 2018) which supports the similarly high rate this study found. Studies by Owusu-Dabo et al., previously have also reported higher rates of 23.5% of primary infection resistance in Ghana (Owusu-Dabo et al., 2006). This they indicated that ranks Ghana among African countries with a high prevalence of drug-resistant TB.

In other African countries like Sierra Leone and Kenya, resistance amongst new cases have been reported as 52.9% and 37% respectively in previous studies (Odone et al., 2016). These findings come to awaken us to continuous strengthening the DOTS system to improve case management as we are all at risk. The increasing burden cannot be over emphasized considering the incidence of drug resistance recorded amongst new cases. The high MDR-TB rate in new cases predicts the existence of active person-to-person transmission of MDR strains in the region and could tell general weakness in TB prevention and control measures.

For people with HIV positive test results, high proportions (41.7%, 5/12) were classified as MDR-TB in this work. It was statistically significant as further analysis depicted that individuals with positive HIV test had 7.8 times odds of association with MDR-TB

compared to HIV negative clients. This finding is supported by some work done in Latvia and Ukraine which also reports significant association observed between MDR-TB and HIV infection (Tola, Tol, & Shojaeizadeh, 2015). In Southern Ethiopia, a study showed that "HIV have statistically significant association for both acquired MDR-TB and primary MDR-TB (Abebe et al., 2012). The observed higher prevalence in the study could be linked to the fact that HIV-positive patients are more likely to have TB/MDR-TB compared to HIV negative patients due to their immunocompromised status. In supporting this findings, several studies showed that HIV infection was the major associated risk factor for spread of MDR-TB infection in populations" (Glaziou, Sismanidis, Floyed, & Ravigglione, 2013; Lukoye et al., 2015; Tola et al., 2015; Villegas et al., 2016). It is not surprising, as Eastern region have noticed high rates (2.1% in 2017 to 2.5% in 2018) of HIV infection over the years in most districts and evidenced by reports of yearly national HIV sentinel survey. Koforidua, the regional capital has witnessed gradual rise from 2.8% in 2017 to 4.0% in 2018 (NACP, 2019). In the latest 2018 report, Koforidua site prevalence was the highest. These are however, contradicted by an Ethiopian study by Tsega et al., (2017) that reports no observation between MDR-TB and HIV statistically (Tsega et al., 2017).

Considering sputum smear microscopy results, this study reports it to be significantly associated with MDR-TB in the Eastern region during the period under review. Individuals with positive results for smear microscopy had 12.9 increased odds of association with MDR-TB. A previous study also supports this finding by reporting a significant association between sputum smear and MDR-TB cases. It further indicated that patients with MDR-TB had a significantly higher sputum smear-positivity rate than those with mono-resistant

or drug-sensitive TB (Goswami, Chakraborty, Mahapatra, Mahapatra, & Pal, 2014). Chuchottaworn et al., in their study also identified "a sputum AFB sputum smear-positive score of 3+ (OR 13.09) and the presence of cavities (OR 3.82) upon chest radiography as independent risk factors for the development of MDR-TB (Chuchottaworn et al., 2015).

A 2015 study to investigate the factors that contribute to the occurrence of multidrug-resistant tuberculosis among Malaysian tuberculosis patients, identified positive sputum smears at diagnosis and in the 2nd month of treatment as factors that independently contribute to the occurrence of multidrug-resistant tuberculosis" (Mohd Shariff et al., 2016). In China a study found that positive sputum smears are one of the predictors for the occurrence of MDR-TB (Lv et al., 2018). However, in Delhi – India, findings contradicted previous significant association. Their study reports that MDR-TB prevalence was low among new cases of sputum-positive pulmonary TB cases (Hanif et al., 2009).

5.1: Limitations of the study

The use of secondary data limited the researcher in collecting information on some variables that are not collected routinely. As with cross-sectional studies, incidence could not be measured in the study and available data was unable to offer direct casual relationships.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1: Conclusion

The study identified that one in every ten suspected MDR-TB case was confirmed MDR-TB case. MDR-TB burden was high in newly infected cases. The overall resistance to at least any of the first line anti-TB drugs is high with Rifampicin being the most resistant. HIV positive test results, type of patient status and sputum smear positive results were significantly associated with MDR-TB.

6.2: Recommendations

Based on the findings of the study, the following recommendations are made to help reduce the burden of MDR-TB in the region and Ghana as a whole.

6.2:1: At the Health facility and District level

1. Health providers should continuously adhere to the criteria for suspecting MDR-TB cases
2. Improve case management and IPC standards to reduce primary infection
3. Intensify case finding and strengthen DOTS strategy prevent re-treatment cases

6.2:2: At the Regional and National level

1. Build capacity of additional laboratories to undertake Drug Susceptibility Testing
2. Scale up the implementation of e-tracker in dhis2 which keeps transactional data on TB cases to make electronic records of all cases readily available for decision making

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APPENDIXES

Appendix 1: Population profile by districts, E/R

Municipal/District	Population	Children (0-11 Months) - 4.0%	WIFA (12 - 49 Years) - 24.0%
Afram Plains South	139,836	5,593	33,561
Akwapim North	165,271	6,611	39,665
Akwapim South	44,492	1,780	10,678
Akyemansa	117,588	4,704	28,221
Asuogyaman	117,597	4,704	28,223
Atiwa	133,482	5,339	32,036
Ayensuano	92,156	3,686	22,117
Birim Central Municipal	174,807	6,992	41,954
Birim North	95,345	3,814	22,883
Birim South	143,014	5,721	34,323
Denkyembour	95,339	3,814	22,881
East Akim Municipal	203,403	8,136	48,817
Fanteakwa	130,295	5,212	31,271
Kwaebibirem	136,655	5,466	32,797
Kwahu East	92,165	3,687	22,120
Kwahu North	123,941	4,958	29,746
Kwahu South	82,626	3,305	19,830
Kwahu West	114,409	4,576	27,458
Lower Manya Krobo	108,049	4,322	25,932
New Juaben Municipal	222,459	8,898	53,390
Nsawam-Adoagyiri Municipal	104,873	4,195	25,170
Suhum Municipal	108,053	4,322	25,933
Upper Manya Krobo	85,810	3,432	20,594
Upper West Akim	104,885	4,195	25,172
West Akim Municipal	130,305	5,212	31,273
Yilo Krobo	104,888	4,196	25,173
EASTERN	**3,171,743**	**126,870**	**761,218**

Source: Ghana Statistical Service, Population and Housing Census estimate from 2010

Appendix 2: Health Facility profile by facility type and district, E/R

Municipals/ Districts	CHPS	Clinic	District Hospital	Health Centre	Hospital	Maternity Home	Polyclinic	Private Facility	Regional Hos	Total
Afram Plains S	21	0	0	7	0	0	0	0	0	28
Akwapim N	46	9	1	5	1	3	0	9	0	74
Akwapim S	24	0	0	5	0	0	0	0	0	29
Akyemansa	20	1	0	6	0	1	0	1	0	29
Asuogyaman	17	11	1	4	0	0	0	2	0	35
Atiwa	26	2	1	5	0	1	0	3	0	38
Ayensuano	20	0	0	7	0	0	0	0	0	27
Birim Central	44	1	1	1	3	2	0	6	0	58
Birim North	14	4	1	6	0	0	0	3	0	28
Birim South	22	1	0	5	0	0	0	0	0	28
Denkyembour	10	0	1	5	1	0	0	1	0	18
East Akim	47	2	1	4	3	3	0	5	0	65
Fanteakwa	34	4	1	3	0	1	0	1	0	44
Kwaebibirem	27	1	1	4	0	0	0	1	0	34
Kwahu East	16	3	0	5	0	4	0	5	0	33
Kwahu North	37	0	1	4	0	0	0	0	0	42
Kwahu South	22	0	1	5	2	1	0	3	0	34
Kwahu West	36	1	1	9	2	2	0	4	0	55
Lower M. K	33	3	1	5	2	1	0	2	0	47
New Juaben	52	13	1	4	1	1	1	10	1	84
Nsawam A	32	8	1	4	1	1	0	9	0	56
Suhum	21	3	1	5	2	0	0	5	0	37
Upper M. K	24	1	1	4	0	3	0	3	0	36
Upper West A	26	5	0	4	0	1	0	6	0	42
West Akim	32	4	1	5	0	1	0	5	0	48
Yilo-Krobo	44	4	0	10	0	3	2	5	0	68
Eastern	747	81	18	131	18	29	3	89	1	1117

Source: DHIMS2 (https://dhims.chimgh.org/dhims/dhis-web-pivot/, 13.11.2018 @ 2:15pm)

Appendix 3: Health Facility profile by Ownership and district, E/R

Municipals/Districts	CHAG	Government	Private Facility	Quasi-Government	Total
Afram Plains South	4	24	0	0	28
Akwapim North	0	56	9	0	65
Akwapim South	1	28	0	0	29
Akyemansa	1	26	1	0	28
Asuogyaman	1	27	2	1	31
Atiwa	0	32	3	0	35
Ayensuano	0	27	0	0	27
Birim Central	0	46	6	0	52
Birim North	1	20	3	0	24
Birim South	1	26	0	0	27
Denkyembour	3	13	1	0	17
East Akim	1	53	5	1	60
Fanteakwa	1	38	1	0	40
Kwaebibirem	0	32	1	0	33
Kwahu East	1	21	5	0	27
Kwahu North	2	40	0	0	42
Kwahu South	0	28	3	0	31
Kwahu West	2	46	4	0	52
Lower-Manya Krobo	1	41	2	1	45
New Juaben	2	62	10	0	74
Nsawam-Adoagyiri	0	38	9	0	47
Suhum	0	27	5	0	32
Upper Manya-Krobo	0	30	3	0	33
Upper West Akim	0	30	6	0	36
West Akim	0	38	5	0	43
Yilo-Krobo	0	57	5	0	62
Eastern	22	906	89	3	1020

Source: DHIMS2 (https://dhims.chimgh.org/dhims/dhis-web-pivot/, 13.11.2018 @ 2:15pm)

Appendix 4: List of district and facilities with GeneXpert services, Eastern Region

SN	DISTRICT	FACILITY
1	Akwapim North	Tetteh Quarshie Memorial Hospital
2	Asuogyaman	VRA Hospital
3	Atiwa	Enyiresi Government Hospital
4	Birim Central	Oda Government Hospital
5	Birim North	New Abirim Government Hospital
6	Denkyembour	St Dominic's Hospital
7	East Akim	Kibi Government Hospital
8	Fanteakwa	Begoro District Hospital
9	Kwaebibirem	Kade Government Hospital
10	Kwahu North	Presby Hospital, Donkorkrom
11	Kwahu South	Atibie Government Hospital
12	Kwahu West	Holy Family Hospital
13	Lower Manya Krobo	Atua Government Hospital
14	New Juaben	Eastern Regional Hospital
15	Nsawam Adoagyiri	Nsawam Government Hospital
16	Suhum	Suhum Government Hospital
17	Upper Manya	Asesewa Government Hospital
18	West Akim	Asamankese Government Hospital

Source: Eastern Regional Health Directorate, Annual Tuberculosis control report - 2018

Appendix 5: Data extraction tool

SN	Variable	Responses	Response code	Variable Code
Section A: Background characteristics				
01	Serial Number		01, 02, ….	SID
02	Unique ID	Lab number		UID
03	Year of registration	2014 2015 2016 2017 2018	0 1 2 3 4	Yreg
04	Age (completed years)		whole #	Age
05	Sex	Male Female	0 1	Sex
06	Residence	Rural Urban	0 1	Res
07	Reporting district	District code		Dist
Section B: Anthropometric factors				
08	Weight (Kg)			Weight
09	Height (cm)			Height
10	BMI (Kg/m^2)			BMI
Section C: Clinical characteristics				
11	Disease Classification	Pulmonary Extra-pulmonary	0 1	DxClass
12	Type of patient	New Retreatment	0 1	tpatient
13	HIV status	Negative Positive Not Done	0 1 2	HIVtest
14	Smear results	Negative Positive Scanty	0 1 2	Smr_result
15	Category of MDR-TB suspect	Treatment failure Previously treated New MTB-RR TB/HIV	0 1 2 3	MDRTB_suspect
16	Culture results	No growth MTB Contaminated NTM	0 1 2 3	Cresults

SN	Variable	Responses	Response code	Variable Code
17	Drug susceptibility testing: Isoniazid (H) resistant?	No Yes	0 1	Dst_H
18	Drug susceptibility testing: Rifampicin (R) resistant?	No Yes	0 1	Dst_R
19	Drug susceptibility testing: Streptomycin (S) resistant?	No Yes	0 1	Dst_S
20	Drug susceptibility testing: Ethambutol (E) resistant?	No Yes	0 1	Dst_E
21	MDR-TB	No Yes	0 1	MDRTB

Appendix 6: GHS/ERC approval letter

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

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

MyRef. GHS/RDD/ERC/Admin/App
Your Ref. No. 19/096

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20th March, 2019

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

GHS-ERC Number	**GHS-ERC060/02/19**
Project Title	Factors Associated with Multi-Drug Resistant (MDR) Tuberculosis among Suspected MDR-TB Cases in Eastern Region, 2014-2018
Approval Date	20th March, 2019
Expiry Date	19th March, 2020
GHS-ERC Decision	**Approved**

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 CHAIRPERSON)

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