COLLEGE OF HEALTH SCIENCES
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PREDICTORS FOR MULTIDRUG-RESISTANT TUBERCULOSIS AMONG TUBERCULOSIS PATIENTS, BRONG AHAFO REGION, GHANA, 2019

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THIS THESIS IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF PHILOSOPHY IN APPLIED EPIDEMIOLOGY AND DISEASE CONTROL DEGREE

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DECLARATION

I, Charles Gyamfi Gyimah, author of this thesis, hereby declare that apart from specific references which have been duly acknowledged, this research is my own independent work undertaken under the supervision of Dr. Anthony Danso-Appiah. I further declare that no part of this thesis, either in whole or in part has been submitted elsewhere for the award of another degree

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DEDICATION

I dedicate this work to the most high God, who by His abundant grace and mercies has led me this far, glory be to His name. I further dedicate this thesis to the Gyimah family of Techiman and Nsawam.

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TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATION

TB	Tuberculosis
MDR	Multidrug Resistance
RR	Rifampicin Resistance
WHO	World Health Organization
PLWHIV	People Living with Human Immune Virus
GTR	Global Tuberculosis Report
NTP	National Tuberculosis Control Program
BCG	Bacilli Calmette-Guérin
HIV	Human Immune Virus
AIDS	Acquired Immune Deficiency Syndrome
XDR	Extensively Drug Resistance
GSS	Ghana Statistical Service
GoG	Government of Ghana
BAR	Brong Ahafo Region
CHPS	Community-based Health Planning and Services
OR	Odd Ratio
CI	Confidence Interval
DOTS	Directly Observed Treatment Short Course
FDC	Fixed Dosed Combination
DST	Drug Sensitivity Test

DEFINITION OF TERMS

Term	Definition
TB client	A patient with Mycobacterium tuberculosis complex identified from a clinical specimen, either by culture or a newer methods such as molecular line probe assay (LPA) or a pulmonary case with one or more sputum sample positive for acid-fast bacilli (AFB)
Pulmonary TB	A client with TB disease involving the lungs
Smear-positive TB	A client with one or more sputum smear examinations i.e. AFB-positive or one sputum examination AFP-positive plus radiographic abnormalities consistent with an active pulmonary TB as determined by a health service provider
Smear-negative TB	A client with a positive culture but negative AFB sputum examination
Extra-pulmonary TB	A client with TB of organs other than the lungs such lymph nodes, bones, meninges, skin, pleura, brain, kidneys and joints
New TB client	Any TB patient who has never had treatment for TB or who has been taken anti-TB for less than one month
Defaulter	A client who completed at least on month of treatment and do not return after interrupting treatment for two (2) or more months
Cured	A pulmonary or smear positive TB client whose smear or culture examination outcomes shows and remains negative with improved levels of serum at months 2, 5 and 6 and are declared as haven limited bacilli to cause another infection

Treatment completed	A smear negative or extra-pulmonary whose examination results shows negative at month 2, 5 and 6 haven taken the full course of the regimen
Loss to follow-up	A client who have previously been diagnosed with TB, treated for Tb and was declared 'loss to follow up' at the end of their most recent course of treatment
MDR-TB	It is resistance to the most effective anti-TB first line drugs, rifampicin and isoniazid
Primary MDR - TB	An MDR-TB client who is initially to and infected with resistant organism
Secondary MDR-TB	A TB client who develops resistance in the course of the TB therapy, either client was treated with inadequate regimen , or did not take the prescribed regimen appropriately, or due to drug malabsorption or drug interactions that led to low serum levels
XDR - TB	It is resistance to both isoniazid and rifampicin, plus any flouroquinolone and at least one of the injectable second line drugs (i.e. amikacin, kanamycin or capreomycin)

ABSTRACT

Background: Multidrug resistant tuberculosis (MDR-TB) has not been given the necessary attention in Africa and particularly Ghana where incidence of TB and risk factors are high. Nearly 600,000 new MDR/RR-TB clients with 240 000 deaths reported worldwide. Regionally, Africa accounted for 25% of the reported clients. However, Ghana reported a total of 528 MDR-TB with 63 (10.3%) deaths from 2012 to 2018. Of these cases, 44 (13.6%) were reported in Brong Ahafo Region over the same period. Possible resistance to the second line drugs is eminent. This can lead to increased new infections and mortalities. This study seeks to primarily identify the factors that independently could predict MDR among TB clients.

Method: We conducted an unmatched case-control study (1:3 ratio) to assess the socio-demographic, behavioral, health facility factors associated with MDR-TB using a structured questionnaire. Seven districts in BAR were selected for the study with approval from the KHRIRC. Cases were selected purposively whilst a simple random sampling to select their controls. A total of 36 cases and 108 controls were selected from smear positive TB clients (with cured/MDR outcome) between 2016 to 2018 were used for the study for the period of March to June, 2019. GIS was also employed to determine spatial patterns of MDR-TB. The data were entered into Epi Info 7.2.0 and analysed using STATA 15.0 versions. Descriptive statistics was performed to generate summary values for the variables and those that showed statistical significance in the bivariate level were entered into multivariate analysis to identify independent factors. Statistical significance was pegged at *p*-value less or equal to 0.05.

Results: In all, 36 cases and 108 controls were enrolled unto the study with a mean age of 42.7 (SD±11.6). Ages of participants ranged from 21years to 70 years. The mean age of cases was 44.4 (+-9.9) years, and controls 42.3 (+-12.1) years with majority within the age group of 20 to 40 years.

Females constituted 25 (69%) of cases and 53 (49%) of controls. Presence of HIV infection [AOR=12.3, 95% CI (2.49 – 60.77)] and taking more than one month of onset of first symptom to report at health facility [AOR=13.2, 95% CI (2.95 – 59.47)], treatment supporters [AOR=0.1, 95% CI (0.0 – 0.34)], living within a family [AOR=0.10, 95% CI (0.03 – 0.34)] and timely follow ups [AOR=0.2, 95% CI (0.76 – 0.79)] were discovered to independently predict the development of MDR-TB among TB clients.

Conclusion: Presence of HIV/AIDS infection and late capture of clients by the health system were found to have strong association with the occurrence of MDR-TB. Based on these findings, we concluded that strategies in combating multidrug resistant should be emphasize on clients with presence of HIV/TB co-infection, strengthening TB surveillance for early case detection, motivate treatment supporters and frequent follow-up of clients during first line treatment

Keywords: MDR-TB, predictors, case-control study, Brong Ahafo region, Ghana

CHAPTER ONE

1. INTRODUCTION

1.1 BACKGROUND

Tuberculosis (TB) is a contagious bacterial disease caused by an airborne bacterium *Mycobacterium tuberculosis* (WHO, 2017). It mostly attacks the lungs (pulmonary TB) but it can affect any organ in the body (extra Pulmonary TB). TB that affect other parts of the body is not as infectious as TB of the lungs. The infectious agents for TB was described as a mycobacterium complex to include other mycobacteria; *Mycobacterium bovis* - transmitted from cattle through unpasteurized milk, *M africanum* and *M canettii* - responsible for small number of cases in Africa whiles *M microti, M caprae, M pinnipedii* - also occasionally cause human disease (Heymann et al, 2016).

Pulmonary TB is transmitted from a sick TB patient as a droplet infection through coughing, singing and sneezing. Inhalation of these droplets by an uninfected person may cause infection. The risk of contracting TB increases with the frequency and duration of contact with people who have the symptomatic disease. The cardinal symptom of pulmonary TB is a cough lasting 2weeks or more. For people living with HIV (PLHIV), a cough for 24hours with other constitutional symptoms is strongly suggestive of pulmonary TB. Other symptoms are weight loss, tiredness, night sweats, chest pain and cough with blood stained sputum.

Eventually, between 5 to 15% will come down with the TB disease during their lifetime out of the estimated 1.7 billion people infected with *M. tuberculosis* (Global TB Report, 2017). However, the chances of being infected with TB disease is much higher among HIV infected persons, as well as individuals predisposed to under-nutrition, diabetes, smoking and alcohol consumption among other factors (WHO, 2017).

Current TB control is mainly challenged with the emergence of antimicrobial resistance. Drug resistant TB occurs when a TB patient's sample, after testing, is observed to have resistance to any of the first line TB medicines. There are two forms of drug resistance; mono and poly resistant TB. Of significance to the World Health Organization (WHO) and TB control programmes the world over, is the occurrence of Rifampicin Resistance (resistance to Rifampicin alone or in combination with other medicines) and Multidrug Resistance (resistance to Rifampicin and Isoniazid especially in combination with other medicines). The global strategy to mitigate the development and spread of TB currently is by effective infection prevention i.e. through effective case finding and treatment. This primarily helps to mitigate the progression of the infection to an active disease.

1.1.1 Global burden of TB

Tuberculosis (TB) can be found on all the continents of the world. It is a major global public health problem and most-frequent cause of death among adult (Global TB Report, 2017), though curable. It is one major public health concern in many countries especially resource poor countries. TB is the ninth leading cause of infection from a single infectious agent. An estimated 10.4 million new cases; made up of adults (90%), male (65%) and HIV infected persons (10%)) of TB were reported worldwide (Global TB Report, 2017).

Collectively, India together with China, Indonesia, Philippines and Pakistan make up 56% of the global prevalence burden of TB. Approximately, 400,000 cases of MDR-TB emerge every year globally due to; low-investment in the basic control TB activities, inadequate anti-TB drugs management, transmission of antimicrobial-resistant strains (WHO, 2017).

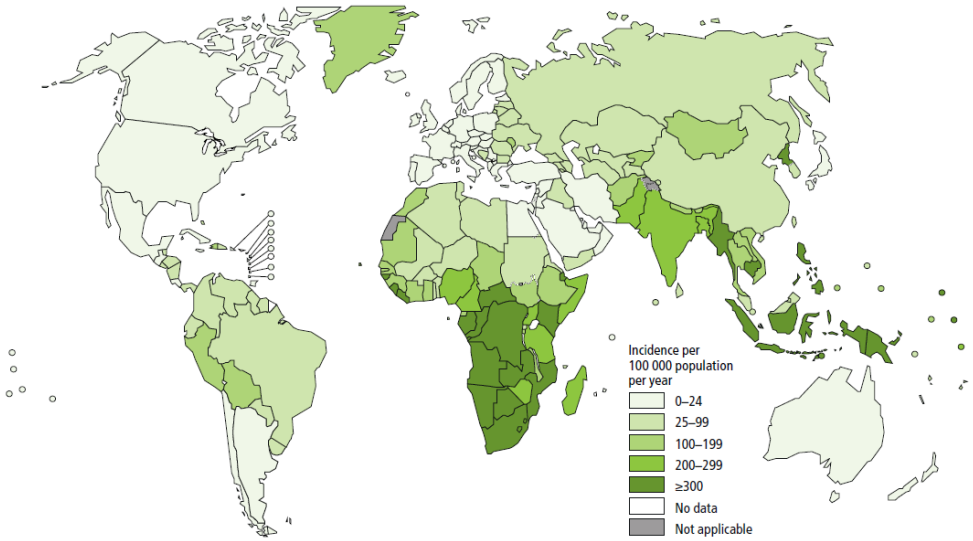

Figure 1: Estimated incidence rate of TB globally, 2016

Source: Global TB report, 2017

1.1.2 TB burden in Africa

The distribution of TB disease is heavily skewed towards low-income and poor countries globally, since it is known to be a poverty driven disease. Africa, and more particularly sub-Saharan Africa, contributes almost a quarter of the burden of TB the world over. The rates of both cases and deaths relative to population is high in Africa (280 clients per 100,000), more than two-folds the world's average figure of 126 (Global TB Report 2014). Of the 10.4 million reported cases in 2016, WHO AFRO region accounted for 25% (Global TB Report, 2017). Again, the region is home to 15 of the 30 and 7 of the 10 high burdened countries with TB and TB/HIV globally respectively.

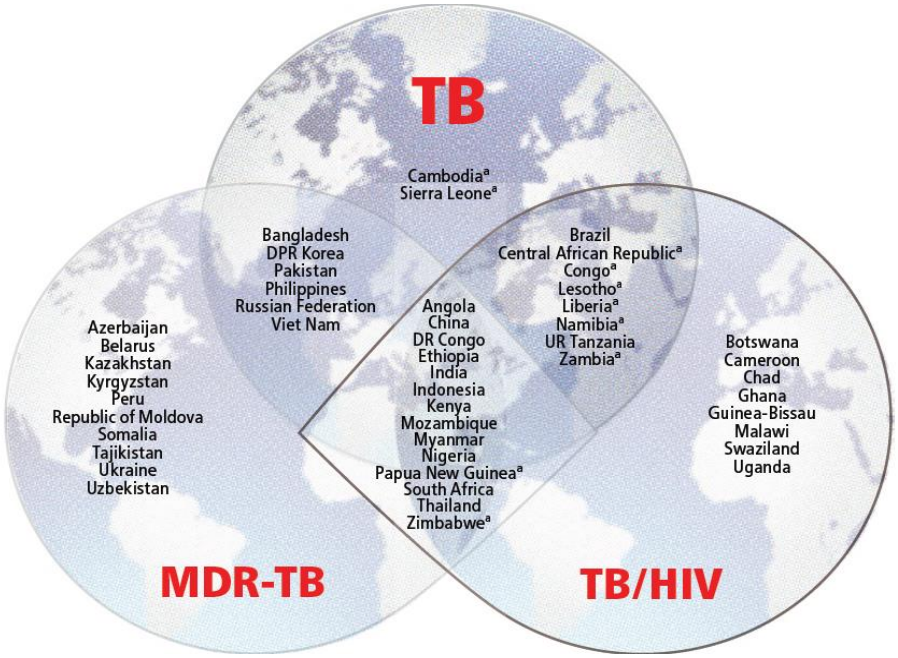

Figure 2: Distribution of TB, TB/HIV and MDR-TB endemicity worldwide, 2016

Source: Global TB report, 2017

1.1.3 TB Burden in Ghana

The Ghana National Tuberculosis Control Program began enrolling multidrug resistant TB (MDR-TB) cases onto treatment in 2012. As at end of 2016, 182 patients had been enrolled onto treatment nationwide with the breakdown viz: - (2012 = 6; 2013 = 25; 2014 =14; 2015 = 60; and 2016 = 77). Of these numbers, 15 (8.2%) have been declared cured, 12 (6.6%) have died, 6 (3.3%) have defaulted from treatment, 51 (28%) are still on treatment (NTP Report, 2017).

A recent survey in 2014 showed a national prevalence of 26% TB patients in Ghana (NTP, 2015). Furthermore, prevailing MDR rates in Africa could be more than originally anticipated as suggested by other statistical modeling. This is because figures from the continent could deviate from of the actuals since as most TB burdened African countries lagging the necessary personal

capacities and the financial muscle to perform routine drug sensitivity test (DST) for suspected clients.

In spite of the low knowledge level on the risk factors in the region, most studies done focused on the strains causing the drug-resistant but not necessarily the risk factors. However, history of diabetes mellitus, alcohol use, malnutrition presence of HIV infection, and low socioeconomic status among others have been hypothesized to be some of these risk factors. But these notwithstanding, many African countries appears to be reporting an increased MDR-TB prevalence. Enhanced surveillance data are needed urgently to support activities of the control programmes towards reducing the incidence.

1.2 Life cycle of TB bacilli

Drug resistant TB is spread the same as pulmonary TB (CDC, 2018). Through coughing and sneezing, the bacilli are released into the air when an infected person sneezes. The bacilli can float in the air for several hours depending on the environment. It then rapidly pass through the nose and mouth and into the lowest and smallest parts of the airways when inhaled. They move into the terminal bronchiole and alveoli of the lung.

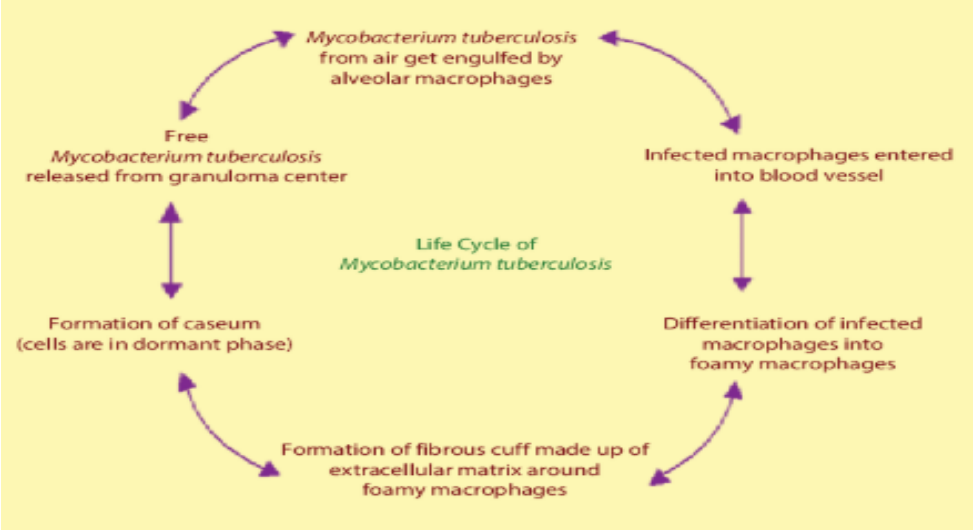

Figure 3: Life cycle of the *Mycobacterium tuberculosis* (www.who.int/tunerculosis)

TB infection occurs in four stages: the initial macrophage response, the growth stage, immune control stage and the lung cavitation stage. All these stages happens between 2 weeks to one month.

Stage one - The first stage takes place in the first week after the inhalation of the TB bacilli. It then gets to the alveoli of the lungs, it gets picked up by special cells of the immune system called the macrophages. These macrophages are usually found within the tissue of the alveoli; and its role is to swallow and inactivate any foreign object that enters the alveolar space. The macrophage then swallows the bacilli. The amount of the TB bacilli and the strength of the macrophage determine the next course of action. If the amount of bacilli is too large with a reduced strength of the macrophage to resist, it then reproduce many copies. This ultimately leads to the destruction of the macrophage and the infection of new and nearby ones that attempts to swallow the bacilli.

Stage two – if the macrophage cannot contain the TB bacilli, the infection then enters the second a week after. The bacilli start reproducing exponentially; which implies that for every initial bacilli, two more emerges and that also form new ones. This leads to rapid expansion of the initial bacilli

and macrophages can no more contain the spread. This last until about 3 weeks after the initial infection

Stage three – At this stage the bacilli growth and macrophage destruction are balanced. More immune are produced by the body to stabilize the site and the infection is brought under control. At least nine of ten patients infected with *Mycobacterium tuberculosis* stop at this stage with no development of symptoms of active TB. This is because, in the lungs, the bacilli and macrophages that swallowed them build a round complex; with the bacilli and the infected macrophages in the middle of a surrounded health macrophage. This shields the bacilli from the lung tissue but can however, survive for years inside the macrophage. Since the bacilli cannot enter the airways and be coughed out, patients at this stage are not contagious.

Stage four – This occurs as result of bacilli re-activation. It is because, in about 5% of TB clients, the primary complex does not completely heal and the bacilli become re-activated after 12 to 24 months of the initial infection. It then reproduces rapidly and form cavity in the tissue, where it is difficult for the body's immune system to reach. From the cavity, the bacilli quickly spread through the tissue and the person develop signs and symptoms of active TB. It can also the facilitated by HIV infection and malnutrition.

1.3 Presentation and transmission of TB

Pulmonary tuberculosis is an air-borne infectious disease caused by the bacillus called Mycobacterium tuberculosis (Heymann, *et al* 2016). Typically, pulmonary TB affects the lungs but can as well affect other parts of the body outside the lungs. This is called extra-pulmonary TB. Once a person is exposed to the TB bacilli, the minimum incubation period last between 2 weeks to 10 weeks (Heymann, *et al*, 2016). During this period, the exposed person can exhibit positivity

to the Interferon Gamma Release Assay (IGRA) or the Tuberculin Skin Test (TST). In spite of the fact that no specific time period exist for the IGRA appear in blood, it is expected after 10 weeks of incubation. WHO estimates that about 10% of persons infected with bacilli will develop TB in their life time eventually (WHO, 2013). Out of the 10%, about half will show progression of the disease within two year after first infection (Heymann, *et al* 2016). In one's entire life latent TB can persist one infected. However, when the immune system is compromised or presence of conditions such HIV, malnutrition, underweight, children under 5 years, diabetes and certain forms of cancers increases the subsequent risk of up to 50% progressive pulmonary or extra pulmonary TB. It also reduces the interval for the development of TB diagnosis among substance abusers such as alcoholics and smokers and leaves them at a greater risk of progressing to MDR-TB. The first 12-24 months of life constitute the period of greater risk for developing clinical TB disease (WHO, 2013).

Figure 4: The structure of *Mycobacterium species* under a microscope

Source: www.bioquel.com

The clinical presentation of the physical signs and symptoms by a TB client is paramount for the screening and diagnosis. Some of these include;

Major signs and symptoms;

- Persistent cough for 2 weeks or more or 24 hours in an HIV positive client
- Drenching night sweats
- Fever for more than 2 weeks
- Unexplained weight loss (more than 1.5kg in a month)

Physical signs;

- Fever – high but irregular body temperature (38.5 ℃)
- Chest – no abnormal signs may be present, but crackles in the lung apices with deep breath; localized wheeze in local obstruction or pressure
- Pulse - increased pulse rate due to the fever

TB is transmitted from an infected person to the susceptible one when they forcefully expel the bacilli into the air through sneezing, coughing, singing or spitting. Persons with cavity lesions are particularly infectious because their sputum normally contains from 1 to 10 million bacilli per milliliter (Heymann, *et al* 2016). Exposed and vulnerable persons inhale the droplet nuclei which mainly contain *Mycobacterium tuberculosis* into their pulmonary alveoli. This is finally digested by the alveolar macrophages and infection occurs beginning with the swelling of the endothelial cells. This result in alveolitis with the replication of the tubercle bacilli and the influx of polymorpho-nuclear leukocytes. However, a balance between the number and virulence of the microorganisms and the bacteria activity of the alveolar macrophages determines one's ability to either overcome the infection or develop the TB disease in the long run. Additionally, the risk of

exposure as well as subsequent infection may be associated with close and length of contact with a known case, cross ventilation within the immediate environment and the degree of how contagious the index case is (Heymann, *et al* 2016).

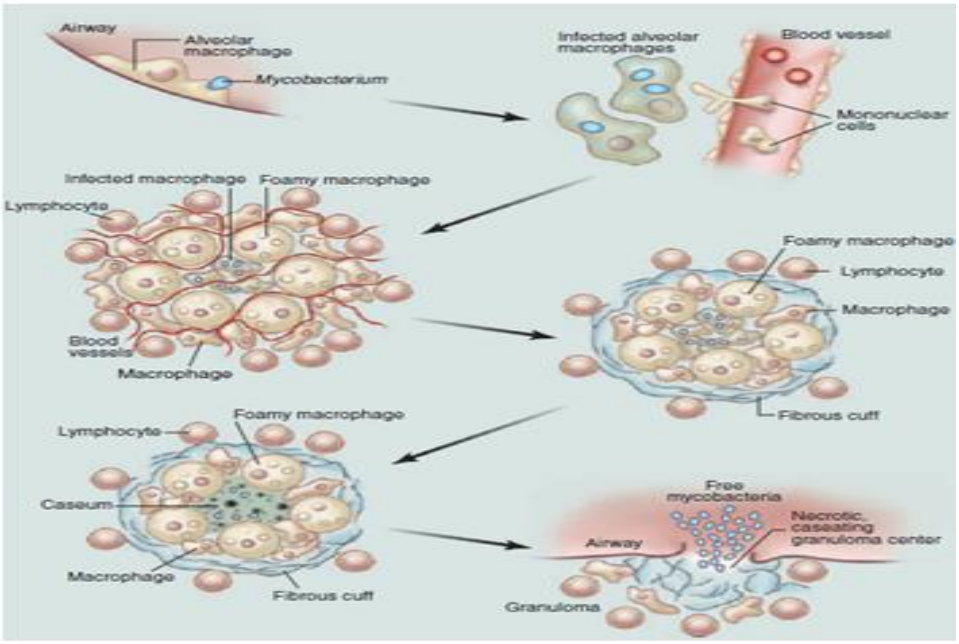

Figure 5: Pathogenesis of *Mycobacterium tuberculosis* (Russell et al., 2010)

1.4 Detection, Diagnosis and Treatment of TB in Ghana

1.4.1 Detection

Like most other African countries, Ghana has a well-organized and standard TB surveillance system incorporated into the integrated disease surveillance response (IDSR) framework (IDSR Revised edition, 2017). In effect, this system should have actively capture all suspected forms of TB from communities. But this notwithstanding, cases are largely found through passive case finding at almost all levels of healthcare within the country. This implies a situation where patients present themselves to health facilities if they suspect of having TB. As a result, Ghana is ranked as one of the countries with the lowest TB case notification rate. The current TB surveillance

system in Ghana is detecting about 54.2 per 100,000 population (World TB day, 2017) as against the WHO standard of 133 clients per 100,000 (Global TB Report, 2018). This represents a third of expected 44,000 cases annually (World TB day, 2017). Case detection rate, nationally is 33% with male to female ratio of diagnosed cases as 2:1 (World TB day, 2017). This is far below the target. Notification data from the National Tuberculosis Control Programme of Ghana showed a decline of 2.5% new TB clients notified over the previous years. Additionally, the proportion of notified paediatric clients (all forms) dropped gradually from 5.4% in 2010 to 4.8% in 2016 (GHS, 2017).

1.4.2 Diagnosis

TB diagnosis is primarily by bacteriologically identifying the *Mycobacterium tuberculosis* bacilli in a sputum sample of a suspected TB client. TB of the lungs (pulmonary), the commonly reported form, is ideally diagnosed by sputum smear microscopy, which remains the cornerstone of TB diagnosis even in both PLWHIV and non-HIV clients, followed by chest x-ray or sputum culture for the less common form (extra-pulmonary TB) which is more aggressive.

Rapid molecular tests is on ascendancy worldwide, with smear microscopy diagnostics being phased out by many control programmes, though the gold standard for TB treatment monitoring (Global TB Report, 2018). Tests for first-line and second-line anti-TB drugs are available now. These include GeneXpert, which test for TB and rifampicin drug resistance simultaneously (the most powerful first-line anti-TB drug); first-line probe assays (LPAs) test for rifampicin and isoniazid resistance; rapid LPA for resistance to fluoroquinolones and anti-TB injectable (second-line) and sequencing (Global TB Report, 2017). WHO firstly recommended first-line and second-line LPAs for use in 2008 and 2016 respectively (Global TB Report, 2018). Globally, culture-based methods remains the gold standard for drug susceptibility diagnosis (WHO, 2018).

1.4.3 Treatment of TB

Mortality rates would be high without effective TB treatment. This sterns from the fact that, studies of treatment with anti-TB drugs in natural history of TB disease in the absence found that about almost 70% smear-positive pulmonary TB and 20% culture-positive pulmonary TB died within 10 years of being diagnosed (Global TB Report, 2018). In 1940's, effective drug treatments were first developed. The recommended and widely accepted treatment regimen currently for newly diagnosed clients is a 6 month regimen of four (4) first-line drugs namely: isoniazid, rifampicin, ethambutol and pyrazinamide. This is supplied by the Global TB Drug Facility for about US$ 40 per person. WHO members countries have chalked at least 85% treatment success rates since the introduction of this package (Global TB Report, 2017). Rifampicin and multidrug resistant treatments are longer, expensive (approximately US$ 1000 per client) and use of more toxic drugs. WHO latest data showed 55% MDR-TB treatment success rate worldwide (WHO, 2018).

The TB and TB/HIV clinical management guidelines by the Ghana Health Service (GHS, 2007), stated that, diagnosis of usually consisted of clinical screening by assessment of signs and symptoms, followed with sputum smear microscopy. Unfortunately, periphery facilities such as the clinics, health centers and CHPS compounds lack the requisite resources and technical know-how to carry out such diagnostic activities.

Figure 6: TB management drugs

Source: www.indiamart.com

TB has been treated successfully with powerful chemotherapy since the discovery of the anti-TB drugs namely; streptomycin (STR) in the 1940's, isoniazid (INH) in the 60's, ethambutol (EMB) and rifampicin (RIF) but for the presence of drug resistance in recent times. Different from other bacterial diseases where single regimen is usually used for treatment, TB has been treated for over 5 decades with a combined therapy. The combination therapy is used for reasons including;

- Reducing the chances of acquiring drug resistance
- Aid in effectively clearing the bacteria

The standard treatment for new TB patients consist of daily uptake of INH/RIF/PZA/EMB, for 2 (intensive phase), followed by INH/RIF daily for 4 months (continuous phase).

Re-treated clients have 5 times probability to come back with MDR strain causing TB, and therefore should accordingly be treated based on drug sensitivity test results. The drugs mostly used for MDR-TB are grouped into three, which includes injectable aminoglycosides; i.e.

- Group 1- STR, kanamycin (KAN) and amikacin that inhibits the synthesis of protein.
- Group 2- (flouroquinolones); ofloxacin, levofloxacin that also targets DNA replication
- Group 3- (oral bactericidal); ETD, cycloserin which targets cell wall biosynthesis

Based on new evidence from several WHO member countries, the treatment guideline was updated with a shortened regimen of 9–12 months rifampicin resistant or MDR-TB not resistant to second-line drugs. This is exclusive of pregnant women

The private sector including the faith-based organizations and the traditional medical practitioners plays a crucial role in the healthcare in Ghana including TB case detection, diagnosis and treatment especially in the rural areas. Sadly, in planning and executing healthcare interventions especially in resource allocation and capacity building, there is mostly poor collaboration between governments the private sector partners.

1.5 Problem statement

Multidrug resistant tuberculosis (MDR-TB) is an emerging area in TB care and a global public health threat currently as far as the fight against TB control is concerned. An estimated 600,000 cases of multidrug-resistant TB with 240,000 deaths emerged in 2016 (WHO, 2017). Of the reported clients, 39% were confirmed bacteriologically and re-treated clients notified globally. This figure were also reported to have been tested for rifampicin resistance, an improvement of 31% from 2015. Coverage for new TB patients was 33% and 60% for relapse TB clients. Aside the resistant to Rifampicin and other first line medicines, there is also a microbiological transmission involving bacteria strains. Bacteriologically, transmission of multi or single drug resistant strains in new clients is influenced by being a relapse client.

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS (Global TB Report, 2017). Same report estimated 10.4 million

people (90% adults; 65% male; 10% people living with HIV) came down with TB in 2016 globally (i.e. new clients). The WHO African Region accounted for (25%) of the total cases. There were also an estimated 1.3 million TB deaths among HIV negative people.

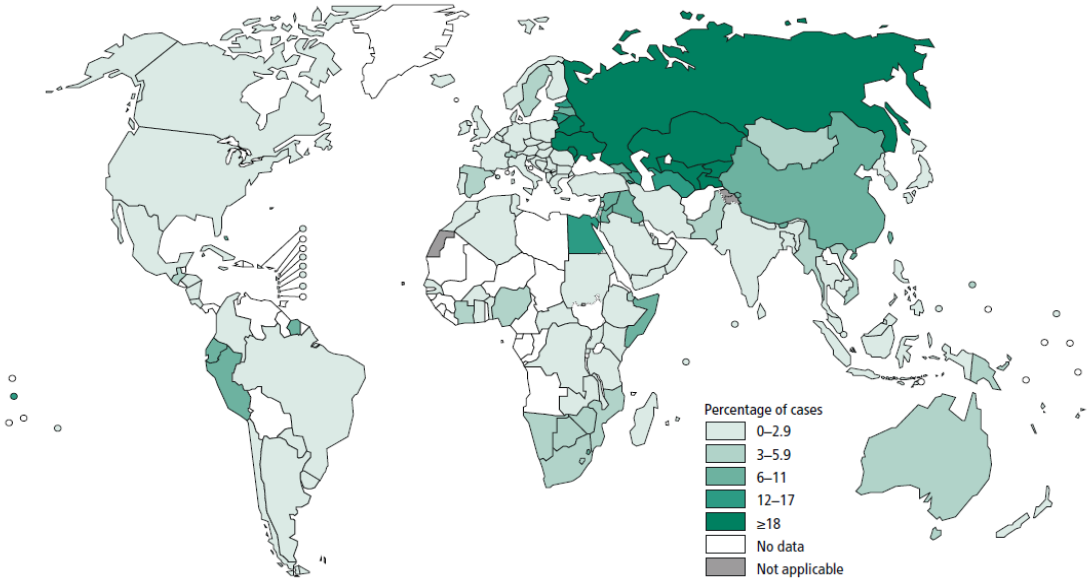

Figure 7: Reported MDR-TB clients globally, 2016

Source: Global TB report, 2017

Locally, 14,632 new TB cases were reported in Ghana and a total of 528 MDR-TB with 63 (10.3%) deaths from 2012 to 2018 (NTP, 2018). Of these cases, 44 (13.6%) were reported in Brong Ahafo Region (NTP, 2017).

Due to errors committed by physicians during diagnosis and prescription as well as patient non-compliance during treatment, MDR-TB is increasingly becoming a global problem as most cases are occurring (Abdulhalik et al.,2017). Other factors such as alcohol use, low socio-economic status, HIV co- infection and history of previous TB infection have been espoused as the drivers for facilitating the occurrence of MDR-TB. The magnitude of country-specific and regional burden varies significantly from each other but the worst affected are the resource poor countries.

Treatment of drug resistant TB is very difficult and expensive. Until August 2018, WHO typically recommended treatment regimen lasted for 20 months; including a minimum of 8 months injections at a cost of about US$ 2000–5000 per person. WHO has since updated the treatment guideline with a reduced regimen from 20 months to between 9 to 12 months. In spite of this update, medicines still cost up to 40 times more than first line medicines ($25 compared to $1,000). Side effects of medicines are very severe including hearing loss and death. Morbidities, mortalities and disabilities will continue to surge if nothing is done about the underlying factors and solutions tailored towards its control. Treatment outcomes are much poorer with the possibilities of evolving Extensively Drug Resistant TB (XDR-TB). Resistance to second line drugs is eminent and poses a bigger threat to TB care and prevention.

With persistent increases in the number of MDR-TB and a reported XDR case in the country (NTP, 2017) due to the introduction of the GeneXpert for both diagnosis and rifampicin sensitivity testing at the district level. A total of number of 32 MDR-TB cases has been reported from 2016 to 2018 after the initiative in 2014 at BAR. It is therefore prudent to find out the potential risk factors of MDR-TB for such a sharp increase to avoid a possible total inefficacy or resistance to the first line TB treatment regimen. Therefore, this study is aimed to also afford the program evidence-based solutions to inform policy and improve strategies to ensure enhanced favourable treatment outcomes.

1.6 Justification

Until recently, not much premium was placed on MDR-TB in sub-Saharan Africa. This is inclusive of the countries where significant numbers of TB incidence and risk factors are believed to occur without enough empirical evidence. Many factors such male sex among the youth, HIV infection,

presence of diabetes mellitus, contact with known TB client, use of alcohol and low socioeconomic status have been hypothesized to be some of these risk factors. New data by (WHO, 2017) showed a global an MDR-TB treatment success rate of 54%. This indicates high number of loss to follow-up, unevaluated treatment outcomes and relapse clients. It therefore calls for serious attention to unravel the underlying risk factors to avert potential jeopardy of the strides chalked in TB control locally and the world over.

Nonetheless, as GeneXpert MTB/RIF test grows for simultaneous *M. tuberculosis* detection and rifampicin resistance, an increasing number of drug resistant clients are being detected. In spite of this development, there is limited documented findings on the potential risk factors of MDR-TB in Ghana which could lead to a total resistance of the first line TB treatment regimen. To formally document the risk factors, afford the program evidence-based solutions to inform policy and improve strategies to ensure enhanced treatment outcomes thereby reducing the incidence of MDR-TB as well as adding on to literature, hence the need for the study.

1.7 Conceptual framework

The gold standard globally to control TB currently is through preventing the infection from progressing to an active disease. Obviously MDR-TB is increasingly becoming an emerging field and one major global public health challenge in controlling TB in recent times. Multidrug resistance tuberculosis is resistance to at least rifampicin and isoniazid. When a client is diagnosed as an active case and enrolled unto the treatment regimen, it is expected that he converts into the inactive stage after the two initial month's intensive phase, the 5th and 6th months in the continuation phase and finally declared cured after the 6months treatment period. However, several factors shown in figure 2 interplay to affect a clients' treatment outcome once enrolled

unto the regimen including patient level factors, health facility factors and program factors. But for the purpose of this study, the focus is on the patient's socio-demographics, patient's behavioral and the health related factors and its association with treatment outcomes.

1.7.1 Patient factors

Demographic and socio-economic factors: several studies have identified some demographic factors to be significant predictors for occurrence of MDR-TB among TB clients. These includes age, where a study in Ethiopia where clients' ≤ 30 years had seven times likelihood of MDR-TB due to reluctance in adhering to medications. Number of rooms in a house where clients and other dependents live in less than two rooms had 5 the probability of having MDR-TB than households with more than two rooms (Abdulhalik et al, 2017). Monthly income, another major indicator of one's socio-economic status, a higher burden of MDR-TB exists among individuals with low socio-economic background was found (Desissa et al, 2018).

1.7.2 Patients' health related and behavioral factors

Similarly, certain patients' behavioral and health related factors are known to be factors for influencing MDR-TB among clients. Notable among these factors is the presence of HIV where clients with an HIV coinfection had three times increased risk of developing MDR-TB than those with no HIV status. This is because, with a compromised immune status due to the co-morbidity, it always difficult to treat or adhere to treatment, therefore resulting in MDR-TB in most cases. Again, clients with history of previous treatment had higher risk of developing MDR-TB as compared to clients with no previous TB treatment. Additionally, alcohol consumption increases

clients' chances of developing MDR-TB due to potential poor adherence to treatment, impaired immune response and an increased risk of adverse drug effects. Clients with such behavioral and health related attributes stands a greater risk of developing MDR-TB if much importance is not given to their management. Though the behavior and lifestyle of a TB client can directly determine the outcome of his treatment, invariably, it can also do so through the health facility factors. That is, patient's health history (use of alcohol, presence of diabetes or HIV co-morbidity, etc. can affect the diagnosis as subsequently the drug adequacy thereby influencing the treatment outcome. On the other hand, patient's behaviors or lifestyle such as smoking, use of illicit drugs, non-compliance treatment supporter, etc. can also affect the important role of the treatment supporter, time of reviews to also influence the treatment outcome.

1.7.3 Health facility level factors

Many factors come together to determine the outcomes of diagnosed TB clients on a treatment regimen including diagnosis, counselling, medications, reviews and staff attitude at the health facility level. These factors could determine the performance on treatment and the final outcome. When a patient is misdiagnosed as false negative TB and treated with any drugs, the client may come back in a worse form during which treatment and adherence becomes very difficult. Also, when treatment initiation and review protocols are not duely followed with an assignment of a treatment supporter, clients may not see the need to take the drugs for treatment and revisiting the health facility in particular periods for six months, thus may end up as MDR-TB client. Inadequate medications; the dosage per each clients' regimen is very crucial in determining his treatment outcome. Therefore, if the measurements and quantity of drugs required are not correctly done, clients may be taken through all the appropriate diagnosis, counselling and with a treatment

supporter, but will yield no positive outcome at the end. Adequate knowledge and adherence to treatment is a major pre-requisite for prevention and determining treatment outcomes of clients on treatment regimen. Similarly, addressing patient and health facility factors can ensure timely reporting, adequate diagnosis and better management to forestall adverse treatment outcomes of clients.

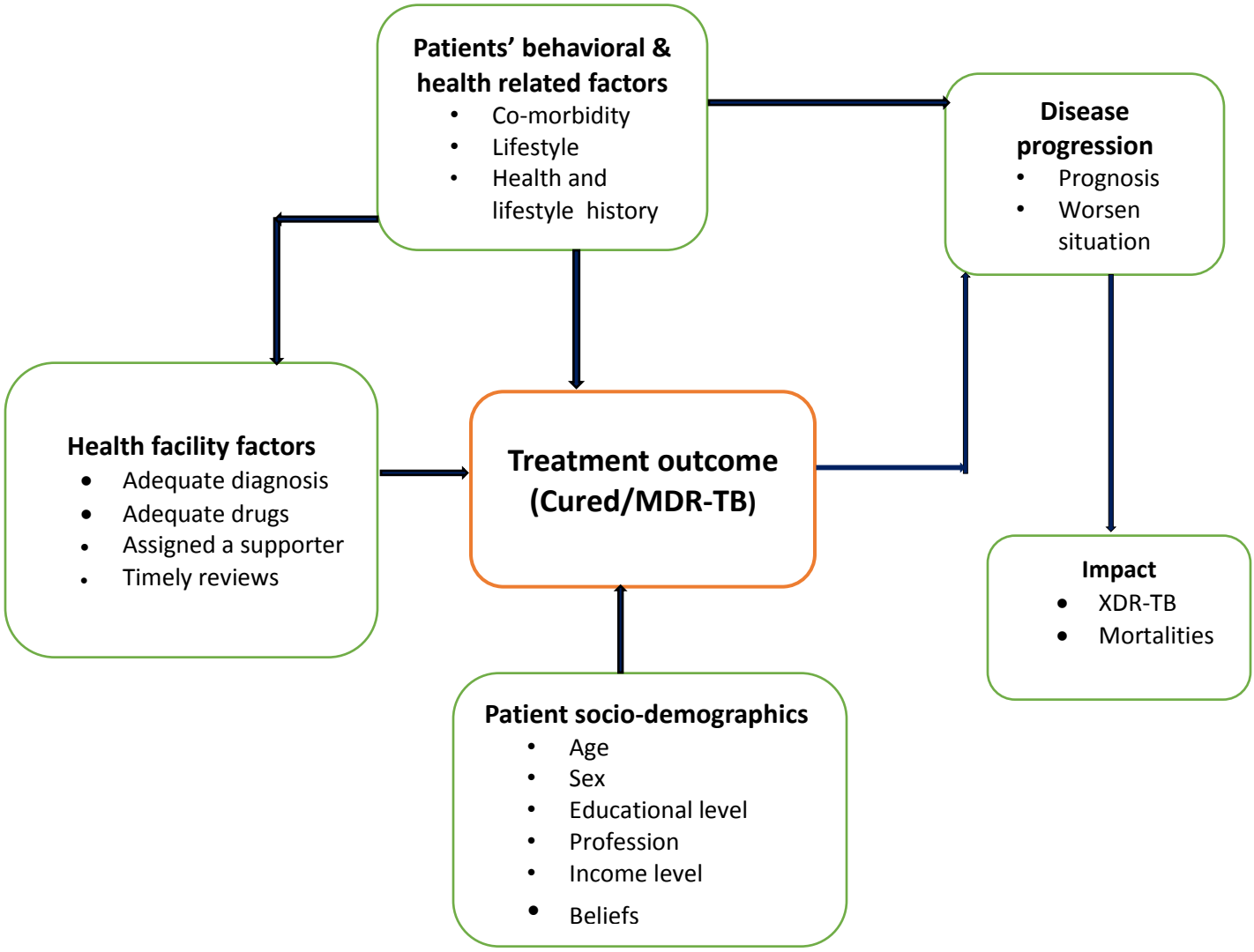

Figure 4: Conceptual Framework

1.8 Spatial pattern of clients

Many studies on TB have implicated several factors as predictors for the causation of the disease. With an improved diagnostic, treatment and control systems as viable mechanism of working towards the achievement of the SDG goal of ending TB epidemic by 2030, the focus must now be shifted to the interplay between those documented factors and the use of an incredibly powerful tool of Geographical Information System (GIS). The GIS has the ability to identify locations that are heavily affected by a specific medical condition of an investigator's interest, such as tuberculosis treatment outcomes. Tuberculosis intervention can use GIS-based, remotely sensed model to predict the prevalence in an area and thereby proceed to enter into these communities to engage community leaders in formulating a TB management and control plan. Public health and medicine have mostly been reactionary; where they identify areas that are currently suffering from a particular disease condition and seek to respond, rather than identifying areas that shows signs of potential suffering in the future, which could be prevented. GIS could be used to identify areas and vulnerable people to the spread of TB due to environmental and social factors as well as proximity to many of these clients. Essentially, mapping out disease in geographic space, local and national health authorities can easily identify the triggers, distribution and spread across districts and regions, optimize planning of interventions and monitor their effectiveness.

Research questions

1. Which demographic and socio-economic characteristics of TB clients affect the treatment outcome?
2. What are the patient related factors that influences MDR-TB?
3. What are the health facility factors that facilitates MDR-TB treatment?
4. What are the spatial patterns the clients within the districts?

Main objective

To determine the risk factors for MDR-TB among previously treated tuberculosis patients

Specific objectives

1. To assess clients' demographic and socio-economic characteristics associated and their relationship with treatment outcomes
2. To evaluate patient related factors that influences treatment outcomes
3. To evaluate health facility factors that determines treatment outcomes
4. To determine the spatial patterns of the clients within the study sites

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Epidemiology of Tuberculosis

One major global public health problem with long standing history as an opportunist is tuberculosis (WHO, 2015) but the emerging trends in multidrug resistance TB will worsen the situation. The fact is that, apart from the cost and duration of treatment, it comes with its own dire difficulties and tendency of defaulting. This, if not well managed, may have serious consequences on both the client with a higher risk of death and the community in which they find themselves in by probably giving rise to many infections and strains in circulation. TB occurs in every part of the world and affect all countries, sex and age groups.

In 2018, the World Health Organization estimated that over 10 million new clients of TB were reported in 2017, which equates to 133 clients per 100,000 population (Global TB Report, 2018). On average, 27,397 people acquire TB infection whilst 4,383 people lose their lives daily (TheUnion, 2017). An additional 1 million children also became ill from TB infection with 230,000 deaths including those associated with HIV co-morbidity (Mesfin *et al*, 2014). South-East Asia accounted for 62% of the new cases followed by Africa with 25%. A significant number of these cases came from low and middle income countries in Africa. The overall statistics for 2017 showed that 90% of cases were adults in their youthful and most productive years (aged above 15 years), males constituted 64%, whilst 9% were HIV infected and 72% lived in Africa. Of all the WHO member states who report on TB, 30 are often referred to as the TB "high burden countries". About 87% of the new TB cases occurred in these countries including India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South

Africa (3%) (Global TB Report, 2017). European and the WHO region of the Americas recorded only 6% and 3% of the cases respectively.

Multidrug resistant TB (MDR-TB) remains a public health crisis and a health security threat. In 2017, WHO estimated that there were 558,000 new cases with resistance to rifampicin; the most effective first-line drug, of which 82% eventually became MDR-TB (Global TB Report, 2018). Of this figure, only 1 in 4 clients needing treatment actually received, contributing to about 55% of those who started MDR-TB treatment and declared as cured in 2017 (TheUnion, 2017). Also, about 8.5% of the MDR-TB reported in 2017 resulted in extensively resistant TB (XDR-TB) (WHO, 2018). India alone accounts for nearly one-quarter (24%) of the worlds cases of MDR-TB (TheUnion, 2017).

Ending the TB epidemic by 2030 is among the health targets of the Sustainable Development Goals (SDG's). Generally, the world is on course to achieving the SDG's target 3.3 which states vividly that: "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases"(SDG's, 2015). Globally, TB incidence is gradually declining at about 2% per year. From 2013 to 2017, the fastest regional decline were in the WHO European region and African region with 5% and 4% respective decline annually (Global TB Report, 2018). An estimated 54 million lives were saved through TB diagnosis and treatment between 2000 and 2017 (WHO, 2018). Cases and death rates has also fallen steadily. Nevertheless, "the end of TB as an epidemic and a major public health problem" is still a mirage for many countries including Ghana and Africa as a whole. To close this gap, better reporting, diagnosis and access to care is urgently required. Alternatively, better prevention, detection and treatment can also address the MDR-TB crisis (WHO, 2018).

2.2 TB and HIV

Approximately, there are currently 36 million persons infected with HIV globally and about one-third of them are also infected with TB (USAID, 2018). Hitherto, 1.2 million had HIV out of the 10.4 million persons who developed TB in 2016 (USAID, 2018). The dual epidemics are a growing concern in the world, especially Asia, which accounts for two-thirds of all TB cases and 40% of HIV/AIDS deaths due to TB (USAID, 2018). Eastern Europe and Russia have the fastest growing HIV epidemic in the world, a factor that further exacerbate the expanding problem of MDR-TB in those regions and the entire world. The overlap of TB-HV co-infection with MDR-TB and XDR presents a tremendous challenge and poses a great threat to the successes chalked in controlling TB and HIV/AIDS and in mitigating the mortality associated with these deadly diseases, despite being preventable and treatable.

HIV co-infection is one of the main factors for predicting TB in Ghana, like other countries. TB/HIV client often manifest the symptoms of HIV infection as a first symptom in most African nations, and largely the leading cause of death among HIV- infected clients (Linguissi *et al*, 2014). It is also the main cause of deaths related to antimicrobial resistance and the leading killer of people with HIV. In 2016, there were an estimated 374,000 deaths among HIV-positive people (Global TB Report, 2017). Despite the relative low HIV sero-prevalence in the general population (1.3% - HIV/AIDS report, 2013), the net influence of HIV on TB/HIV co-morbidity increased from 14% in the 80's to 24% (Global TB Report, 2018). In spite of the mandatory HIV screening of all TB clinics and vice versa, TB/HIV death is still high in Ghana. The rate of TB deaths due to HIV increased from 3.2% in the 1980's at the beginning of the epidemics to 5.1% in the 90's and is pegged at 7% currently, next to malaria which is 13% (Ansa et al, 2014).

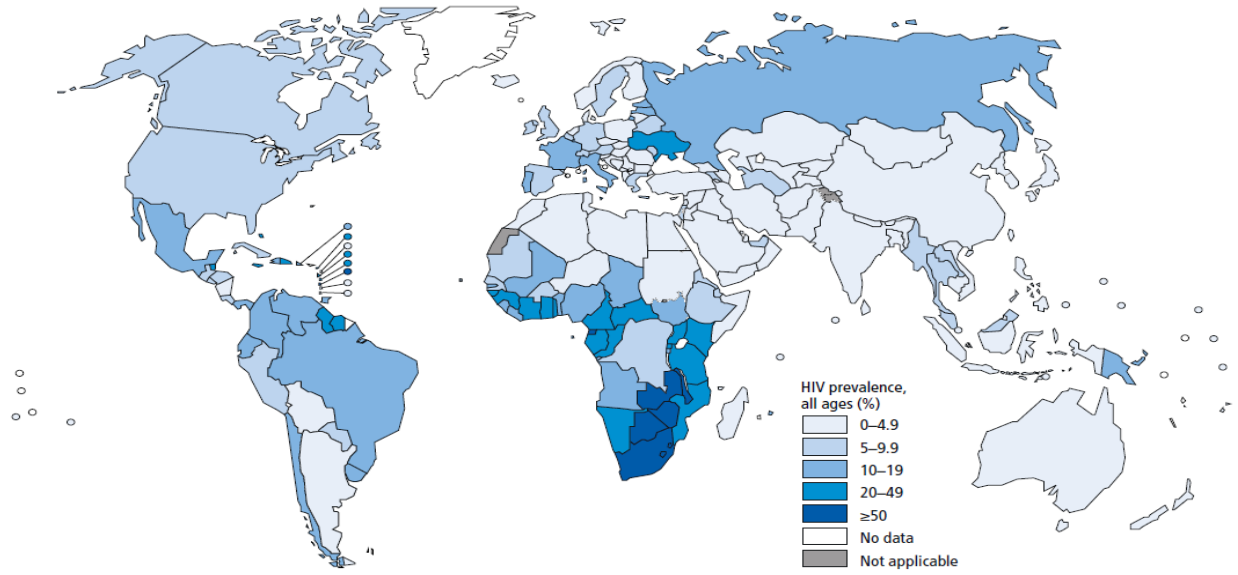

Figure 8: Distribution of estimated prevalence of HIV among TB clients by ages globally, 2016

Source: Global TB report, 2017

2.3 Multidrug Resistance TB

In TB control, drug resistance is defined clinically as the increased ability of the TB bacilli at any given time, to tolerate high levels of specific anti TB drugs. It is categorized into two types; primary and acquired resistance. Primary resistance is when a TB client is infected by an already drug resistant strains. Conversely, acquired resistance could be described as the drug resistance development on a treatment regimen. Particularly, primary resistance poses a major threat to TB control. This is because, a little over 20% of estimated drug resistant clients worldwide are believed to be inadequately diagnosed, largely due to lack of appropriate laboratory infrastructure and capacity in low-income endemic countries (Müller *et al*,2013). Irrespective of the type or path of emergence, drug resistant TB is very difficult to cure. A prevalence study in Ethiopia reported 27.1% of MDR-TB were susceptible to all four first-line drugs, 73% of MDR-TB were resistant to at least on drug (Abate et al., 2012)

The two (2) most important forms of drug resistance are MDR and XDR TB. MDR-TB is resistance to at least rifampicin and isoniazid, the two most powerful anti-TB drugs. Whereas XDR-TB occurs when MDR-TB cases are additionally resistant to at least one injectable drug such as Amikacin, Kanamycin or Capreomycin and one fluoroquinolone (WHO, 2012). Invariably, XDR emerges when the management of MDR is inadequate. Streptomycin according to a study by Abate et al., 2012 found Streptomycin as the most common anti-TB drug susceptible to resistance. In 2017, WHO estimated that on average, 9% of all XDR cases are MDR (Global TB Report, 2018). This however, implies that for an effective control of drug resistance TB, early identification, appropriate diagnosis, timely initiation of adequate medications is essential to prevent further development and spread of resistance.

Ideally, with the introduction of the GeneXpert diagnosis technology, all clients should be tested for drug resistance before enrolling them unto the treatment regimen with the most appropriate drug. Unfortunately, this is not the case in most facilities and areas, especially private and rural respectively, where infrastructure and expertise are needed to perform drug sensitivity test and interpret results. The GeneXpert works as a fully automated system based on real time amplification of specific regions of the gene (DNA) for the detection of drug resistance strains during testing (Global TB Report, 2018).

2.4 Patients' demographic and socio-economic characteristics influencing TB treatment outcome

The treatment outcome of any confirmed TB client is greatly affected by a myriad of factors of which the socio-demographic make-up is no exception. Both health facility, patient behavioral and socio-demographic factors interplay to play a major role. However, demographic and socio-

economic characteristics of the population plays a vital role in determining both the causation and treatment outcome of a disease including TB.

Effective TB management depends on the age categorization and the immune response level of the client. The paediatric (≤ 15years) and the aged (>60 years) tends to have low immune response to bacilli and the rate of absorption of the TB drugs. A case control study by Zhang et al., (2016) in China showed 65% of 60+ years as the most affected age group. A retrospective study to show the trends and patterns of MDR-TB in Ethiopia also revealed that 15 to 45 years age group were the most affected Abate et al., (2012).

The biological and the physical make-up of humans can influence TB treatment outcome. These largely determines lifestyle and physical engagements to survive. Males sex seem to be more exposed to the predisposing factors of TB transmission in terms of the work type (e.g. mining, farming, quarrying, etc.) and behavior (e.g., smoking, alcoholism, illicit drug use, etc.). In spite of this, various studies have come up with divergent findings. This was affirmed by a study in China that male gender was more affected by MDR-TB than females Zhang et al., (2016). Abate et al., in 2012 and 2016 also reported male sex in studying the trends and patterns in MDR-TB in Ethiopia. Contrarily, in Pakistan, a study on the prevalence of MDR-TB among risk groups identified female gender as the most affected (Ejaz et al., 2010).

There exist a strong relationship between TB and poverty. Poor people are mostly vulnerable to tuberculosis due to their living conditions, living in houses with larger family size have been found to be an associated factor with tuberculosis Asefa & Teshome, (2014). A meta-analysis study on factors associated with TB patients and diagnostic delays in China Ying Li et al., (2013) found that socio-demographic and economic factors including most importantly, poverty, rural residence, lower educational attainment and poor knowledge on TB were largely associated with TB.

Additionally, global TB prevalence is particularly higher in poor and developing countries. Many of these high burdened countries accounting for about 80% of the global TB clients are in low middle income countries (LMICs) (Global TB Report, 2017).

TB-related stigma is an important social determinant of outcomes of treatment in TB care. Societal or family exclusion of clients can have a considerable impact with regards to treatment support, adherence to treatment and adversely affect outcomes of their treatment. In Ethiopia, clients who experienced family or social stigmatization had a greater probability of MDR-TB compared to those who lived within their families Assefa, (2017). Hirpa et al., (2013) also found social neglect or stigma as a predictor for MDR-TB. A similar in Napal also suggested stigma or family exclusion as an independent predictor of MDR-TB (Marahatta *et al*., 2010).

2.5 Patients' behavioral and health related factors influencing TB treatment outcomes

In many studies, socio behaviors have always been the least likely to be analysed with respect to diseases. However, the burden of any disease, including TB, cannot be ascertained without first examining how it affects the person, their daily habits and lifestyle. The contribution to the control of diseases by social scientist was due to the links they established between diseases and the social behavior of the population. Non-adherence to treatment was also found to be a direct linked with MDR-TB in Ethiopia university hospital by Biruk et al., (2016) established the relationship between treatment outcomes and development of MDR-TB. Similar to findings by Stosic et al., (2018), in Serbia, Khan et al., (2017), in Myanmar, Abdulhalik et al., (2017) in Ethiopia and a survey in South Africa by Weyer et al., (2009), they reported that patients who previously defaulted more than once a week had a substantially greater risk of MDR-TB than those reported to have

never missed their medication. An Ethiopian study by Desissa et al., (2018) revealed that clients with history of alcohol consumption were more exposed to MDR-TB although Marahatta et al., (2010) saw no association between history of alcohol and MDR-TB. The presence of TB/HIV co-morbidity was also established to be a higher risk factor for the development of MDR-TB by (Biruk et al., 2016), same as (Abdulhalik et al., 2017). Other case control study by Hirpa et al., 2013, found no association and meta-analysis in Ethiopia by Mesfin et al., 2014 with a marginal risk between HIV and MDR-TB. In case-control study in Serbia, by Stosic et al., 2018, reported illicit use of drugs (sedatives) was a predictor for MDR-TB. History of smoking was also reported to be associated with the development of MDR-TB in an unmatched case control study to explore the risk factors for MDR-TB in Tanzania (Matee et al.,2010) and Thailand (Marahatta et al., 2010). Contact history with a known TB client was independently identified as a strong determinant of MDR-TB in a study in Ethiopia (Assefa, 2017) same as discovered by Desissa et al., (2018). A study in Myanmar indicated that patients with diabetes had a twice the risk of MDR-TB (Tun et al., 2016).

2.6 Health facility factors influencing TB treatment outcome

Despite the interplay between patient factors, social, physical and psychological health of clients and the health systems operation to determine outcomes of clients' treatment, several factors within the health system as well dependently or independently influences the health outcome of clients who patronize the system. Early detection and prompt initiation of treatment are crucial for an effective TB control. Late detection and treatment further were found to increase the burden by raising the probability of transmission and speeding up the emergence of MDR-TB (Sreeramareddy *et al.*, 2009). A study on the determinants of MDR-TB among clients on first-line

treatment in Addis Ababa, indicate that treatment not directly observed by health staff was found to be an independent risk factor for MDR-TB. The provision of supporters to assist clients on their regimen, was reported by Marahatta et al., (2010), as strongly associated with the development MDR-TB. Contrary to these findings, clients provided incentivised treatment supporters was found to reduce the risk of MDR-TB by positively influencing treatment outcome (Kliner et al., 2015). Similar to Khan et al., (2017), there existed a weak association between having a treatment supporter in previous treatment and the development of MDR-TB. In a qualitative study in Pakistan, 85% of clients provided with treatment support had treatment success as an outcome (Ejaz et al., 2010).

The rise in antimicrobial resistance is largely caused by improper practices in the use of antimicrobial drugs and therefore requires combative measures to be implemented at the service delivery point and policy levels of the health system (Laxminarayan et al., 2013). Although inadequate diagnosis and treatment have been identified as a major underlying cause of acquired resistance (Ahmad & Mokaddas, 2012), information about how and why inadequate treatment occurs in TB clients; which is very crucial to inform changes in health service delivery and policy is lacking (Deye *et al.*, 2014). For instance, little evidence exist about whether the main predictor for MDR-TB in previously treated TB clients is non-compliance, inappropriate medication from healthcare providers or lack of guidance and social support during treatment. However, a study by Ejaz *et al.*, (2010) showed that all these factors play significant roles but their relative contributions are not well characterized. It is increasingly recognised that MDR-TB may be growing in Asian countries with an active, unregulated private health sector; such as Ghana, and that specific risk factors operating at the individual and health system levels must be urgently identified to inform MDR-TB control strategies.

The health seeking behavior of clients are also very crucial in the determination of outcomes of their treatment. This is usually influenced by the consideration of access to a health facility. When there is a difficulty in accessing a health facility, it inadvertently result in delayed seeking of care. When these obstacles are surmounted, other health facility-based factors such as timely diagnosis and adequate prescription, timely reviews and follow-ups play out in achieving successful treatment results of TB clients (Vries et al., 2017)

2.7 Spatial patterns in relation to TB treatment outcomes

In recent times, GIS has been employed extensively in public health fields for disease surveillance of several infectious diseases. The usefulness of GIS in predicting and controlling diseases the world over in recent times cannot be overemphasized. Like other diseases, different approaches have been explored to geographically and geospatially map out TB in many countries with different GIS versions. Understanding the geographic distribution and spread of MDR-TB in relation to the predictors for contributing to their occurrence in specific areas will allow for better planning interventions, monitoring and control of MDR generally. A study by Dangisso et al, (2015) revealed that an increased distance from diagnostic centers increases the chances of an adverse treatment outcome, higher population density was identified as a factor to determine treatment outcomes by the same study. This is similar to a study in China which also identified high population density as a determinant of TB treatment outcome (Mahara et al.,2018). Industrial location, urban migration and socio-economic levels among urban dwellers favoured the development and influence treatment outcome of TB in Malaysia (Rauf et al., 2019) contrary to Kolifarhood et al., (2015) who found no statistical significance between urban dwelling and adverse treatment outcomes. A South African spatial analysis study showed that TB clients were

clustered around local drinking spots in Cape-town and were predicted as responsible for MDR-TB transmission. Also a study by Touray et al., (2010) found a significant clustering of TB cases around the capital which subsequently guided the allocation and deployment of resources to improve treatment outcomes. A study by Tiwari et al., (2010) on geospatial analysis also identified the clustering of TB in Almora district but not as perceived to be in every district of India. Significantly high rates of spatial clusters were identified in three (3) areas of the district with useful information on the occurrence and distribution of TB in the country. This inadvertently aided the use of evidence-based strategies for more effective and efficient TB control by the health authorities and other relevant stakeholders.

CHAPTER THREE

3.0 METHODS

3.1 Study design

The study design was an unmatched case-control study (1:3 ratio) in reported districts/communities. Multi-stage sampling was used for the study. Firstly, purposive sampling was used to select districts with MDR-TB cases. Simple random sampling was then used to select controls randomly from similar backgrounds from 2016 to 2018. The study was conducted in health facilities and communities in the seven (7) districts identified as recording MDR-TB cases in the region. Data on patients' demographics, behavioral and health related factors were collected and analysed to determine the associated factors among cases and controls.

3.2 Study area

The study was conducted in seven selected districts with MDR-TB cases in the Brong Ahafo Region (BAR) namely, Techiman municipal, Kintampo north, Pru, Asunafo north, Asutifi north, Sunyani west and Wenchi as shown in figure 9. It is one of the ten administrative regions of Ghana. It lies between longitude 0^0 15 E and 3^0 W and latitude 8^0 45 N and 7^0 30 S. The region with a territorial size of 39,557 square kilometers is the second largest in Ghana with an estimated population of 2.5 million (Ghana Statistical Service (GSS), 2014). It is bordered to the north with Northern region, south east with Volta and Eastern regions, south with Ashanti and western regions and internationally with Ivory Coast to the West. The central point of the land mass of Ghana is located in the region in Kintampo North District. The Region is further divided into 22 administrative districts, which were increased to 27 in 2012 (GoG, 2015). There are two main

ecological zones in the region; the forest and savanna transition zones. The savannah zone have 15 districts whilst the forest zone have 12 districts.

Like all regions in Ghana, BAR runs a vertical public health service system from the community level to the regional level. The smallest health care unit at the community level is the Community Health Planning and Services (CHPS).

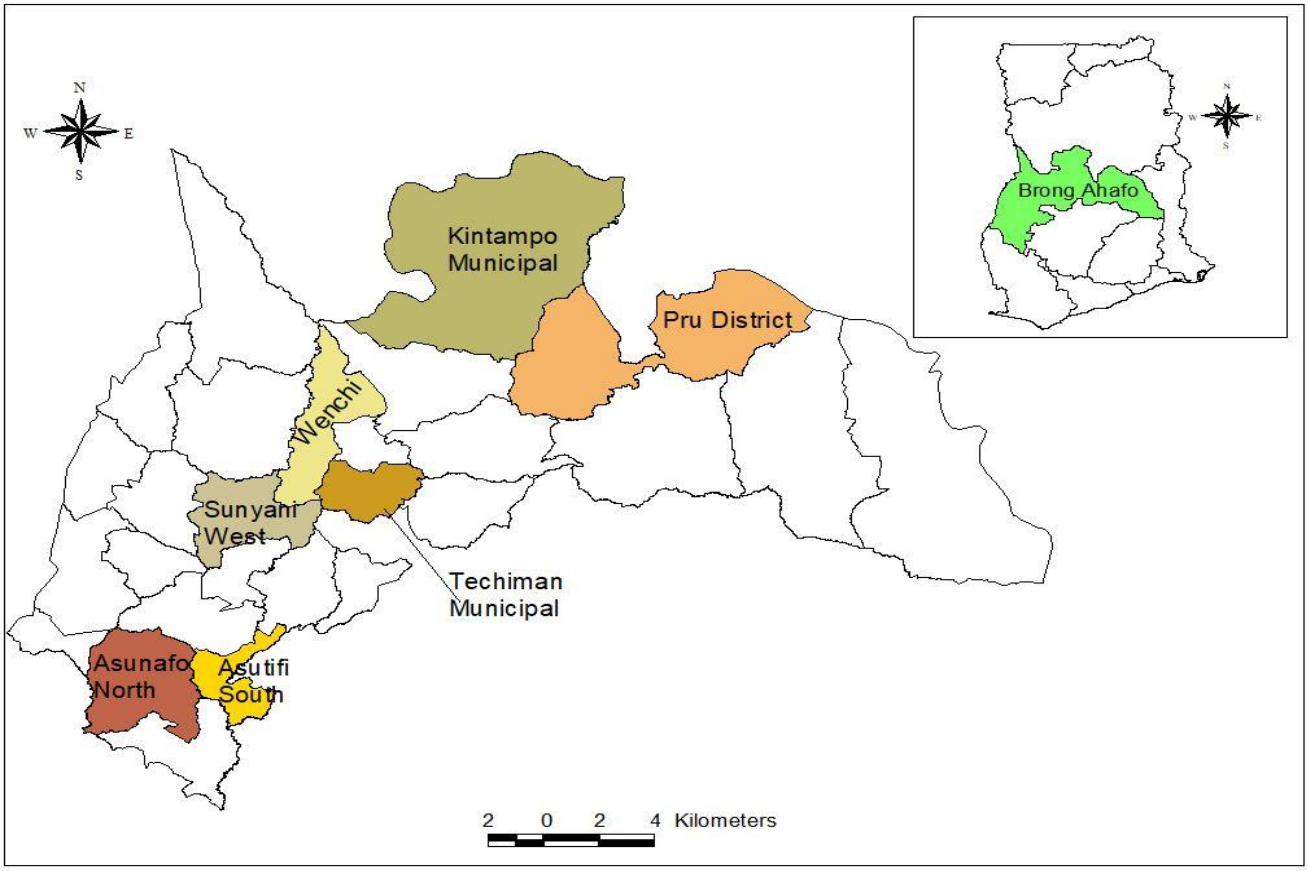

Figure 9: Map of the study area, BAR

3.3 Study population

The study population was made up of smear positive TB clients who attended any of the health facilities of the selected districts in the region and was declared by a prescriber as either with

adverse (MDR) or successful (Cured) treatment outcome between January, 2016 and December 2018.

Cases: Culture positive *Mycobacterium tuberculosis* TB clients resistant to at least isoniazid and rifampicin after month 2, 5, or 6 on the treatment regimen.

Controls: Smear-positive TB clients who became smear-negative after month 2, 5, or 6 on the treatment regimen.

3.4 Inclusion criteria

Cases: All smear positive clients including TB/HIV co-infected individuals aged 18years and above who attended any health facility of the selected districts in the region and were newly diagnosed of MDR-TB between January, 2016 and December, 2018 in BAR.

Controls: All smear positive clients including TB/HIV co-infected aged 18years and above who attended any health facility of the selected districts in the region and were declared as cured between January, 2016 and December, 2018 in BAR

3.5 Exclusion criteria

Cases: Any smear positive TB client who is above 18years previously diagnosed as smear positive TB but transferred out of the jurisdiction of the study site were excluded

Controls: Any smear positive TB client who is above 18years previously diagnosed as MDR-TB but transferred out of the jurisdiction of the study site were excluded.

3.6 Variables

3.6.1 Dependent variable

The main outcome variable is multidrug resistant TB; defined as clients with culture positive *Mycobacterium tuberculosis* outcome resistant to at least rifampicin and or isoniazid.

3.6.2 Independent variables

Table 1: Definition of independent variables and scale of measurement

Variable	Operation definition	Scale of measurement	How it was measured
Demographic factors			
Age	Age of client	Years	≤40 =Youth ≥ = Aged
Sex	Sex of client	Male/Female	1 =Yes 0 =No
Educational level	Level of formal education	No education to Tertiary level	1 = Formal 0 = No education
Marital status	Client having a partner	Married/Cohabiting/Not married	1 = Married 0 = Not married
Monthly income	Average income earned by client	Gh¢100 band (100 to >500/month)	<Gh¢100 = Poor >Gh¢100 = Middle income earner
Living situation	Was client living within a family	Individually/Within a family	1=Yes 0=No
Type of settlement/house	Residence of client	Rural/Peri-urban/Urban	1= Rural 0= Urban

Table 1 *continued*

Variable	Operation definition	Scale of measurement	How it was measured
Patient's behavioral and health related variable			
History of contact	Client ever come in contact with any TB case	Yes/No	1= Contact 0= Not
History of illicit drug use	Was client ever engaged in hard drugs	Yes/No	1= Drug addict 0=Not
History of times of treatment	Number of times of default or reinfection and treatment	Yes/No	1= Relapse 0= Not
Presence of HIV/AIDS	Was client infected with HIV/AIDS	Yes/No	1= TB/HIV 0= Not
History of alcohol use	Was client ever an alcoholic	Yes/No	1= Alcoholic 0= Non-alcoholic
History of traditional treatment	Did client ever sought traditional treatment	Yes/No	1=Used herbal medicine 0= Not
Health facility variables			
Time to capture client	Length of time to capture client at health facility	2 weeks or more	1= Late 0= Early reporting
Timely follow-ups	Did staff visited client in the course of treatment	Yes/No	1= Late follow-ups 0= Timely
Assigned treatment supporter	Was there a relation to support client during treatment	Quarterly visits	1= Regular 0= No visits

3.7 Sampling

3.7.1 Sample size determination

Epi-Info 7.2.0 statistical software was used to calculate the sample size with the Fleiss' statistical method for calculating rates and proportions. Using a 17.8% prevalence of MDR-TB among previously treated TB patients in a similar study in Ethiopia by Desissa et al., (2018), with odds ratio of 2.9, 1:3 ratio between cases and controls, 80% power and a confidence level of 95% as other parameters used, accordingly, the calculated sample size was 144 (36 cases and 108 controls).

3.7.2 Sampling method

Seven districts in the BAR were selected for the study. The districts with reported MDR-TB cases for the period 2016 to 2018 were purposively selected. All the MDR-TB clients for these districts were selected to represent the cases. The controls were then proportionately allocated to the districts based on the reported number of MDR-TB and their cohorts with cured treatment outcomes clients ratio (1case: 3controls) until the required sample size was met. Simple random sampling was used to select controls where they outnumbered the required number in a cohort for the period.

Table 2: Study sites and projected sample population (2016 to 2018)

District	# of Smear positive TB clients	# of TB Smear positive clients with MDR outcomes	# of TB Smear positive clients with successful outcomes	Sample	
				Cases	Controls
Techiman Municipal	194	14	59	14	42
Asunafo North	157	5	40	5	15
Sunyani West	75	4	20	4	12
Asutifi South	164	2	40	2	6
Wenchi	134	4	44	4	12
Kintampo Municipal	84	2	22	2	6
Pru	138	5	14	5	15
Total	946	36	239	36	108

3.7.3 Selection of participant

Health records were reviewed using a checklist to determine all the smear positive TB clients recorded between January 2016 and December 2018. All TB registers at all study sites were reviewed and smear positive case-patients details were abstracted including their address and contact numbers. Using the checklist every MDR-TB client was selected with a corresponding controls of similar treatment cohorts over the same period. Cases were selected from a list of all smear positive TB clients with MDR outcome either at month 2, 5 or 6 between January 2016 and December 2018. Controls were also sampled from same list of smear positive TB clients whose

treatment outcomes were successful (cured) after month 2, 5 and 6 test result proved same or cured. Participants who did not consent or could not be traced were replaced by the next available client. Clients within reach were visited and interviewed but those far from reach were interviewed via phone call. Others were also captured during their regular retreatment appointment dates. Consented clients were asked questions on their demographic and socio-demographic characteristics and well as some client behavioral and health related factors.

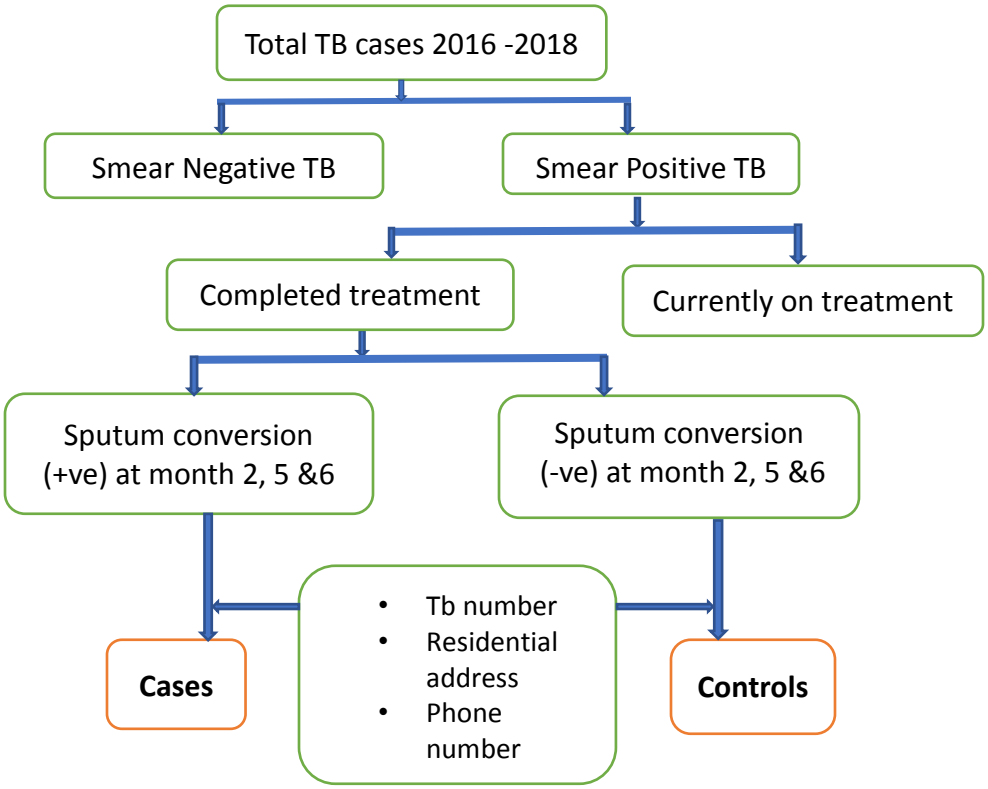

Figure 10: Sampling process

3.8 Data collection Techniques and Tools

3.8.1 Clients' Records review

Health facility records of smear positive clients who were on first line treatment but became MDR-TB cases at the end or in the course of treatment will be reviewed between January 2016 and December 2018. Their corresponding controls between same period (January 2016 and December 2018) from the TB registers at the treatment centers or health facilities in the selected districts using a checklist. The structured questionnaire was designed to document the following information; sex, age, geographic location, diagnosis, date diagnosed with TB, date treatment started, treatment outcome of TB patient. Responses provided were verified from the treatment card, TB register, treatment supporters and programme coordinators at the lower level.

To further determine whether spatial information could improve the prediction of MDR-TB within the study sites, residential coordinates of cases were picked to model the outcome.

3.8.2 Structured questionnaire

An interview assisted structured questionnaire was used to collect the data. Cases were selected from list the of all smear positive TB clients with MDR outcome either at month 2, 5 or 6 between January 2016 and December 2018. Controls were also sampled from same list of smear positive TB clients whose treatment outcomes were cured after month 2, 5 and 6 test result proved same. We also captured other vital patient information such as socio-demographics, educational level, economic status, date of first line treatment and adherence, type of settlement and other patient history including previous treatment, illicit drug use and TB/HIV co infection among others. The patient's health passport; i.e. the TB treatment card, and the TB registers were evaluated and treatment supporters as well consulted where appropriate to verify the responses.

3.8.3 Data quality control

This included training of data collection assistants involved in abstracting data from the registers and interview process. During data collection in the field, all completed forms for cases and controls respectively were checked to identify errors and omissions and corrective actions taken. These checks were replicated during data entry. Data were double entered into Epi Info and merge in order to detect possible errors. All data were backed up with and external storage device under lock and key. Pretest was done in a district not selected as part of the study sites.

3.8.4 Data management and analysis

To ensure data quality, collected data were double checked in the Epi Info 7.2.0 each day; since it is a real time data collection software, and validated to correct errors that would arise during the days' data collection. For cleaning purposes, data were then exported to Microsoft Excel 2013. Discordant records during the validation process were then resolved by consulting the questionnaire and later imported into STATA 15.0 for analysis. Data were analysed descriptively firstly by analysing for frequencies and proportions. Continuous variables such as age; were summarised into mean and range. The age was be re-categorized into age groups of 10 years interval according to the WHO recommendation (WHO, 2015). Patient's behavioral and health related factors with binary outcomes were represented by (Yes/No). Variables with multiple outcomes were also be represented by discrete numbers (0, 1, 2, etc.). Health facility factors included diagnosis, adequate medications, timely reviews and follow-ups for adherence. Bivariate analysis were conducted to determine significance differences between cases and controls and presented as contingency tables with p-values and fisher's exact test done for variables with less than five (5) frequencies. Variables with p-values <0.05 at bivariate level were considered as

statistically significant. The variables which proved to be significant and as well plausible in literature to be the risk factors for MDR-TB were controlled for in a multiple logistic regression model to detect factors that are actually significantly predictive of MDR-TB. The results were presented in two-by-two tables and displayed as frequencies, percentages, crude and adjusted odd ratios (ORs) and 95% confidence interval (CIs) and p-values.

Coordinates picked at the residence of clients were also cleaned in Microsoft Excel 2016 and imported into GIS. Choropleth maps were drawn with graduated scale and colours; from deeper to lighter, to showcase districts with higher numbers of reported MDR-TB clients.

3.9 Ethical consideration

Ethical consideration for the study was obtained from Kintampo Health Research Centre Institutional Ethics Committee with approval number (KHRCICE/2019-3). Permission was also sought from the Brong Ahafo Regional Health Directorate and the District health management teams. Written inform consent was also sought from individual clients before administering the questionnaire. Consent forms and permission letters were written in English and explained extensively in the local language (Twi) to ensure participants' enough comprehension of the study objectives, potential risks and benefits and assurance of confidentiality. Participants were also given the opportunity to refuse to participate and the right to opt out at any point in time in the course of the interview. Participants' confidentiality and privacy was respected during the questionnaire administration and interactions. To ensure proper confidentiality and privacy, names of participants' were not used in the write-up since the questionnaire was coded. The findings from the study were not reported such that the names of the respondents were used. All information were treated as confidential. Data collected could be accessed by only those involved in the study.

All electronic data were stored under a strong password and hard copies under lock and key in the Principal Investigators home library to avoid access to any third party. It would be used as reference or evidence when necessary and destroyed after ten (10) years.

3.10 Pre - testing of data collection tools

Pre – test was conducted in the Techiman North district which involved one (1) case and three (3) controls to identify the errors in the questionnaires. Participants included clients registered from January to March 2019. To ensure that questions are clear, and respondents understood the questions as intended, it was done outside the study area during the training of research assistants. Final data collection was done by the trained research assistants.

CHAPTER FOUR

4.0 RESULTS

4.1 Socio-demographic characteristics of study participants

A total of 144 respondents, 36 eligible cases and 108 controls were involved in the study. Participants from seven districts namely (Techiman, Pru, Kintampo, Wenchi, Sunyani west, Asutifi south and Asunafo north) who met the inclusion criteria were enrolled in the study between March and June, 2019. For the period under study (2016 – 2018), 5 cases and 12 controls had died and the treatment supporter or family member had to be interviewed instead of the actual respondent. There were 54.2% (78/144) females. Ages of participants ranged from 21years to 70 years. The mean age of cases was 44.4 (±9.9) years, and controls 42.3 (±12.1) years with majority within the age group of 20 to 40 years. Females constituted 25 (69%) of cases and 53 (49%) of controls. Table 3 below shows the sex distribution and age group of participants with majority, 47% 67/144 within the 20years to 40 year age group.

Results from the descriptive analysis of the characteristics of participants (cases and controls) is summarised in Table 3 and 4. Among cases and controls, Christians 60% (85/144), married 56% (81/144), secondary education 44% (64/144), and artisans 32% (46/144) dominated the study sample. Three (3) of the control participants were students. Majority of cases 61% (22/36), and controls 47.2% (51/108) had an estimated average monthly income of ≤ 100.00 Ghana cedi (Gh¢). Twenty two (63%) and fifty seven cases (53%) had more than four members in their family. A total of 64; 53% (19/36) cases, 42% (45/108) controls had up to secondary level of education. Of cases and controls, 55.2% (79/144) were peri-urban settlers with 70% (100/144) living in block built houses. Sixteen (16/36) cases and fifty four (54/108) controls, representing 50% each of cases and controls had either ≤2 or >2 sleeping rooms respectively.

Table 3: Demographic characteristics of cases and controls enrolled

Variables	Cases N= 36 (%)	Controls N=108 (%)
Age group (years)		
20-40	11 (16.4)	56 (83.6)
40-60	23 (36)	41 (64)
60+	2 (15.4)	11 (84.6)
Sex		
Male	25 (32.1)	53 (67.9)
Female	11 (16.7)	55 (83.3)
Educational level		
Primary	7 (20)	16 (15)
Secondary	19 (53)	45 (42)
Tertiary	3 (8)	32 (30)
No formal education	7 (19)	15 (14)
Marital status		
Single	5 (26.3)	14 (73.7)
Married	16 (19.8)	65 (80.2)
Cohabiting	11 (61.1)	7 (38.9)
Divorced	4 (15.4)	22 (84.6)
Occupation		
Farmer	10 (31.3)	22 (68.8)
Artisan	8 (36.3)	14 (63.6)
Formal work	6 (14.6)	35 (85.4)
Unemployed	12 (26.1)	34 (73.9)
Student	0	3 (100)
Religion		
Christian	23 (27.1)	62 (73.9)
Moslem	8 (18.2)	36 (81.8)
Traditionalist	5 (38.5)	8 (61.5)

Table 4: Socio-economic characteristics of cases and controls enrolled

Variables	Cases N= 36 (%)	Controls N=108 (%)
Monthly income		
≤ Gh¢100.00	22 (30)	51 (70)
Gh¢101.00 - 250.00	4 (15.4)	22 (84.6)
Gh¢251.00 - 500.00	5 (35.7)	9 (64.3)
≥ Gh¢500.00	3 (10.3)	26 (89.7)
Social status		
Low	17 (47.2)	23 (21)
High	19 (52.8)	85 (79)
Family size		
≤ 4 children	13 (20.3)	51 (79.7)
> 4 children	22 (27.9)	57 (72.1)
Type of settlement		
Rural	16(42)	22 (58)
Peri-urban	14 (17.7)	65 (82.3)
Urban	6 (23)	20 (77)
Have a house to live in		
Yes	34 (24.6)	104 (75.4)
No	2 (33.3)	4 (66.7)
Type of house		
Mud	0	1 (100)
Block	17 (17)	83 (83)
Wooden	0	1 (100)
Brick	18 (45)	22 (55)
Number of sleeping rooms		
≤ 2 rooms	19 (26.4)	53 (73.6)
> 2 rooms	17(23.6)	55 (76.4)
Living situation		
Individually	17 (63)	10 (37)
Within a family	18 (15.7)	97 (15.7)

4.2 Socio-demographic factors associated with development MDR-TB

The bivariate analysis of the socio-demographic factors of clients that influence the odds of developing MDR-TB are summarised in Table 3. The analysis showed significant differences in the outcome between monthly average income ($p<0.04$), marital status ($p<0.01$), social status ($p<0.01$) and clients' living situation ($p<0.01$). Clients with an average monthly income of ≤ Gh¢100.00 had 4 times the odds of becoming MDR-TB compared to those with average monthly income of >Gh¢100.00, [COR=3.74 (1.02 - 13.66, 95% CI)]. Having a low social status had increased odds of MDR-TB by 3-folds compared to those with high social status [COR=3.32 (3.31 (1.49 - 7.36, 95% CI)]. With marital status, those cohabiting had eight times the odds of developing MDR-TB compared to the married and single clients [COR=8.64 (2.08 - 35.97, 95% CI)]. Again the living situation of clients (as individual), increases the odds of becoming an MDR-TB by 9.2 times in cases compared to controls [COR=9.2 (3.61 – 23.19, 95% CI)]. Similarly, there was also significant associated between sex ($p<0.04$), tertiary education ($p<0.03$) and type of house ($p<0.01$) and the development MDR-TB but protective. Male clients had 42% reduced odds of having MDR-TB outcomes compared to females [COR=0.42 (0.19 - 0.95, 95% CI)]. Clients with tertiary education were also found to have reduced 20% reduced odds of becoming MDR-TB compared to those with no formal education or up the secondary level [0.20 (0.05 - 0.89, 95% CI)]. Also clients' type of house proved to be protective. Living in a block house had a 25% reduced odds of becoming an MDR-TB in controls compared to cases [0.25 (0.11 - 0.56, 95% CI)]. However, socio- demographic factors investigated that did not show significance were age group, religion, occupation, type of settlement, family size, house to live in and number of sleeping rooms.

Table 5: Bivariate analysis of the socio-demographic characteristics of cases and controls, Brong Ahafo region, March - June 2019

Variables	Cases N= 36 (%)	Controls N=108 (%)	COR (95% CI)	*p-value*
Age group (years)				
20 – 40	11 (16.4)	56 (83.6)	1.08 (0.21 - 5.56)	0.93
40 – 60	23 (36)	41 (64)	3.08 (0.63 - 15.14)	0.17
60+	2 (15.4)	11 (84.6)	1.00	
Sex				
Male	25 (32.1)	53 (67.9)	0.42 (0.19 - 0.95)	0.04*
Female	11 (16.7)	55 (83.3)		
Educational level				
Primary	7 (20)	16 (15)	0.94 (0.27 - 3.31)	0.92
Secondary	19 (53)	45 (42)	0.90 (0.32 - 2.57)	0.85
Tertiary	3 (8)	32 (30)	0.20 (0.05 - 0.89)	0.03*[0]
No formal education	7 (19)	15 (14)	1.00	
Marital status				
Single	5 (26.3)	14 (73.7)	1.96 (.45 - 8.59)	0.37
Married	16 (19.8)	65 (80.2)	1.35 (0.41 - 4.48)	0.62
Cohabiting	11 (61.1)	7 (38.9)	8.64 (2.08 - 35.97)	0.001*
Divorced	4 (15.4)	22 (84.6)	1.00	
Occupation				
Farmer	10 (31.3)	22 (68.8)	1.29 (0.48 - 3.49)	0.62
Artisan	8 (36.3)	14 (63.6)	1.62 (0.54 - 4.81)	0.39
Formal work	6 (14.6)	35 (85.4)	0.49 (0.16 - 1.44)	0.19
Unemployed	12 (26.1)	34 (73.9)	1.00	
Student	0	3 (100)	1.00	

Table 5 *continued*

Variables	Cases N= 36 (%)	Controls N=108 (%)	COR (95% CI)	*p-value*
Religion				
Christian	23 (27.1)	62 (73.9)	0.52 (0.15-1.80)	0.30
Moslem	8 (18.2)	36 (81.8)	0.31 (0.08 - 1.24)	0.10
Traditionalist	5 (38.5)	8 (61.5)		
Monthly income				
≤ Gh¢100.00	22 (30)	51 (70)	3.74 (1.02 - 13.66)	0.04*[0]
Gh¢101.00 - 250.00	4 (15.4)	22 (84.6)	1.58 (0.32 - 7.81)	0.58
Gh¢251.00 - 500.00	5 (35.7)	9 (64.3)	4.81 (0.95 - 24.32)	0.06
≥ Gh¢500.00	3 (10.3)	26 (89.7)	1.00	
Social status				
Low	17 (47.2)	23 (21)	3.31 (1.49 - 7.36)	0.003
High	19 (52.8)	85 (79)		
Family size				
≤ 4 children	13 (20.3)	51 (79.7)	1.00	
> 4 children	22 (27.9)	57 (72.1)	1.51 (0.69 - 3.31)	0.30
Type of settlement				
Rural	16(42)	22 (58)	2.42 (0.79 - 7.41)	0.12
Peri-urban	14 (17.7)	65 (82.3)	0.72 (0.24 - 2.11)	0.55
Urban	6 (23)	20 (77)	1.00	
Have a house to live in				
Yes	34 (24.6)	104 (75.4)	1.00	
No	2 (33.3)	4 (66.7)	0.76 (.083 - 7.078)	0.81
Type of house				
Mud	0	1 (100)	1.00	
Block	17 (17)	83 (83)	0.25 (0.11 - 0.56)	<0.001*[0]
Wooden	0	1 (100)	1.00	
Brick	18 (45)	22 (55)	1.00	

Number of sleeping rooms				
≤ 2 rooms	19 (26.4)	53 (73.6)		
> 2 rooms	17(23.6)	55 (76.4)	0.86 (0.41 - 1.83)	0.70
Living situation				
Individually	17 (63)	10 (37)	9.16 (3.62 - 23.19)	<0.001*
Within a family	18 (15.7)	97 (15.7)	1.00	

* Statistically significant, *p-value refers to statistical comparison of proportion of cases to controls and the development of MDR-TB, COR = crude odds ratio, CI=confidence interval, ^{0} =Fishers exact test

4.3 Clients' behavioral and health related factors associated with the development of MDR-TB

Table 5 displays clients' behavioral and health related factor associated with the development of MDR-TB. In a bivariate analysis, history of smoking ($p<0.01$), history of number of times of treatment ($p<0.01$), illicit drug use ($p<0.01$), history of contact ($p<0.04$) and presence of HIV/AIDS infection ($p<0.01$) showed significant association with the development of MDR-TB. Clients with history of smoking had 5-folds of becoming MDR-TB compared to those who did not smoke [COR= 5.23 (2.16 -12.59), 95% CI)]. History of illicit drug use had a higher chance of 9.2 times of developing MDR-TB compared to those who use no drugs [COR=9.2 (0.08 – 0.45, 95% CI)]. Also clients with presence of HIV/AIDS infection had a substantially greater risk 12 times of becoming MDR-TB compared to the HIV/DIDS non-infected clients [COR=12.1 (4.12 – 34.94, 95% CI). History of alcohol use proved to have 3 times the chance of resulting as an MDR-TB client compared to clients with no history of alcohol use [COR=2.89 (1.32 - 6.33, 95% CI)]. History of contact with infected TB clients also showed to have 3 times the odds of developing MDR-TB compared to those without any previous history of contact [COR=3.1 (1.43 – 6.94, 95%

CI)]. Meanwhile, history of no traditional treatment (p<0.2) and history of number of times of just 1 time of treatment (p<0.01) had reduced odds of ending up as MDR-TB clients during or after the treatment course. The odds of becoming an MDR-TB was 80% less in clients with no history of no traditional treatment during treatment regimen [COR=0.19 (0.08 – 0.45, 95% CI)]. As well, clients with history of first time treatment had a significantly 99% reduced odds of developing MDR-TB compared to those with more 2 times history of treatment times [COR=0.01 (0.01 – 0.05, 95% CI)].

Table 6: Bivariate analysis of TB clients' behavioral and health related factors in Brong Ahafo, March – June 2019

Variables	Cases N= 36 (%)	Controls N=108 (%)	COR (95% CI)	*p-value*
History of smoking				
Yes	21 (18)	95 (82)	5.23 (2.16 - 12.59)	<0.001*
No	15 (53.6)	13 (46.4)	1.00	
History of alcohol use				
Yes	18 (41)	26 (59)	2.89 (1.32 - 6.33)	0.08
No	18 (18)	82 (82)	1.00	
History of exposure to second hand smoke				
Yes	21 (25)	63 (75)	1.00 (0.47 - 2.15)	1.00
No	15 (25)	45 (75)	1.00	
History of being in prison				
Yes	3 (60)	2 (40)	4.82 (0.77 - 30.08)	0.10
No	33 (24)	108 (76)	Na	

Table 6 *continued*

Variables	Cases N= 36 (%)	Controls N=108 (%)	COR (95% CI)	*p-value*
History of traditional treatment				
®Yes	27 (41)	39 (59)	1.00	
No	9 (11.7)	69 (88.3)	0.19 (0.08 - 0.45)	<0.001*[0]
History of illicit drug use				
Yes	7 (33.3)	14 (66.7)	9.18 (3.32 - 25.41)	<0.001*[0]
®No	101 (82)	22 (18)	1.00	
History of contact				
Yes	26 (59)	18 (41)	3.15 (1.43 - 6.94)	0.004*
®No	82 (82)	18 (18)	Na	
History of number of times of previous treatment				
1time	14 (12)	105 (88)	0.01 (0.01 - 0.05)	<0.001*[0]
® >2 times	22 (96)	1 (4)	1.00	
Presence of HIV				
Yes	15 (71.4)	6 (28.6)	12.14 (4.22-34.94)	<0.001*[0]
®No	21 (17)	102(83)	1.00	
Contracted Diabetes Mellitus				
®Yes	10 (27)	28 (73)	1.00	
No	26 (24.5)	80 (75.5)	0.88 (.38 - 2.05)	0.76
Good mental status				
Yes	35 (26.7)	96 (73.3)		
®No	1 (9)	12 (91)	0.27 (0.03 - 2.22)	0.23

* Statistically significant, *p-value refers to statistical comparison of proportion of cases to controls and the development of MDR-TB, COR = crude odds ratio, CI=confidence interval, ^{0} =Fishers exact test, ®= Reference, Na= Not applicable

4.4 Health facility related factors associated with the development of MDR-TB

Table 7 displays the development of MDR-TB and the associated health facility related factors. The length of time of capture clients at the facility ($p<0.001$), timely review of clients ($p<0.02$), follow ups conducted ($p<0.01$) and assigned a treatment supporter ($p<0.01$) were significantly associated MDR-TB outcome. However, odds of developing MDRT-TB were protective for all factors that showed significant association with the health facility factors. Clients with which frequent and timely reviews conducted on them had 93% reduced odd of becoming MDR-TB compared to those did not receive same service [COR=0.07 (0.01 – 0.67, 95% CI)]. Conducting frequent follow-up visits by health staff to TB clients also reduced their odds of ending up as MDR-TB by 80% compared to those with no follow-ups [COR=0.20 (0.09 – 0.47, 95% CI). Being a client with assigned treatment supporter to assist on their course showed a reduced odds of 0.89% developing MDR-TB compared to a client with no treatment supporter [COR=0.11 (0.04 – 0.30, 95% CI]. Weak association existed between other factors such as adequate diagnosis, appropriate prescription and appropriate drug supply.

Table 7: Bivariate analysis of health facility related factors and development of MDR-TB in Brong Ahafo region, March - June 2019

Variables	Cases N= 36 (%)	Controls N= 108 (%)	COR (95%CI)	*p-value*
Length of capture at health facility				
≤ 2weeks	4 (8.2)	45 (91.8)	0.03 (0.01- 0.13)	0.001**
2 weeks- 1 month	13 (19)	56 (81)	0.09 (0.03 - 0.26)	0.001**
® > 1 month	18 (72)	7 (28)	1.00	
Adequate diagnosis				
Yes	30 (78.3)	108 (78.3)	1.00	
®No	6 (100)	0	1.00	
Appropriate prescription				
Yes	35 (24.5)	108 (75.5)	1.00	
®No	1 (100)	0	1.00	
Adequate drug supply				
Yes	35 (25)	106 (75)	0.66 (0.06 - 7.51)	0.74
®No	1 (33.3)	2 (66.7)	1.00	
Timely reviews conducted				
Yes	32 (23)	107 (77)	0.07 (0.01 - 0.69)	0.02^{*0}
®No	4 (80)	1 (20)	1.00	
Times of reviews				
Completed (4 visits)	27 (75)	54 (50)	0.33 (0.14 - 0.77)	0.01
®Defaulted (<3 visits)	9 (9)	54 (50)	Na	
Follow up visits conducted				
Yes	20 (17.7)	93 (82.3)	0.20 (0.09 - 0.47)	<0.001**
®No	16 (52)	15 (48)	1.00	
Frequency of visits				
Fortnightly	0	5 (100)	Na	
Monthly	10 (17)	49 (83)	Na	
Quarterly	10 (21.3)	37 (78.7)	Na	
Assigned a treatment supporter				
Yes	21 (17.4)	100 (82.6)	0.11 (0.04 - 0.30)	0.001**
®No	15 (65)	8 (35)	Na	

* Statistically significant, *p-value refers to statistical comparison of proportion of cases to controls and the development of MDR-TB, COR = crude odds ratio, CI=confidence interval, ^{0} =Fishers exact test, ®= Reference, Na= Not applicable

Table 8: Multiple logistic regression analysis of Socio-demographic factors for predicting MDR-TB among TB clients in the Brong Ahafo region, March - June 2019

Variables	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Age group^				
20-40 years	1.08 (0.21 - 5.56)	0.93	Na	
41-60 years	3.08 (0.63 - 15.14)	0.17	7.9 (1.12 - 57.18)	0.04
® >61years	1.00	Na	Na	
Type of settlement^				
Rural	2.42 (0.79 - 7.41)	0.12	1.5 (0.50 - 4.52)	0.46
Peri-urban	0.72 (0.24 - 2.11)	0.55	Na	
®Urban	1.00	Na	Na	
Sex^				
Male	0.42 (0.19 - 0.95)	0.04*	0.7 (0.17 - 2.72)	0.58
®Female	1.00	Na	Na	
Clients living situation				
®Individually	1.00	Na	Na	
Within a family	0.10 (0.04 - 0.28)	<0.01*	0.10 (0.03 – 0.34)	<0.01*

* Statistically significant, ^= known confounders, COR = crude odds ratio, AOR = adjusted odds ratio, CI=confidence interval, ®= Reference, Na= Not applicable

Table 9: Multiple logistic regression analysis of Clients' behavioral and health related factors for predicting MDR-TB among TB clients in the Brong Ahafo region, March - June 2019

Variable	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
History of HIV/AIDS				
Yes	12.14 (4.22-34.94)	<0.001*[0]	12.3 (2.49 – 60.77)	0.02*
®No	1.00	Na	Na	

* Statistically significant, ^= known confounders, COR = crude odds ratio, AOR = adjusted odds ratio, CI=confidence interval, ®= Reference, Na= Not applicable

Table 10: Multiple logistic regression analysis of Health facility related factors for predicting MDR-TB among TB clients in the Brong Ahafo region, March - June 2019

	Crude OR (95% CI)	*p-value*	Adjusted OR (95% CI)	*p-value*
Time of capture at health facility				
®< 2 weeks	0.03 (0.01- 0.13)	0.001*	Na	
2weeks – 1month	0.09 (0.03 - 0.26)	0.001*	13.2 (2.95 - 59.46)	0.001*
>1month	1.00			
Timely follow-ups				
Yes	0.20 (0.09 - 0.47)	<0.01*	0.24 (0.08 - 0.79)	0.02*
®No	1.00	Na	Na	
Assigned a treatment supporter				
Yes	0.11 (0.04 - 0.30)	<0.01*	0.10 (0.03 -0.34)	<0.01*
®No	1.00	Na	Na	

* Statistically significant, ^= known confounders, COR = crude odds ratio, AOR = adjusted odds ratio, CI=confidence interval, ®= Reference, Na= Not applicable

4.5 The overall predictors of developing MDR-TB

Bivariate and multivariate analysis of factors associated with the development of MDR-TB are summarised in Table 8, 9 and 10. The study revealed that client living as an individual, history of traditional treatment, history of times of treatment more than twice, presence of HIV/AIDS infection, length of time to capture client, timely and frequent follow up on clients and clients with treatment supporters were found to be independently associated with MDR-TB in the multivariate analysis with all p-values < 0.05 after controlling for the known confounders.

The odds of a client living within a family was reduced by 90% to become an MDR-TB both univariate and multivariate analysis [AOR=0.10 (0.03 – 0.34, 95% CI)] compared to clients living individually. Similarly, clients with had frequent follow-ups visits by health staff also have 76% reduced odds of MDR-TB compared to clients with less or no follow ups [AOR=0.2 (0.76 – 0.79, 95% CI)]. Having a treatment supporter to assist in the course of treatment was protective as well. The likelihood of becoming an MDR-TB is 90% reduced in clients with treatment supporters as compared to clients with no treatment supporters [AOR=0.1(0.0 – 0.34, 95% CI)].

However, there was an increase odds of MDR-TB in a client with presence of HIV/AIDS infection by 12 times compared to clients with no HIV/AIDS infection [AOR=12.3 (2.49 – 60.77, 95% CI)]. The inability of the health system to capture clients in less than one month of onset of symptoms of TB increases their risk of becoming MDR-TB during or after their treatment by 13-folds compared to clients captured earlier than one month of onset of symptoms [AOR=13.2 (2.95 – 59.47, 95% CI)].

4.6 Spatial pattern of MDR-TB clients

The result of the spatiotemporal information is showcased in Figure 13. The map suggested Techiman municipal reported between 7 – 14 MDR-TB clients within the study period. It has the highest reported MDR-TB 39% (14/36) of all the reported cases for the period. This is suggestive that, the likelihood of a TB client developing MDR-TB in Techiman is higher compared to other endemic districts. Pru and Asunafo north districts also reported 14% (5/36). The least clustered districts were Kintampo north and Asutifi south with 5.6% (2/36). Districts with the highest clustering are noted for their strategic markets, booming cashew and cocoa trade which attract thousands of people giving rise to a persistent increase in their populations. These factors were also found in a Malaysian study to map-out high risk MDR-TB clusters(Rauf et al., 2019), similar to Alene et al., 2017 and Mahara et al., 2018, which also reported urbanization to predict clusters of MDR-TB clients in Ethiopia and China. Contrarily, (Kolifarhood et al., 2015), reported no statistical significance between population density and MDR-TB clustering.

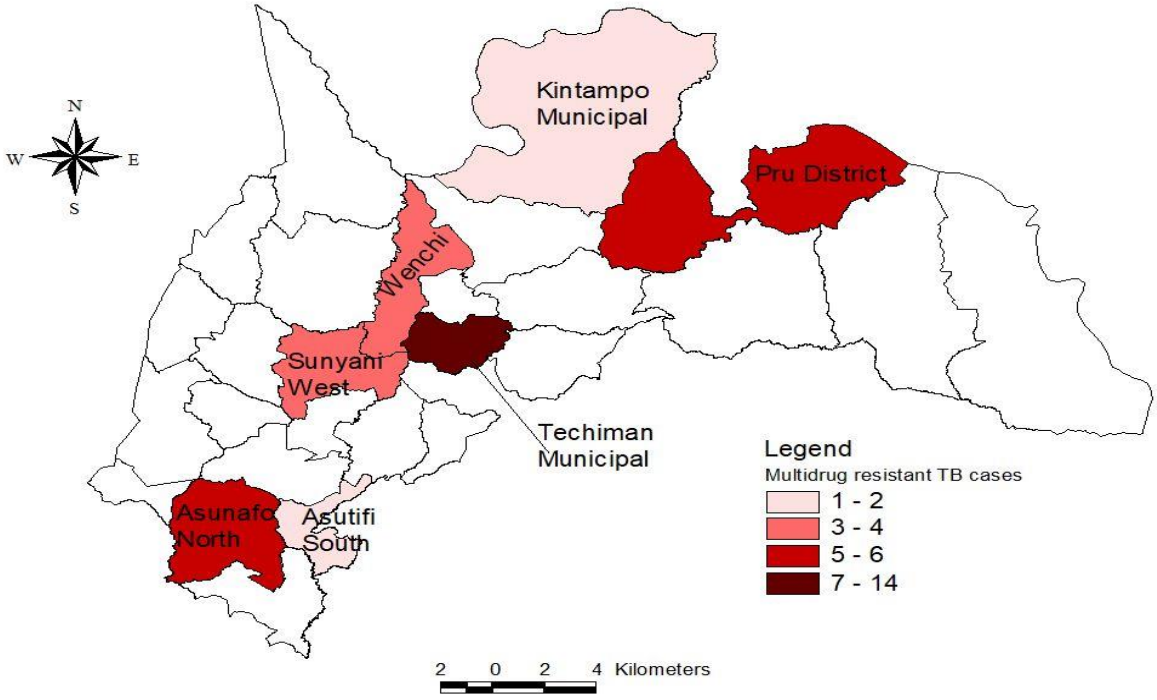

Figure 11: Spatial pattern of MDR-TB per district, Brong Ahafo region, July 2019

Source: Author's construct

CHAPTER FIVE

5.0 DISCUSSION

This was a case control study conducted to determine the predictors for MDR-TB among TB clients in the Brong Ahafo Region, Ghana. This is the first documented study to investigate the drivers of the emergence of anti-TB drug resistance in the region adding to the limited epidemiological evidence in the country in general. The result revealed that clients with HIV/AIDS co-morbidity and late capture of clients by the health surveillance system were strong predictors for MDR-TB with higher statistical significance; whilst clients living within a family, timely follow ups by staff and clients assigned treatment supporters had an association but were protective predictors.

Regardless of age, sex, occupation or race, TB affects everyone. In this study, there were more females who developed MDR-TB than males. These were mostly the youthful age group 20 to 40 years. This is similar to a global finding and a prevalence study on MDR-TB in Pakistan (Ejaz et al., 2010; WHO, 2014). Across cases and controls, peri-urban dwellers dominated the study contrary to rural dwellers in China (Ying, 2013).

Among the socio-demographic factors, age and living situation was statistically significant with a reduced odds of MDR-TB occurrence after controlling for confounders. Compared age groups below 40year and 60+, there is an 8 times increase odd of TB patients developing MDR-TB among clients within age group of 41-60years. This is contrary to Abate et al., (2012), Zhang et al., (2016) and who found this among between age groups 15 to 45 and 60+ years respectively. Also, clients living within a family had 90% reduced odds to have MDR-TB outcome compared to those living individually due to family or social exclusion. Contrarily, in Ethiopia, clients who experienced family or social exclusion had higher odds of MDR-TB compared to those who lived within their

families (Assefa, 2017). Another report in Napal as reported stigma as an independent predictor of MDR-TB (Marahatta *et al*.,2010).

HIV/TB co-infection has been noted as a fertile ground for MDR-TB. This study further supported the claim that clients with presence of HIV/AIDS infection were 12 times increased odds of MDR-TB than those who had no HIV history to develop MDR-TB. With such a stronger statistical significance, it shows that HIV is a stronger predictor for MDR-TB among TB clients generally. This finding is consistent with WHO that persons living with HIV/AIDS had greater of developing MDR-TB than those without HIV to have MDR (WHO, 2014). In another study in India and Southern Ethiopia, HIV was found to be a predictor to MDR-TB (Abate et al., 2012; Zhang et al., 2016). In a systematic review and meta-analysis in Ethiopia, TB/HIV positive clients were 24% at higher risk of becoming MDR-TB compared to non-HIV infected clients (OR-1.24, 1.04 – 1.43, 95% CI) (Mesfin *et al*, 2014). This high prevalence of TB/HIV co-infection might best be explained to cause the TB bacilli to resist the TB drugs. But conversely, findings from different parts of Africa did not identify any association between presence of HIV infection in TB clients and MDR-TB. Again, a South African did not showed any differences in HIV prevalence among MDR-TB and non- MDR-TB clients, although MDR-TB clients had slightly higher rates of HIV infection (60% against 55%, p-value =0.58) (Weyer et al., 2007). Another study in Ethiopia did not find any positive association between HIV/TB co-infection and the development of MDR-TB (Hirpa et al., 2013).

Treatment supporters have been fully incorporated into community-based TB care. Their contribution to the control programmes; in terms of outcomes of clients, the world over cannot be underemphasized. Hitherto, this current study proved that having a treatment supporter during previous TB treatment was associated with a reduced risk of MDR-TB which is consistent with a

study in Swaziland in suggested that having treatment supporter significantly improves TB treatment results (Kliner et al., 2015). Contrary to this, an Ethiopian study discovered weak association between having a treatment supporter in previous treatment but a higher risk of MDR-TB (AOR=1.7, 0.99 – 2.86 95% CI) (Hirpa et al., 2013).

TB control programmes largely thrives on early case detection, adequate diagnosis and early but timely initiation of treatment with optimum level of treatment adherence. The fragile nature of the integrated disease surveillance system of the health service; including TB surveillance, coupled with clients' choice of whether to seek orthodox, self or traditional care has a direct influence on when he is captured at the health facility. In this study we observed that, having spent more than a month from first of time onset of symptoms to be captured by the health system substantially increases the risk of MDR-TB. Although different factors leads to the MDR-TB development, our finding are consistent with some studies across the world including; a case control study in Ethiopia and Napal, which found more than a month delay from time of onset of symptoms to diagnosis at health facility as an independent predictor to MDR-TB. Consistent with another finding on the associated factors with TB treatment in Southwest Ethiopia indicated that delay in seeking healthcare to be a major reason for high transmission of TB (Tegegn, 2009).

Clients who had timely and frequent follow-up from health staff had reduced odds of MDR-TB from our study. This is similar to a qualitative study in Norway which reported lack of adequate communication and contact with health professional as a factor influencing treatment adherence and in turn, increase the risk of MDR-TB (Gebremariam et al, 2010). In a study on the factors with regards to loss to follow-up of MDR-TB clients in Philippines, Thelma et al, (2016) also found rapport with and support from physicians and TB staff as a protective factor for predicting MDR-TB.

Under spatial patterns, we found that MDR-TB were geographically densely clustered around Techiman, Pru and Asunafo north districts. This could be explained by the population density, increasing TB cases and immigration due to the booming economic activities around their strategic markets, cash crops (cashew and cocoa) and mining activities which constantly attract people to these districts. Our finding is similar to spatial pattern study in Ethiopia which reported urbanization in predicting the clustering of MDR-TB clients (Alene et al., 2017). In Malaysia, Rauf et al., (2019), reported urbanization and immigration as predictive factors for clustering of MDR-TB. On the contrary, Kolifarhood et al., (2015), found no association between population density and MDR-TB clustering in Saudi Arabia.

5.1 Limitations to the study

Possible limitation in this study was recall bias

We anticipated recall bias to an extent since clients had to remember almost all responses due to the retrospective nature of the study. To minimize this, we therefore adopted the use of local calendar, illustrations, national and religious events, seasons and other timelines within the period of study to solicit for responses.

5.2 Implication for future research

There is a clear need for ongoing education around aspects of the disease, spread of the bacteria and duration required for treatment completion. Further research looking at the knowledge disseminated to patients by families. Studies on the prevalence of MDR TB are also necessary for further information as found in the study and to further understand the spread of the disease and ways to reduce its transmission since it is an emerging field.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusion

In conclusion, presence of HIV/AIDS infection and late capture of clients by the health system were found to have strong association with the occurrence of MDR-TB. However, living within a family, timely and frequent follow-up of clients and provision of treatment supporters could also predict MDR-TB but are protective.

6.2 Recommendation

Based on the findings in this study, we recommended the following

Ministry of Health/National Tuberculosis Control Programme should;

- Should liaise with the regional, district and facility levels to ensure strict adherence to protocols on diagnosis and management of TB clients to ensure positive outcomes after the first line treatment course.
- Devise innovative means of sustaining the enablers' package for treatment supporters. This is because, the study found that having history of assigned treatment supporters was protective against development of MDR-TB.

The Regional Health Directorates should;

- Promote any concerted effort available to increase awareness on the risk factors of MDR-TB and encourage strict adherence to treatment

District health directorate should;

- Intensify surveillance activities by involving all stakeholders such as private facilities, traditional healers, chemical sellers to ensure early reporting and appropriate diagnosis and treatment.
- Improve timely follow-up of clients in the course their treatment.
- An operational research can be conducted to further explore risk factors to forestall the increasing rate of incidence of MDR-TB.

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http//:who.int/tuberculosis

www.bioquel.com

www.indiamart.com

APPENDICES

APPENDIX I: PARTICIPANT INFORMED CONSENT FORM

	PREDICTORS FOR MULTIDRUG-RESISTANT TUBERCULOSIS AMONG TUBERCULOSIS PATIENTS, BRONG AHAFO REGION, GHANA, 2019 **Participant Informed Consent Form**	

IRB Research Approval Number: (KHRCIEC/2019-3)

This approval will elapse on: (30th September, 2019)

University of Ghana (Principal Investigator): Gyamfi Gyimah Charles

Sponsorship agency: No sponsorship

INTRODUCTION:

My name is Gyamfi Gyimah Charles from School of Public Health, University of Ghana. I am partially fulfilling a requirement towards an award of MPhil Applied Epidemiology and Disease Control. This study seeks to assess the factors contributing to an emerging trend of multidrug resistant among tuberculosis clients in the Brong Ahafo Region of Ghana. We will like to invite you to take part in this study to enable us establish the factors.

PURPOSE OF STUDY/BACKGROUND

We propose to bring to bear the potential risk factors of MDR-TB in Brong Ahafo Region of Ghana. Multidrug resistant is an emerging serious public health problem globally. TB treatment is associated with many obstacles (from program, patient and health) during which clients are vulnerable to non-adherence and may lead to adverse outcomes. Resistance to the second line

drugs is eminent if care is not taken and a bigger threat to TB care and prevention. This research will contribute to improving the care for TB clients during the first line of treatment.

PROCEDURES

With the emerging trend in MDR-TB cases in the region, we purposely selected those with the MDR outcome either at month 2, 3 or 6 and randomly selected those who begun treatment with them but came out with successful outcomes (cured) at same periods, and you happened to be one of the selected few. The study will be conduct for the next 3 months but we will engage you just once for your side of the story and move to the next client. Nonetheless, we plead to take about 30 minutes of your time.

With your consent to participate in this study, we will ask questions mainly on your experiences during your episode of the TB disease. Study participants (cases and controls) will be recruited from seven district with MDR-TB cases in the Brong Ahafo Region of Ghana. Investigator will obtain information from respondents through the use of investigator-administered questionnaire. Questionnaires will be administered to both cases and controls in their respective locations with the assistance of the TB coordinators. Respondents' demographic and other health facility related variables will be validated from the client card or folder at the treatment centers.

RISKS FOR PARTICIPATING IN THIS STUDY

There would be no consequences to you as a participant in this study. You will not be forced to respond to the questions and you are free to stop participating at any time when you feel uncomfortable. The only risk that participants may face will be the risk of divulging confidential information provided to study members. This will be mitigated by ensuring that all the information provided by respondents will be saved on a password-protected computer that will only be

accessible to only the study team members. Also, participants will be assured of anonymity and the study team will conceal any information that can be linked to study participants.

BENEFIT

There would be no direct benefit for your participation in this study. However, we anticipate that the information you provided through the interview will enable us to documents ways of improving TB care to mitigate the incidence and spread of MDR-TB within the country and beyond.

COST

You will not be paid for your participation in this research and it will not cost you anything for participating in this study. We will therefore plead with you to spare us this time for us to conduct the interview.

CONFIDENTIALITY

The information that will be collected from you, if you agree to be part of the study, will be used only for the purpose of this study and will not be used in any other way. Your identity will remain anonymous: we will not use your name or any information that will make it possible to identify you personally when we are reporting or writing about this study. We will also not share this information with anybody apart from those involved with the study.

VOLUNTEER PARTICIPATION

Your participation in this research is entirely voluntary. You have every right to decide not to participate or withdraw your participation at any point in time without any penalty. You will not be affected if you decline to participate or later stop participating.

If you decide to participate, you will be asked to provide either your signature or thumbprint on a form on the next page.

QUESTIONS ABOUT THE STUDY?

If you have any questions about your participation in this research, you can contact the principal investigator, Gyamfi Gyimah Charles at School of Public Health, University of Ghana, Legon. The Phone number and e-mail address are +233 (20) 778 8990 and myckgyamfi1583@yahoo.com. You can also contact the Supervisor of this project, Dr. Anthony Appiah-Danso at the Department Epidemiology and Disease Control, School of Public Health, University of Ghana, Legon.

If you have questions about your rights as a research participant, please contact the Administrator of Kintampo Health Research Centre Institutional Ethics Committee, by telephone at 0504270501.

Participant's Statement

This study has been read and explained to me or I have had the chance to read the information about the study, and I have had the chance to ask questions. I understand that my interview will remain confidential and my answers will not be linked with my name. I understand that researchers will use the information from my interview for the purposes of this study. I volunteer to take part in this study. If I have questions during the study period or later about the study, I can ask a member of the study team who will answer or direct me to a place where I can get answers. I will receive a copy of this consent form. I give permission to the researchers to use my interview.

By signing/thumb printing below, the participant acknowledges that he/she has read and understood the information, is of age 18 or older, and will receive a signed copy of the consent form.

CONSENT SIGNATURE

NAME OF PARTICIPANT (PRINT): _____

SIGNATURE OF PARTICIPANT: _____ DATE _____

Participant Thumbprint

WITNESS

A witness should be a literate and sit throughout the whole consenting process. The witness must, write his or her name, date and sign this document.

‘‘I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.”

NAME OF WITNESS (PRINT): _____

SIGNATURE OF WITNESS: _____ DATE _____

STUDY TEAM MEMBER SIGNATURE

Name of Study Team Member (print): _____

Signature of Study Team Member: _____ Date: _____

APPENDIX II: QUESTIONNAIRE ON MULTIDRUG RESISTANCE TUBERCULOSIS STUDY

This is a confidential assessment tool to be used to identify predictors for multidrug resistance tuberculosis (MDR-TB) among TB clients in the Brong Ahafo Region, Ghana. It will bring to fore factors contributing to MDR-TB among cases and controls to enhance TB care. Your cooperation will be very much appreciated. Thank you.

Interview date

Respondent's category

Demographic and socio-economic information

1. Sex
   a. Male
   b. Female

2. Age

3. Marital status
   a. Single
   b. Married
   c. Cohabiting
   d. Divorced

4. Educational level
   a. Primary
   b. JHS
   c. SHS
   c. Tertiary
   d. None

5. Profession
   a. Farmer
   b. Trader
   c. Formal work
   d. Miner
   e. Artisan
   f. Unemployed
   g. Other (Specify)

6. Religion
   a. Christian
   b. Moslem
   c. Traditionalist
   d. Other (Specify)

7. Average monthly income

a. < Gh¢100.00
b. Gh¢101.00-250.00
c. Gh¢251.00 – 500.00
d. >500.00

8. Family size [ ]

9. Do you own any of the following assets
   a. Car
   b. Fridge
   c. Livestock
   e. Television
   f. Plot of land

10. Do you have a house to live in
    a. Yes
    b. No

11. Type of house
    a. Mud
    b. Block
    c. Wooden
    d. Brick

12. Number of rooms in the house [ ]

13. Clients' living situation
    a. Individually
    b. With a family

14. Type of respondent's settlement
    a. Rural
    b. Urban

15. Does the family has a common sources of entertainment
    a. Yes
    b. No

16. Do they enjoy it together
    a. Yes
    b. No

Behavioral and health related factors

17. Does client engage in illicit drug use
    a. Yes
    b. No

18. If yes, which type of drug ☐

19. Was there any history of smoking with the client
    a. Yes
    b. No

20. Was there any exposure to second-hand or any form of smoke
    a. Yes
    b. No

21. Does client has any history of contact with a newly confirmed or previously treated case
    a. Yes
    b. No

22. Does client has any history of past experience with a congregate setting (i.e)
    a. Prison
    b. Refugee camp
    c. Prayer camp
    d. Other (Specify)

23. Was there any history of traditional treatment after suffering the TB infection
    a. Yes
    b. No

24. Was there any history of presence of HIV/AIDS infection with the client
    a. Yes
    b. No

25. Clients' history of times of treatment
    a. 1 time
    b. >2 times

26. Does client has any history of defaulter in previous treatment course(s)
    a. Yes
    b. No

27. Was there a history of alcohol use with the client
    a. Yes
    b. No

28. Was there presence of Diabetes mellitus with the client
    a. Yes
    b. No

29. Was client in good mental health status
    a. Yes
    b. No

Health facility factors

30. How long did it take (from onset of symptoms) to capture of client at the facility
    a. <1 week
    b. 2weeks – 1 month
    c. >1 month

31. Was client adequately diagnosed with the TB disease
    a. Yes
    b. No

32. Did client receive thorough counselling before treatment initiation
    a. Yes
    b. No

33. Were the requisite and adequate drugs prescribed for the client during treatment
    a. Yes
    b. No

34. Was client supplied with adequate drugs supplies during treatment
    a. Yes
    b. No

35. Were timely reviews (sputum examination) done during treatment
    a. Yes
    b. No

36. If yes, how often
    a. Month 2
    b. Month 3
    c. Month 5
    d. Month 6

37. Were timely follow-ups by staff conducted in the course of treatment
    a. Yes
    b. No

38. If yes, how frequent
    a. Fortnightly
    b. Monthly
    c. Quarterly

39. Were client assigned with treatment supporter in the course of treatment
    a. Yes
    b. No

Coordinates

Latitude

Longitude

APENDDIX III: FULL ETHICAL APPROVAL CERTIFICATE

Kintampo Health Research Centre (KHRC) Institutional Ethics Committee (IEC)

P.O Box 200
Kintampo, B/A
Ghana, West Africa

Tel: +233(3520)92037/+233504270501
E-mail: ethics@kintampo-hrc.org
fred.kanyoke@kintampo-hrc.org

FULL ETHICAL APPROVAL CERTIFICATE

Charles Gyamfi Gyimah
College of Health Sciences
School of Public Health
University of Ghana
Ghana, West Africa

Date: 28th March, 2019

Study ID: KHRCIEC/2019-3

Title of study: Predictors for Multidrug-Resistant Tuberculosis among Tuberculosis patients, Brong Ahafo Region, Ghana, 2019.

Principal Investigator: Charles Gyamfi Gyimah, MPhil Candidate

Supervisor: Dr. Anthony Appiah Danso

Type of Review: Full Board Review

Approval Date: 28th March, 2019

Expiration Date: 30th September, 2019

1. The Kintampo Health Research Centre Institutional Ethics Committee (IEC) is constituted and operates in conformance with requirements of 45 CFR 46, 21 CFR 50, 21 CFR 56 and section 3 of the International Council on Harmonization Guidelines, as well as all applicable regulatory, legal, and other ethical requirements governing human subject research in Ghana. The OHRP Federal Wide Assurance number for the committee is 00011103; the IRB registration number is 0004854.

2. The above study in title was reviewed by the IEC on 26th March, 2019 and given conditional approval.

3. The Committee acknowledge the response to the conditional approval letter and submission of revised protocol. The response and revised protocol has been reviewed and considered to be satisfactory. The Committee therefore grants you full ethical approval for implementation of the study.

4. The following documents have been reviewed and approved for use;
   4.1 Predictors for Multidrug-Resistant Tuberculosis among Tuberculosis patients, Brong Ahafo Region, Ghana, 2019. Version 2, Dated March 2019.
   4.2 Participants Information sheet and informed consent form. Dated 2019
   4.3 Questionnaire on Multidrug Resistance Tuberculosis

Study File number: 2019-3

THE CHAIRMAN
KINTAMPO HEALTH RESEARCH CENTRE
INSTITUTIONAL ETHICS COMMITTEE.

Kintampo Health Research Centre (KHRC) Institutional Ethics Committee (IEC)
P.O Box 200
Kintampo, B/A
Ghana, West Africa

Tel: +233(3520)92037/+233504270501
E-mail: ethics@kintampo-hrc.org
fred.kanyoke@kintampo-hrc.org

4.4 Study Budget
4.5 Curriculum Vitae of study Investigator

5. During study implementation, the IEC must be informed within 72 hours by the principal investigator (PI) of learning of any (a) unexpected, serious, study related adverse events; (b) disclosed adverse events, or (c) unanticipated problems with the study which may pose risk to study participants or others, if applicable.

6. All safety monitory reports, including DSMB summaries and reports, must be submitted to the IEC as soon as they become available to PI, if applicable.

7. Changes or modifications to this research activity must be submitted and approved by the IEC before they are implemented.

8. PI(s) would be required to submit application for renewal of this approval certificate (if the study lasts for more than 6 months) plus a progress report.

9. PI(s) is required to notify the IEC of study completion (end of data collection/last follow-up) or early termination of the research project.

10. Submit final report of the study three months after approval certificate expires (study closure).

11. Before conduct of the study, submit original/final copy of your informed consent form for **authentication stamp** before making photocopies for your consent process.

12. Regulated study records, including IEC approvals and signed consent forms, must be securely maintained by PI(s) and available for audits for three years after the study is closed with the IEC.

Sincerely,

.....
Mrs. Charlotte Tawiah Agyemang
Vice Chair
Institutional Ethics Committee
Kintampo Health Research Centre

THE CHAIRMAN
KINTAMPO HEALTH RESEARCH CENTRE
INSTITUTIONAL ETHICS COMMITTEE.

Study File number: 2019-3