Spatial distribution of Tuberculosis in Nigeria and its socioeconomic correlates

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I declare that this thesis is my own work and has not been submitted for the award of a higher degree elsewhere

Abstract

Title: Spatial distribution of Tuberculosis in Nigeria and its socioeconomic correlates by Daniel Olusoji James, MBBS, MPH, MBA, FWACP (Community Health) August 2016.

Background: Tuberculosis remains an important public health problem especially in sub-Saharan Africa. Nigeria currently ranks 4th among the 22 high Tuberculosis (TB) burden countries with an estimated prevalence of 338/100,000 population. Few studies have utilized spatial data analysis techniques in the understanding of the pattern of distribution and possible correlates of TB especially in Africa. This study examines the spatial distribution of TB and its associated socioeconomic determinants in Nigeria.

Methods: The study used an ecological design based on the 774 Local Government Areas (LGAs) in Nigeria as the spatial units. Initial exploratory analysis used measures of spatial autocorrelation (Global and Local Moran's test statistics). The associations between TB incidence and nine covariates were assessed using a spatial regression analysis in the R statistical package.

Result: A total of 100,217 TB cases were notified in 2013. There is significant spatial autocorrelation among case notifications rates (CNR). Spatial regression analysis identifies 138 (17%) of LGAs with high TB risks and finds a significant relationship between household size, urban residence access to transportation, population density, number of TB diagnostic services and TB. An index defining socioeconomic status, living in a single room, TB treatment centres and total health facilities are not significantly associated with TB CNR.

Conclusion: The study presents a national picture of TB spatial heterogeneity at the lowest administrative level in Nigeria with the identification of high risk LGAs. This information can assist policy makers to rationally plan targeted specific interventions

to effectively control TB while addressing the underlying socioeconomic risk factors in the country.

Keywords: Tuberculosis, Bayesian model, INLA, Spatial analysis, Socioeconomic correlates, Nigeria

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List of abbreviations

AFB	Acid Fast Bacilli
AIC	Akaike's Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral therapy
BCG	Bacilli Guerin Calmette
BYM	Besag York and Mollie
CAR	Conditional Auto Regression
CNR	Case Notification Rate
CrI	Credible Interval
CSDH	Commission for Social Determinants of Health
CWIQ	Core Welfare Indicator Survey Questionnaire
DIC	Deviance Information Criterion
DOTS	Directly Observed Treatment Short course
FCT	Federal Capital Territory
FDR	False Discovery Rate
FMOH	Federal Ministry of Health
GDP	Gross Domestic Product
GHCW	General Health Care Worker
GIS	Geographic Information System
GWR	Geographical Weighted Regression
HIV	Human Immunodeficiency Virus
IDPs	Internally displaced persons
INH	Isoniazid
INLA	Integrated Nested Laplace Approximation
IPT	Isoniazid Preventive Therapy
IUATLD	International Union of Tuberculosis and Lung Disease
KMO	Kaiser-Meyer-Olkin
LGA	Local Government Area
LGTBLS	Local Government Tuberculosis and Leprosy Supervisor
LISA	Local indicators of Spatial Association
MCMC	Markov Chain Monte Carlo
MDR-TB	Multidrug-Resistant Tuberculosis

MeSH	Medical Subject Heading
MTB/RIF	Mycobacterium Tuberculosis/Rifampicin
NBS	National Bureau of Statistics
NPC	National Population Commission
NSSEI	Non-standardised socioeconomic index
NTBLCP	National Tuberculosis and Leprosy Control Programme
NTBLTC	National Tuberculosis and Leprosy Training Centre
PCA	Principal Component Analysis
pD	Effective Parameter
PHC	Primary Health Care
PLHIV	Person living with HIV
Pop.	Population
SAP	Structural Adjustment Programme
SDH	Social Determinant of Health
SEI	Socioeconomic Index
SEP	Socioeconomic Position
SES	Socioeconomic Status
SIR	Standardised Incidence Ratio
SMOH	State Ministry of Health
SNR	Standardised Notification Ratio
SSEI	Standardised socioeconomic index
STBLCP	State Tuberculosis Control Programme
TB	Tuberculosis
UNICEF	United Nations Children Fund
WHO	World Health Organization
ZN	Ziehl-Neelsen

CHAPTER 1: Introduction

1.1   Background

Tuberculosis (TB) remains an important public health problem of the 21st century. It is the second leading cause of death from a single infectious disease agent (WHO, 2014a). In 2013 alone, an estimated 9 million new TB cases and 1.5 million deaths occurred worldwide due to TB while 360,000 of these deaths are as a result of HIV (WHO, 2014a). The majority of these infections and deaths occurred in the global south, and countries in sub-Saharan Africa are responsible for about a quarter of the world's TB cases (WHO, 2014a).

Tuberculosis is regarded as a disease of poverty and there appears to be a close relationship between TB and poverty (WHO, 2002). Poverty predisposes individuals to malnutrition which makes them susceptible to tuberculosis infection. Likewise, poverty is associated with poor living conditions such as overcrowding that provides an enabling environment for the bacillus to thrive and thus facilitates TB transmission.

The relationship between tuberculosis rates and community socioeconomic risk factors such as low levels of education, income inequality, unemployment, and social deprivation has been well described in high-income countries of Europe and North America (Holtgrave & Crosby, 2004; Krieger, et al., 2013; Parslow, El-Shimy, Cundall, & McKinney, 2001). Some studies conducted in middle income countries such as Brazil, Mexico and South Africa have documented a higher TB rates in socially deprived areas (Alvarez-Hernández, Lara-Valencia, Reyes-Castro, & Rascón-Pacheco, 2010; Harling, Ehrlich, & Myer, 2008; Munch et al., 2003). There has been however, mixed evidence on the relationship between TB rates and socioeconomic indices in low and middle income countries with some studies reporting an inverse

relationship in Zambia and India respectively (Boccia et al., 2011; Oxlade & Murray, 2012) while other studies found no significant relationship between TB and socioeconomic indices in Eastern Cape South Africa, in three West African countries (Guinee, Guinea Bissau and The Gambia) and India respectively (Cramm et al., 2011; Lienhardt et al., 2005; Shetty et al. 2006). Interestingly, some studies actually observed a positive relationship between high socioeconomic indices and TB in rural Malawi, Zambia and in Karonga district in Malawi respectively (Glynn et al., 2000; Boccia et al., 2009; Odone et al., 2013). The conflicting conclusions from these studies in low income countries brings into question whether indicators used in assessing socioeconomic status in the global north are appropriate for the global south. This present study will contribute towards the on-going debate especially in a country like Nigeria that has the largest population in Africa with diverse economic and social conditions across states and LGAs.

There has been a growing interest in the application of spatial data analysis techniques to the study of the spatial distribution of disease risk and incidence, called spatial epidemiology (Ostfeld, Glass, & Keesing, 2005). Spatial epidemiology covers three main essentials which are: visualization of spatial data using a map (disease mapping); exploration of patterns and relationships; and modelling of spatial data in such a way as to test hypotheses and search for explanations and relationships using statistical models (Elliott & Wartenberg, 2004; Ostfeld et al., 2005). The growing field of spatial epidemiology has therefore provided an opportunity to better understand geographic variation of diseases, explore local risk factors that may be responsible for the observed pattern, identify and detect disease clusters or high risk areas that may require targeted intervention for the control of the disease and by using advanced spatial statistical analysis can predict future occurrences of disease and how

different control strategies will impact the control of diseases (Elliott & Wartenberg, 2004; Ostfeld et al., 2005).

Few studies have utilized spatial data analysis in the study of tuberculosis in Nigeria either at the State or Local Government Areas (LGA) levels (Cadmus, Akingbogun, and Adesokan, 2010; Ibrahim, Hamisu, and Lawal 2015; Igu, Enete, and Olaniyan, 2013; Oloyede-Kosoko and Akingbogun, 2013). Existing studies are largely limited in scope, in methodological rigour or both. The majority of these studies examine either a defined geographical area within a LGA or one or more LGAs within a state. There are very few studies which have utilised rigorous spatial statistical and spatial regression methods to detect and/or model global or local clustering of TB cases. In addition, none of the studies have explored the explanatory variables that may be associated with TB such as socioeconomic, demographic and health related factors. This study will therefore address some of the gaps observed in the previous studies in the country and will be the first comprehensive national study of the spatial distribution of tuberculosis in Nigeria at the lowest administrative 774 LGAs in the country. The study will explore the socioeconomic, demographic and other health related factors that may be responsible for the observed spatial distribution of TB across the country.

1.2 TB in Nigeria and related strategies

Nigeria currently ranks 4th among the 22 TB high burden countries in the world, with an estimated prevalence rate of 326 per 100,000 populations. This translates to about 570, 000 TB cases and an incidence rate of 338/100,000 population (WHO, 2014a). However, only about one fifth of the estimated cases were notified in the same year (WHO, 2014a). The low ratio of the case notification to the estimated TB incidence observed in many high burden countries including Nigeria has been attributed to a

weak TB surveillance system, underreporting of diagnosed TB cases and poor access to health care. Despite the weakness of the TB case notification rate in many countries in the global south, it is often the only available and useful epidemiological measure of TB at the sub-national level that is used to monitor TB situation across the country (WHO, 2014b; Wong, Yadav & Nishikiori 2013).

In order to coordinate international efforts for TB control, the WHO declared TB a global emergency in 1993 and recommended the Directly Observed Treatment short course (DOTS) strategy as the global response to stem the rising TB epidemic (WHO, 1994). The DOTS strategy consists of five elements namely: government commitment to TB control; case finding by smear microscopy to identify sputum positive cases ; supervised short course treatment where patients are observed by a health care worker or a trained volunteer; regular supply of good quality drug without interruption and an information system for monitoring and reporting of treatment outcomes (WHO, 1994). The strategy was launched in the mid-1990's and adopted by many countries as a cost-effective strategy for the control of TB.

The DOTS strategy was replaced in 2006 by the Stop TB strategy in a bid to address the emerging challenges encountered during the implementation of the DOTS strategy, such as the rising Human Immuno-deficiency Virus (HIV) and multidrug resistant TB (MDR-TB) epidemic and the non-engagement of the broader health system including the private sector (WHO, 2006). The Stop TB strategy consists of six components with the original DOTS strategy as the corner-stone. These components include: pursuing high quality DOTS expansion and enhancement; addressing TB/HIV, MDR-TB and other challenges; contributing to health systems; engaging all care providers; empowering people infected with TB and their communities; and enabling and promoting research (WHO, 2006). Cumulatively,

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about 56 million people have been successfully treated under DOTS and 37 million lives have been saved. In addition, the reduction of and the fall in TB incidence in many parts of the world and the reduction of TB mortality by about 45% has been attributed to the global implementation of the DOTS/Stop TB strategy (WHO, 2013).

The Federal Government of Nigeria established the National Tuberculosis and Leprosy Control Programme (NTBLCP) in 1988 with a mandate to reduce the prevalence of TB to a level where it no longer constitutes a public health problem. The NTBLCP adopted the DOTS strategy in 1993 and by the end of 2003 all 36 states and the Federal Capital Territory implemented DOTS with a target of detecting 70% of the estimated TB cases and successfully treating 85% of the detected TB cases (FMoH, 2010). The DOTS strategy was replaced by the Stop TB strategy in the country in 2006 in line with international best practices.

TB still remains a global health threat despite the implementation of global strategies for its control which have raised concerns about the ability of these strategies to bring about global control of the disease. The DOTS and Stop TB strategies have been considered to be biomedical interventions, with emphasis on passive case finding of TB patients and effectively treating them to break the transmission of the infection (Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2009; Rasanathan, Sivasankara Kurup, Jaramillo, & Lönnroth, 2011). Recent global attention has been geared towards addressing the social determinants of TB disease that may be responsible for the disparities observed in the TB prevalence between low/middle income and high income countries, in order to effectively control the disease (Hargreaves et al., 2011; Lönnroth et al., 2009). Consequently, the current post-2015 End TB strategy by the World Health Organization has social protection, poverty alleviation and actions on other determinants of tuberculosis as one of its

components (WHO, 2015). It is hoped that with the implementation of the End TB strategy, the incidence of TB and death as a result of TB will be reduced by 90% and 95% respectively by 2035 and the catastrophic cost experienced by TB affected families as a result of TB will be reduced to zero (WHO, 2015).

1.3 Aim and objectives

The overarching aim of this thesis is to explore the spatial distribution of tuberculosis and its relationship with socioeconomic indices in Nigeria. This broad objective is further divided into three more specific objectives. The first objective is to determine whether there are significant factors associated with non-spatial variation in TB cases notified by the 774 LGAs in Nigeria using Poisson models; this assumes that the outcome variable is independently distributed across the LGAs in the country. The second objective is to examine if there is significant spatial variation between places using autocorrelation in the 774 LGAs in Nigeria. If there is, then the third objective becomes one of fitting spatial models with covariates to try to explain such variation and identify the factors significantly associated with the spatial variation of TB cases notified by 774 LGAs in Nigeria.

The finding from this study can provide useful information on the relationship between explanatory variables and TB especially in Africa which will be of interest to public health practitioners and also provide information that will assist policy makers to identify LGAs with high TB risk and the associated factors. These LGAs can be prioritized for specific local intervention for the prevention, treatment and control of TB in Nigeria.

1.4 Study context: Key features of Nigeria

Nigeria is a relatively large country situated in West Africa bounded in the north by Niger Republic, on the east by Chad and Republic of Cameroon, on the south by the

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Gulf of Guinea (approximately 800km of the Atlantic ocean), and on the west by Benin Republic. It occupies an estimated 923,768 square kilometres area. The country has a population of 174 million people (Population Reference Bureau, 2014) with an annual population growth rate of 2.8 per cent (UNDP, 2015). The average population density is 104 per square kilometre with 45 per cent residing in urban areas (National Population Commision, 2010). Nigeria is made up of about 350 ethnic groups with diverse culture and traditions. Although the official language is English, there are three major languages widely spoken namely Hausa/Fulani, Igbo and Yoruba. Nigeria operates a three-tier system of government consisting of the Federal, States and the Local Government Areas (LGA). The country has 36 autonomous States in addition to the Federal Capital Territory. There are 774 LGAs in the country which is the lowest administrative unit. For socio-political reasons, the 37 states (Figure 1) are grouped into six geopolitical zones namely North-East, North-West, North-Central, South-West, South-East, and South-South (Table1).

The relative poverty rate is the official poverty measurement in the country. It is an indicator of the living standards of majority of the people in the country based on the total household per capital expenditure. Households with expenditure greater than two-thirds of the total household per capita expenditure are regarded as non-poor while those below it are considered poor. The relative poverty rate has been on the increase from 27.2% in 1980 to 54.4% in 2004 and recently 69% in 2010 (NBS, 2012). The poverty situation in the country has largely been attributed to the neglect of the agricultural sector, the long period of political instability and military rule, mismanagement of the nation's resources and depreciation of the nation's currency (Bakare & Ilemobayo, 2013). The North East and the North West geo-political zones

have the worst poverty rates while the South West geopolitical zone has the least poverty rate in the country (NBS, 2012).

Table 1: Geopolitical zones and states in Nigeria

Geopolitical Zones	States	No of LGAs
South-West Zone	Ekiti	16
	Lagos	20
	Ogun	20
	Ondo	18
	Osun	31
	Oyo	33
South East Zone	Abia	17
	Anambra	21
	Ebonyi	13
	Enugu,	17
	Imo	27
South-South Zone	Akwa Ibom	17
	Bayelsa	8
	Cross- River	18
	Delta	25
	Edo	18
	Rivers	23
North-Central	Benue	23
	FCT	6
	Kogi	21
	Kwara	16
	Nassarawa	13
	Niger	25
	Plateau	17
North-East	Adamawa	21
	Bauchi	20
	Borno	27
	Gombe	11
	Taraba	16
	Yobe	17
North-West	Jigawa	27
	Kaduna	23
	Katsina	34
	Kebbi	21
	Kano	44
	Sokoto	23
	Zamfara	14
Total	**37**	**774**

The general policy framework for health care in Nigeria is contained in the National Health Policy promulgated in 1998 and revised in 2004, designed to achieve health for all Nigerians through the national health system (FMoH Nigeria, 2004). The overall goal is to achieve a level of health that will enable all Nigerians to achieve socially and economically productive lives. The policy provides for a national health system based on primary health care. Health care services in Nigeria are organised at three levels of care: primary, secondary and tertiary care (Welcome, 2011). The Local Government is responsible for the provision of primary level of care services organised through the political wards while the State Ministry of health (SMoH) has responsibility for the provision of secondary level of care. The Federal Ministry of Health (FMoH) is generally responsible for tertiary level of care in addition to policy formulation and technical guidance to the states and LGAs (FMoH Nigeria, 2004). Health care service is provided through both public and private health care facilities. Health care financing in Nigeria is done through a combination of tax revenue, donor financing, out of pocket spending and health insurance (FMoH Nigeria, 2004). The country's total health expenditure is less than 5% of the Gross Domestic Product (Olakunde, 2012). Though several attempts have been made to revitalise the national health insurance scheme in the country to provide a more sustainable and efficient means of health care financing, about 70% of financing health care in the country is through out of pocket payments in both public and private health facilities (Olakunde, 2012; Uzochukwu et al., 2015). Therefore, the high cost and burden of health care borne by households have served as a barrier to access modern health care services which result in delay of seeking modern health care service and increasing patronage of alternate unorthodox health care. The government however provides free basic public health services such as treatment for malaria, tuberculosis and other diseases of public

health importance. The Federal Ministry of Health (2012) reports a total of 34,173 facilities in the country in 2012, out of which 22859 (66.9%) are publicly owned while 11,323 (33.1%) are privately owned facilities. About 88.1% of these facilities are primary health care facilities, 11.7% secondary, 0.2% are tertiary health care facilities (FMoH, 2012). The long period of political instability, military rule, mismanagement of the nation's resources and depreciation of the nation's currency led to insufficient investment into the country's infrastructure and basic health service (Bakare & Ilemobayo, 2013). The weak health system with the low coverage of key public health intervention results in the persistence of high disease burden such as TB in the country (UNICEF Nigeria, 2007).
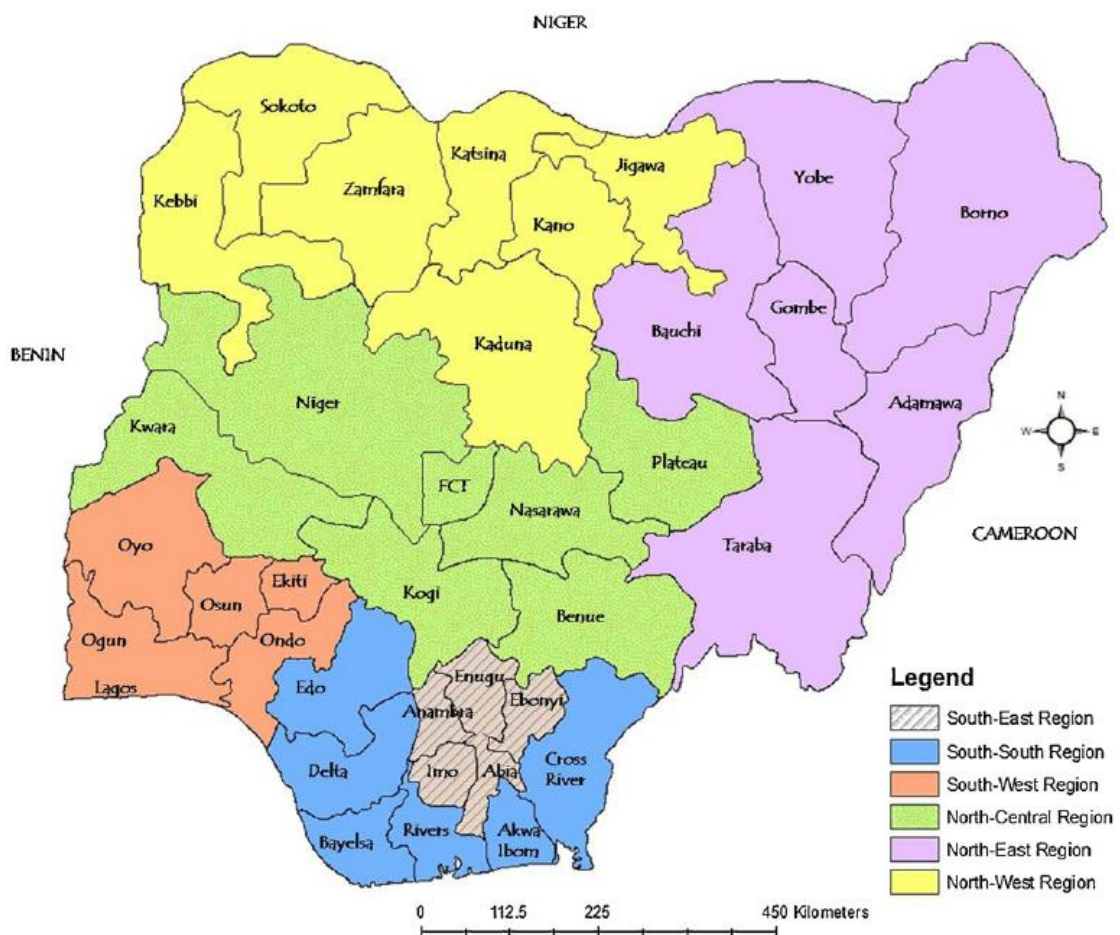
Source: Adapted from researchnet.com

Figure 1: Nigerian states and geopolitical zones

CHAPTER 2: Clinical Epidemiology of Tuberculosis

2.1   Epidemiology of Tuberculosis

Tuberculosis is a chronic infectious disease caused by the bacterium, *Mycobacterium tuberculosis*. About one-third of the world's population are infected with the bacilli. In 2014, an estimated 9.6 million were sick of the disease while 1.5 million people died from the disease (WHO, 2015). The disease is transmitted by the airborne inhalation of infectious droplets nuclei (between 1mm and 5 mm in size) produced by an untreated pulmonary TB patient while talking, coughing, sneezing or singing. The small droplet nucleus reaches the alveolus of the lung where it causes TB infection which can later progress to TB disease. A person with active TB can infect 10-15 persons in the course of a year through close contact (Moghaddam, Moghadam, Khademi, Bahreini, & Masumeh, 2016). About 5% of infected individuals develop active TB within the first two years following infection, while the rest enter a state of latent infection (Narasimhan, Wood, MacIntyre, & Mathai, 2013). An additional 5% of infected individuals develop active disease later than two years after infection, and thus about 10% of infected individuals develop active disease during their lifetime (Narasimhan et al., 2013). However, the risk of progression to disease is increased to about 10% per year in HIV-positive and other immune-compromised individuals (Getahun, Gunneberg, Granich, & Nunn, 2010).

The natural history of the disease reveals that about 70% of untreated TB among smear positive HIV negative patients will die within 10 years while 20% of untreated smear negative culture positive TB cases will die within 10 years (Tiemersma, Werf, Borgdorff, Williams, & Nico, 2011). However, effective chemotherapy is available for the management of the vast majority of drug-susceptible forms of the disease if properly treated.

Tuberculosis primarily affects the lungs (pulmonary TB) in about 80% of the cases but can affect any organ of the body (extra-pulmonary TB) including bones, skin, brain, vertebral spine among others (Moghaddam et al., 2016) . The commonest symptom of TB is cough for a duration of two weeks or more which is usually accompanied with fever, weight loss, night sweats, chest pain, shortness of breath, tiredness, loss of appetite and in some instances haemoptysis (Moghaddam et al., 2016). Extra-pulmonary TB presents with symptoms based on the organ affected in addition to general symptoms such as tiredness, weight loss, fever and night sweats (Moghaddam et al., 2016). Diagnosis of TB is made by examination of sputum by trained laboratory technicians for Acid Fast Bacilli (Parsons et al., 2011).

TB is treatable and curable and the treatment of TB involves the use of a standardized six months regimen of four anti-TB drugs, namely Rifampicin, Isoniazid, Ethambutol and Pyrazinamide (Obermeyer, Abbott-Klafter, & Murray, 2008; Volmink & Garner, 2009). The patients are supported to adhere to treatment either by a health care worker or a treatment supporter from the community which could be family member or community volunteers (Khan, Walley, Witter, Shah, & Javeed, 2005).

 2.2 Risk factors for Tuberculosis

The epidemiological model in Figure 2 describes how an exposed individual can be infected with TB and develops latent infection (subclinical infection) which can progress to TB disease (infectious or non-infectious disease) and death. Several risk factors are responsible for the movement from exposure until death. The model also shows the different areas where interventions can be targeted to reduce exposure, and consequently, reduce the risk of developing TB infection and if infection occurs interventions that can prevent the progression of infection to disease, and when

disease occurs, interventions that can prevent death (Narasimhan et al., 2013). The factors are:

a. Factors that determine the risk of becoming exposed to the tubercle bacilli: the risk of being exposed to the tubercle bacilli is determined by factors related to the level of TB infectiousness in the community and duration of infectiousness of the source case. Smear positive TB cases are known to be more infectious than smear negative and extra-pulmonary TB. The higher the bacillary load in the sputum of an infected individual, the more infectious the individual is (Espinal et al., 2000). However, it has been established that sputum smear negative TB cases can also transmit infection though to a lower extent compared to sputum smear positive TB cases (Hernandez et al., 2004). Thus, sputum smear negative TB cases also remain an important source of TB transmission in the community. The prevalence of infectious TB cases and the duration of infectiousness are important factors that increase the risk of infection in the general population. An untreated TB case will remain infectious unless such patients have access to TB diagnosis and treatment. Close contacts of TB patients such as household contacts and care givers including health care workers are particularly at a higher risk of becoming infected with TB (Cuhadaroglu, Erelel, Tabak, & Kilicaslan, 2002). Recent studies have also observed that casual transmission of TB can take place within a short contact period in both high and low incidence settings (Wang et al., 2014).

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A Model for the Epidemiology of Tuberculosis
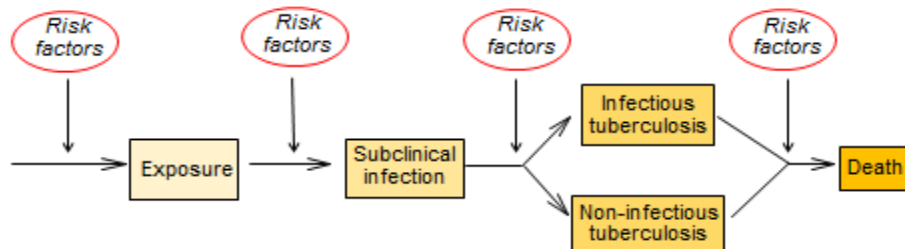
Adapted from the IUATLD (International Union Against TB and Lung Disease) kit developed by Hans L. Rieder.

Figure 2: Epidemiological model of tuberculosis

b. Factors that increase the risk of being infected once exposed to a source of infection: this is determined by the density of bacilli in inhaled air; the duration of exposure of the susceptible host to the contaminated air; the virulence of the specific strain of *M. tuberculosis* and the status of the exposed person's defence systems against infection (Rieder, 1999).

c. Factors that increase the progression of TB infection to disease: these include host related factors such as HIV (Corbett et al., 2003); malnutrition (Lonnroth, Williams, Cegielski, & Dye, 2010); alcohol abuse (Lönnroth et al. 2009; Rehm et al., 2009); diabetes mellitus (Stevenson et al., 2007); smoking (Slama et al., 2007); indoor air pollution (Sumpter & Chandramohan, 2013); silicosis (Rees & Murray, 2007); pregnancy (Loto & Awowole, 2012) and in malignancies and other chronic diseases such as renal failure (Eastwood, Corbishley, & Grange, 2001; Falagas, Kouranos, Athanassa, & Kopterides, 2010). The risk of infection to

disease increases with age usually in adolescents and young adults and among individuals above the age of 60 years (Rieder, 1999).

d. Factors that increase the progression of TB disease to death: this is mainly determined by the site and type of the disease and by the prompt administration of adequate and appropriate treatment. When TB is left untreated, the risk of death is between 30-40% in one year and cumulatively between 50-70% within 5-7 years (Tiemersma et al., 2011).

An update to the clinical epidemiological framework that addresses the social determinants of TB has been developed (Lönnroth, Jaramillo, Williams, Dye, & Raviglione, 2010; Lönnroth et al., 2009). This framework has identified risk factors that go beyond the current biomedical strategy for the control of TB. It suggests some entry points for intervention that relates to social determinants of TB, that demand attention if global control targets are to be achieved.

Figure 3 illustrates how policies of government (economic, social and environmental) and other structural factors shape poverty and determine the strength of the health system which in turn affects downstream factors. Downstream factors such as crowding and poor ventilation (in a variety of settings, including the household, public transportation, and prison) that directly increase the level and duration of exposure of uninfected individuals to TB infection. Downstream factors also include those that impair the host defence; they include HIV, chronic malnutrition, chronic alcoholism, smoking, and indoor air pollution. Therefore, to effectively control TB as a public health problem, interventions must be directed at both upstream factors producing health inequities and downstream social determinants of TB.

In summary, this chapter has discussed the clinical epidemiology of TB and individually-based risk factors of TB and has presented an updated framework that

included the social determinants of TB in order to provide a comprehensive approach to the epidemiology of TB. The rectangles in figure 3 (shaded in grey) represent areas presently not addressed by the current biomedical strategy. These need strategic attention if the global targets for TB control are to be realised.
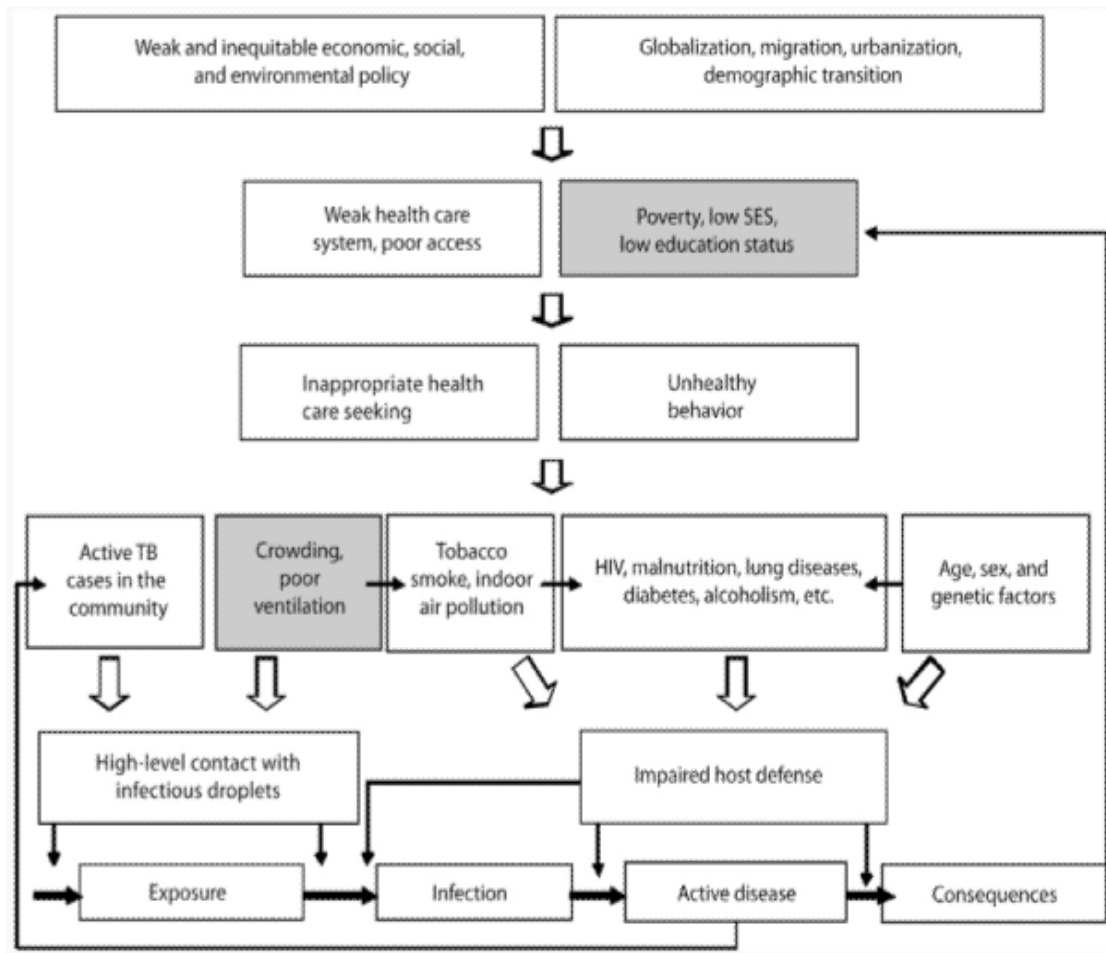
(Source Lonnroth et al, 2009)

Figure 3: Framework for downstream risk factors and upstream determinants of TB, and related entry-points for interventions.

Chapter 3 will look in detail at the theories of social inequalities that are relevant to TB epidemiology and draws up a conceptual or theoretical framework for this study.

CHAPTER 3: Conceptual framework

The Commission for Social Determinants of Health (CSDH) was established in 2005 by the World Health Organisation in realization that the biomedical approaches and technology driven medical care alone cannot address the myriad health challenges and reduce inequities in health (CSDH, 2007; Marmot, 2008; Marmot, 2005). The CSDH therefore developed a comprehensive framework of social determinants of health (SDH) that integrates previous models of SDH such as the ones concerning social selection or mobility, social causation and life course perspectives (CSDH, 2007; Solar and Irwin, 2010).

The social selection or social mobility perspective theorizes that health determines the socioeconomic position that individuals occupy in society and that poor health tend to cause a downward drift of unhealthy individuals to occupy the lower scale of the social ladder (CSDH, 2007; Solar and Irwin, 2010). Conversely, individuals with good health at the lower social strata in society tend to experience an upward movement on the social ladder and therefore leave behind those with poorer health to occupy the bottom of the social scale. Some recent arguments have been that social mobility do not necessarily increase the magnitude of social inequalities since individuals that move down the social ladder relatively have better health than those in the class where they end up thereby generally improving the health status of that class, while individuals with good health that move up social ladder reduce the general health of the upper class where they end up (Arcaya, Arcaya, & Subramanian, 2015; Foverskov & Holm, 2016; Pakpahan & Hoffmann, 2015). Some researchers advocate that the social selection theory do not appear to be a major explanation for the inequalities observed in health (Siegrist & Marmot, 2004; Warren, 2009). Nunn, Johnson, Monro, & Bickerstaffe, (2007) argue that the theory is limited in that it

focusses on the downward mobility of people within the labour market, thus ignore people who exit out of employment or individuals who opt for early retirement because of ill health. Burchardt, (2001) observe that among individuals who are in current employment, one in six lose their jobs during the first year of becoming disabled. Jenkins & Rigg, (2004) reports a higher likelihood of job loss among individuals who are disabled at the onset of disability and that the degree of job loss increases as the disability progresses. Furthermore, Holland, Burström, Möller, & Whitehead, (2006) observe that patients diagnosed with musculoskeletal disease are more likely to leave employment especially women and those who are semi- and unskilled manual workers. In the context of TB, there is evidence of job loss by the TB patient as a result of the disease and in some instances, care givers may also lose their jobs due to the demand of obtaining treatment for members of their family who are sick with TB (Onazi et al., 2015; Ukwaja, Alobu, lgwenyi, & Hopewell, 2013).

The social causation theory on the other hand emphasizes that socioeconomic position determines health possibly through some intermediary factors that are unevenly distributed across socioeconomic classes (Link & Phelan, 2002; Link & Phelan, 2000; Lynch, Smith, et al., 2004; Phelan, Link, Diez-Roux, Kawachi, & Levin, 2004; Phelan, Link, & Tehranifar, 2010). The relationship between socio-economic factors such as income and occupation/social class and health outcomes at the individual level within societies have been observed in several studies (Adler & Newman, 2002; Adler & Rehkopf, 2008; Lynch, Davey, Harper, & Hillemeier, 2004; Lynch, Smith, Kaplan, & House, 2000;Marmot & Wilkinson, 2001; Singh-Manoux, Adler, & Marmot, 2003). For example, Davey Smith and Lynch (2004) in their analysis of longitudinal data in Canada find a causal relationship between individual level income and individual health outcome (mortality). Similarly, a relationship between aggregate

economic measures such as gross domestic product and health outcomes such as life expectancy have been observed at the country or regional level (Deaton, 2003; Lynch et al., 2004; Lynch et al., 2000). Deaton, (2003), explains that a curvilinear relationship exists between national income and life expectancy in their study of both low and high income countries. There was a strong positive relationship between average national income and life expectancy in poorer nations but the relationship weakens or flattens out among the richest nations which suggest that the variation in population health is not as tightly linked to average income; rather, the unexplained variation in average levels of health among affluent nations is linked to the unequal income distribution within these countries (Lynch et al., 2004; Lynch, Davey, Harper, & Hillemeier, 2004). Other studies supported the finding that more unequal societies tend to experience worse health and mortality compared to more egalitarian societies (Deaton, 2003; Marmot & Wilkinson, 2001; Shi et al., 2003; Subramanian & Kawachi, 2004; Wagstaff & van Doorslaer, 2000). Wilkinson & Pickett (2006) in a review of 168 research articles provides extensive evidence on the association between income inequality and health outcomes independent of average income. A similar relationship have been observed between higher income inequality and worse health outcomes including self-rated health, mental health, violence and other health conditions such as asthma and cardiovascular diseases (Franks, Gold, & Fiscella, 2003; Kozyrskyj, Kendall, Jacoby, Sly, & Zubrick, 2010; Lee et al., 2009; Lynch, Smith, et al., 2004). The association between income inequality and health outcomes has also been described in low income countries (Deurzen, Oorschot, & Ingen, 2014). Furthermore, Antai, (2011) and Van Malderen, Van Oyen, & Speybroeck, (2013) also finds a strong association between wealth-related inequality and under-five mortality in Nigeria. The association between income inequality and health inequality

is mediated through the uneven distribution of material, psychosocial, behavioural and biological risk factors between the various socioeconomic groups (Bartley, 2005; Krieger, 2001; Marmot, 2008; Marmot & Wilkinson, 2001; Solar and Irwin, 2010).

The life course perspective postulates that poor health is determined by a life-time accumulation of negative or health damaging environment as a result of socioeconomic position (Cockerham, 2007; CSDH, 2007; Bartley, 2004). The life course perspective identifies two pathways namely the "critical periods" and the "accumulation of risk" models. The critical period model posit that exposure to health damaging environment at some critical points in time have an effect later on in life. For example, the effect of low birth weight on the development of coronary heart disease, diabetes mellitus and high blood pressure later on in life (Chen et al., 2012; Huxley et al., 2007; Leeson, Kattenhorn, Morley, Lucas, & Deanfield, 2001; Negrato & Gomes, 2013). The accumulation of risk model suggest that socially patterned differential exposures at different stages in the life course of an individual may result in accumulation of risk and ill health later in life. For example, children with low birth weight are more likely to live in socially deprived neighbourhoods, exposed to poor nutrition, predisposed to childhood infections and passive smoking which may make them susceptible to respiratory diseases later on in life as a result of the acquisition of cumulative risk over time (Ben-shlomo & Kuh, 2002; Darnton-Hill, Nishida, & James, 2004; Kuh, Lynch, Hallqvist, & Power, 2003).

The conceptual framework for this study is adapted from the World Health Organization's framework on the social determinants of health which defined these as the "conditions in which people are born, grow, live, work that mostly contribute to health inequities - the unfair and modifiable differences in health within and among countries" (CSDH, 2007). Though the term health inequities and health inequalities

are sometimes used interchangeably, health inequities are avoidable inequalities in health between population groups within or between countries. The conceptual framework will provide a foundation for the understanding of how social determinants of health (SDH) affect the exposure, acquisition and progression of infection to disease generally while the next chapter will relate more specifically to TB.
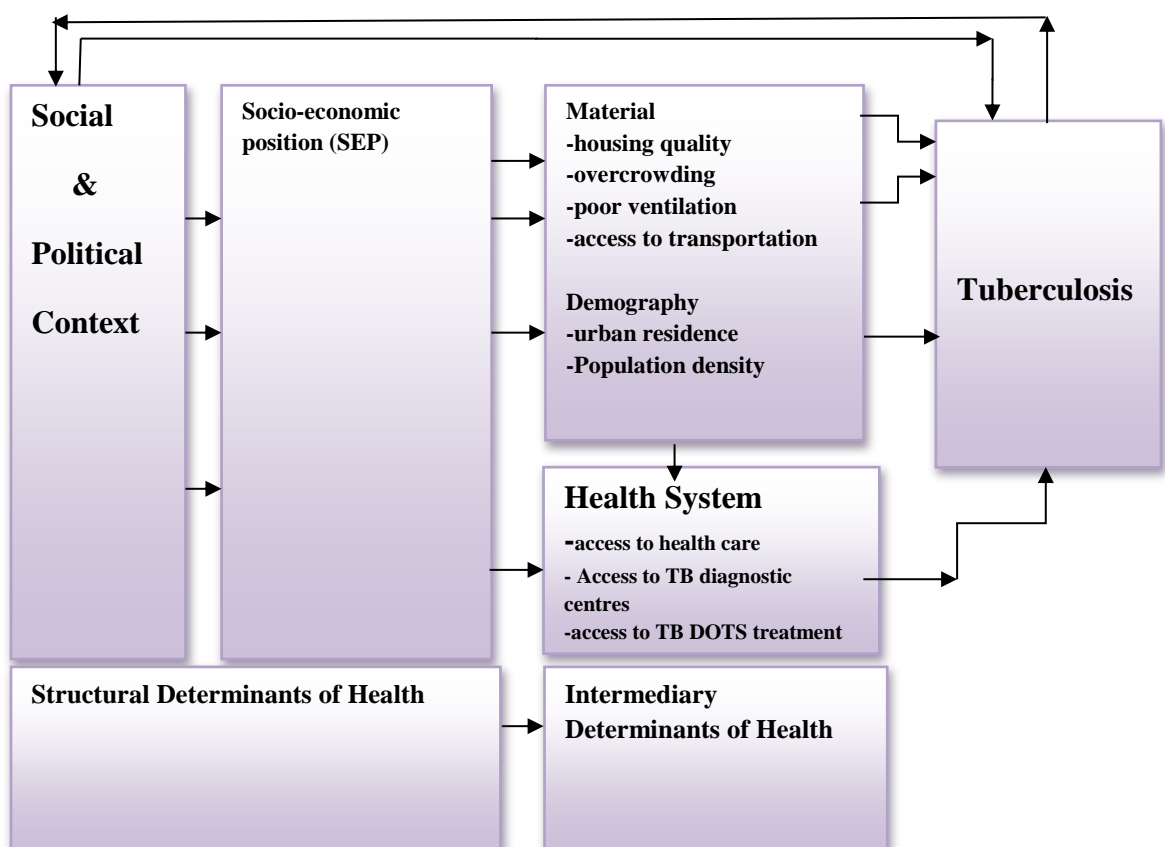
Figure 4: Schematic framework for the social determinants of health.

Figure 4 highlights the processes by which social and political context influence the development of disease and health outcomes generally through intermediary determinants such as material deprivation, demographic processes and the health

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system. The diagram is adapted from the Commission on social determinants of health (CSDH, 2007). The components of the framework are discussed below:

3.1 Socio-economic and political context

The socioeconomic and political contexts are the societal factors that generate and maintain social stratification in society which allocates individuals to different social positions. These factors may be cultural, political or functional aspects of the social system that cannot be measured directly at the individual level but generate unequal distribution of power and resources among groups in society and therefore tend to lead to differences observed in the health status among population groups. These factors include the labour market, educational system, governance system, public policies, political structure and other social and cultural values of society. There are few studies of the effect of political parties and government policies on health. The study by Navarro & Shi, (2001) on the effect of public policies on SDH in Kerachi India observe that the lower income inequality in the state could be traced to the public policies carried out by governing communist party that had ruled in the state for a larger part of the 40 years of her existence. Also, Chung & Muntaner, (2006) finds that 20% and 10% of the infant mortality rate and low birth weight respectively in the 18 wealthiest countries in Europe, North America and Asia-Pacific can be explained by the type of welfare state models operated by these countries. In addition, Wilkinson and Pickett, (2009) resolve that countries with a long history of redistributive governments have smaller income inequalities and therefore have better health outcomes. The policies of governments whether economic, social, political or environmental shape and maintain social stratification in society and these influence the social determinants of health.

3.2 Structural determinants and socioeconomic positions

Structural determinants are factors that produce or reinforce social stratification (i.e. how people are placed within the hierarchy of power, prestige and access to resources) in society and they determine the socioeconomic position (SEP) of an individual in society. The structural determinants in combination with the socioeconomic and political context discussed above give rise to what is called the social determinant of health inequities. The structural determinants define the socioeconomic position (SEP) of individuals within the hierarchy of the social stratification system in society. The SEP of individuals can be determined by income, occupation, education, social class, gender and race/ethnicity which shape power, prestige and economic status. Socioeconomic position in societies determines not only the amount of money a person earns but also the access a person has to the structure of power, opportunities and life chances in the society. This may influence life choices and could determine the health gradient observed in society (Bartley 2005; Dixon 2000; Marmot 2005). The terms social stratification and social class are frequently used in the literatures on social inequalities to denote SEP. Stratification however suggests a social hierarchy where individuals can be ranked by some attributes while social class refers to ownership or control over productive resources. Social class is however preferred because of its inherent relational quality to provide a better understanding of how health inequities are produced by structural determinants (Solar and Irwin, 2010).

3.3 Intermediary social factors or social determinants of health

The intermediary social factors or social determinants of health (SDH) are the offshoot from the social determinants of health inequities and they determine the differences in the risk of exposure, vulnerability, outcome and consequences of

diseases or health compromising conditions on individuals and families. The SDH could be categorised into four major domains namely material, psychological, behavioural/biological and the health system.

3.3.1   **Material circumstances**

The material living standards of people directly or indirectly affect health. Income inequality influences the material living standards such as housing, physical working environment, consumption potential and access to facilities which will affect the health status of population groups. The material living standard is perhaps the most important intermediary factor and housing is one of the most important measures of material aspects of the socioeconomic circumstances of people. The effects of housing (internal housing and neighbourhood conditions) and housing tenure have both direct and indirect effect on health (Gibson et al., 2011; Shaw, 2004). The structure and quality of housing in terms of the indoor conditions such as damp, cold and indoor pollution has a direct effect on respiratory health. Other conditions such as the use of lead piping and lead paints can predispose to poisoning. The neighbourhood conditions such as the availability of recreation facilities, markets, parks, restaurants and so on have indirect effects on health (Gibson et al., 2011; Shaw, 2004). Furthermore, housing tenure (whether owned or rented) has been linked to overall health and psychological wellbeing among home owners compared with those who live in private renting or social homes (Gibson et al., 2011).

Another material circumstance that has an effect on health is the working conditions people are exposed to. The hazards in the workplace can be physical, chemical, biological, environmental and psychosocial. The lifetime accumulation of negative environmental factors from hazards in the work place has an effect on the health gradient observed among population groups and contribute to health

inequalities (Burgard & Lin, 2013). For example, the effect of silica dust (Bang, Attfield, Wood, & Syamlal, 2008), and other chemicals such as asbestos in mining workers on mortality has been established (Donoghue, 2004). Another aspect of work related hazards is shift work sleep disorder, coronary heart disease and peptic ulcer as a result of the rise in working in a 24 hours all day economy (Knutsson, 2003). Psychosocial stressors in the work place such as job strain, job insecurity, low support from supervisors have effects on physical and mental health (Burgard & Lin, 2013) Furthermore, the non-existence or non-enforcement of labour protective laws especially in developing countries contribute to the differential exposure to hazards in the work place and this will have a negative effect on health if it is accumulated over a period of time (Solar and Irwin , 2010).

3.3.2   **Psychosocial circumstances**

Marmot and Wilkinson (2001) argue that health inequalities and the gradient in health observed in industrialised rich societies cannot solely be explained by material scarcity. Brunner & Marmot, (2006) in their analysis of the study on the possible cause of coronary heart disease between men of high (Sweden) and low (Lithuania) socioeconomic status found that the conventional risk factors such as smoking, high cholesterol and blood pressure did not provide an explanation for the national differences in risk. The study concludes that men in low socioeconomic groups in both countries report higher levels of isolation and greater difficulties in coping with life's pressures than men in the higher income groups. Also the men in Lithuania experience more social isolation, more job strain and more depression than the men in Sweden. The differences in the psychosocial environments between the two countries and between the high and the low income groups within the countries were evident in the adversely high levels of cortisol measured among the low income groups which is

an indication of an altered functioning of the neuroendocrine stress pathway. This example bring into focus an alternative explanation for health inequities especially in high income countries where material living standards alone cannot explain the inequality in health outcomes observed within and among population groups. The psychological circumstances of people through the pathway of stress have been accepted as an alternative explanation for health inequities (Adler & Newman, 2002; Adler & Rehkopf, 2008; CSDH, 2007). The psychological stress can arise from several reasons including social exclusion, lack of self-respect, feeling of insecurity and uncertainty, lack of control and autonomy at work and the poor balance between work and home. Individuals at the bottom of the income hierarchy experience psychosocial stress which could affect the biological functioning of the body as a result of reduced levels of social capital and cohesion within the community (CSDH, 2007; Lynch, Smith, Kaplan, & House, 2000). The perception of relative position in the social hierarchy of society based on income inequality affects health by the release of negative emotions such as shame and distrust which through the psycho neuro-endocrine pathway result in the development of antisocial and stress induced behaviours such as smoking, experience of violence or threats of violence (Adler & Newman, 2002; Adler & Rehkopf, 2008; Marmot & Wilkinson, 2001). A direct linkage between coronary heart disease and low control in the workplace and low social support regardless of social status has been observed (Brunner & Marmot, 2006; Dixon, 2000; Kuper, Marmot, & Hemingway, 2002). Some studies have reported that stigma associated with disease states such as TB and HIV, is an important source of stress which can create an adverse effect on health (Hatzenbuehler, Phelan, & Link, 2013). The people affected by stigma often internalise negative emotions which can lead to deterioration in their health.

3.3.3 **Behavioural and biological factors**

The living conditions of people provides the environment for socialization and opportunities for sharing experiences that can influence health related life style choices and behaviours. For example, a study in the United States observe that individuals living in disadvantaged neighbourhoods report less overall positive health, increase in peer drinking and adolescent alcohol use (Browning and Cagney, 2002). The uptake of negative lifestyle behaviours such as substance abuse (alcohol consumption and tobacco use), poor diet (obesity or malnutrition), and physical inactivity may arise because of the life choices made as a result of influences from the environment where people live or as a form of coping mechanism to material deprivation and stress (Uphoff, Pickett, Cabieses, Small, & Wright, 2013). In a related study by Grzywacz & Marks, (2001) in the United States, individuals in the lowest socioeconomic class participated less in physical activity, engaged in risky behaviours such as alcohol abuse and smoking and more likely to experience greater stress and poor diet which are risk factors for the development of coronary heart disease (Link & Phelan, 2000; Ross & Mirowsky, 2001). In contrast, the adoption of positive healthy behaviours and better health seeking behaviours for preventive medical care for example routine medical check-ups, was more pronounced among individuals higher up the socioeconomic ladder. This was associated with a decline in mortality due to coronary heart disease among individuals in the higher socioeconomic class in the United States (Cockerham, 2007). Pampel, Krueger, & Denney, (2010) in their review of the relationship between socioeconomic status and unhealthy behaviours observe that the marked difference that exist in health risky behaviours such as smoking, non-participation in physical exercise, poor maintenance of proper weight and improper diet between low and high socioeconomic groups cannot be ascribed to freely chosen

lifestyle but rather that the lifestyle are socially patterned as a result of the differences that exists in the social circumstances of low and high socioeconomic groups.

3.3.4 The Health system

The health system proposed by the CSDH as a social determinant of health is a departure from the previous models. The health system plays an important role not only in the differences in exposure and vulnerability to illnesses but also to the differences in the health outcomes and consequences of illness in terms of barriers to access quality health care. Ross et al., (2000) in their study on the effect of income distribution on health in Canada and the USA, found that income distribution has an effect on the health differences in the USA primarily because of the fee-for service health care system in America compared to Canada where there is better access to public health services that is not dependent on the ability of the sick to pay at the point when the services are needed. Cockerham (2007), reiterates that despite the introduction of the Medicare and the Medicaid that provides health coverage for the poor and elderly in the United States of America, equity in the access to health care is far from being achieved. Individuals in the lower class present late to access health service partly because of the poor access to health facilities in poor neighbourhoods and where available, these facilities are poorly staffed, underfinanced and overcrowded with patients.

The declaration of Alma Atta with the slogan of "health for all" by the year 2000 raised hope in Africa of the provision of affordable, accessible, acceptable and equitable health care using the primary health care approach (Hall & Taylor, 2003). With substantial external funding, there was initial investment into expanding health care services, improving coverage and the provision of an essential care package.

However, with the scarcity of resources especially during the era of structural adjustment programmes (SAP) of many African countries during the 1980s and 1990s, there was reduced spending in health. This resulted in the weakening of the health system and poor access to modern health care facilities (Kaseje, 2006). The failure of the public health system to perform its role in many African countries opened up an opportunity for the increasing participation of the private sector in the provision of health care service with the emergence of out of pocket payment as a major source of health care financing (Kaseje, 2006; Olakunde, 2012; Uzochukwu et al., 2015). The high cost and lack of access to health care service result in delay in seeking modern health care and the increasing patronage of traditional, faith-based and other informal sources of health care. The situation of the health system is made worse by the human resource crisis caused by inadequate production, brain drain, poor motivation, and the maldistribution and concentration of health workers and other health resources in urban areas (Kaseje, 2006). In addition the unfavourable trade agreements, low deployment of technology and globalization all contribute to the poor health care delivery in Africa (Eshetu & Woldesenbet, 2011).

The health system can also facilitate transmission of disease within the health care setting due to poor infection control guidelines, policies and practices such as inadequate hand washing practices, protective equipment and poor construction of health care facilities (Hussein, Mavalankar, Sharma, & D'Ambruoso, 2011). Therefore, the health system as a social determinant of health can result in increased exposure to infection, increasing vulnerability to disease, inequitable distribution of disease, differing health outcomes and differential consequences of disease on individuals and families.

3.4 Impact of equity in health and wellbeing

The whole processes described above have a substantial impact on the differences in health status and other important health related outcomes observed among relevant population sub-groups. That is, the social and political context gives rise to social stratification in society that shapes people's social and economic positions that produces avoidable health inequalities observed among population groups. Income inequalities are responsible for the differences that exist in level and duration of exposure to infectious diseases, vulnerability to infection and the outcome or ability to recover after being ill with infection. It must however be emphasised that illnesses can have both direct and indirect effect on an individual's socioeconomic position. For example, ill health can affect the social positions of individuals through limited opportunities for employment and reduced income or job loss which can lead to a downward movement to the bottom of the social scale or their exit out of paid employment. In other instances ill-health can have a broader far reaching impact on socioeconomic and political context of society. For example, though low socioeconomic conditions predispose individuals to the acquisition of HIV, the HIV/AIDS pandemic in sub-Saharan Africa had a devastating impact that affected the whole spectrum of society. Apart from the human cost, the HIV/AIDS epidemic had profound effect on the economy in terms of reduced labour supply, labour productivity and exports; and increased imports of expensive health care goods which reduced the average economic growth by 2-4% per year in Africa (Dixon, Mcdonald, & Roberts, 2013). Therefore the impact of the disease had a far reaching effect on the resources available for social and economic development of countries in Africa.

In conclusion, the WHO CSDH conceptual framework focuses on how the social and political context give rise to social stratification in society that shapes

peoples social and economic positions along the hierarchy of society in terms of income, occupation, education and other factors. The social and economic positions through the social determinants of health (intermediary determinants) determine how individuals experience differences in exposure and vulnerability to disease causing agents. It concludes with the feedback effect of ill-health (example is the HIV/AIDS pandemic) on socioeconomic position and in some instances on the socioeconomic and political context of society (Solar and Irwin, 2010).

The above description of the CSDH framework concerned with the social determinants of health provides the general context for this study. The next chapter will consider in detail how the social determinants of health relate specifically to tuberculosis.

CHAPTER 4: Literature review on spatial and social determinants of TB

A thorough literature search was conducted on both the social determinants of tuberculosis and the application of spatial analysis to the study of tuberculosis. This was undertaken as follows.

4.1 Development of a search strategy

The search strategy involved the search of some electronic data bases and hand search of the reference list of journals. In addition, all relevant abstracts from scientific conference proceedings and academic journal articles were also searched.

All relevant studies that satisfied the aim and objectives of this study between 2000 and 2015 were included in the search because the application of spatial analysis in the study of infectious disease epidemiology (especially tuberculosis) is still a relatively new approach. Exclusion criteria included studies on TB conducted on non-human subjects and studies on TB primarily focused on specific organs of the body. Furthermore, reports, presentations, editorials, letter to the editor and studies not written in the English language were excluded from this study.

The general terms used for the search were "Spatial, Tuberculosis and Socioeconomic"

The Mesh Terms used were: Socioeconomic factors; Spatial analysis; Tuberculosis; pulmonary/epidemiology; Risk factors; Poverty; Models; statistical; cluster analysis; Poisson distribution;

The terms eventually used in the literature search are shown in Table 2.

Table 2: Search terms used for the literature search

Terms for spatial	Terms for socioeconomic	Terms for tuberculosis	Terms for Analysis
Spatial analysis	income	TB	Multilevel
Cluster analysis	Social capital	Pulmonary	Poisson distribution
Spatio-temporal	Poverty	Pulmonary TB	Ecological
Spatial pattern	Economic	pulmonary epidemiology	Correlational
GIS	Risk factors	incidence	Bayes theorem
Spatial distribution	Socioeconomic factors	prevalence	Models, statistical
Spatial heterogeneity	Deprivation Social factors Social determinant		Retrospective Autocorrelation Binomial Linear models

4.2 Searching the electronic databases

The databases searched were: Academic Complete, Web of Science, Cochrane data base, Google scholar, CINAHL, JSTOR, MEDLINE, PubMed, PsycINFO, Science Direct, Scopus and some dissertation abstracts of unpublished articles and conference proceedings were also searched for related articles not yet published in scientific journals. For each of the databases searched, the Medical Subject Heading (MeSH) terms were entered into the databases in combination with the use of Boolean operators where necessary. In addition, hand searching of citations and references were done to avoid missing out on relevant articles.

4.3 Assessment of the relevance and quality of retrieved articles

This study is an ecological study design and so all ecological studies related to socioeconomic determinants of TB were mainly considered for inclusion in the search strategy. However, other study designs such as case control and cohort studies were

also included to compare the effects of socioeconomic determinants of TB at the individual level and its interaction with area level risk factors. The process of assessment and retrieval of relevant articles included in this study were as follows: firstly, the titles of the articles generated from the search were manually screened for relevance to the study. Secondly, the relevant titles that met the inclusion and exclusion criteria were considered for abstract retrieval. The retrieved abstracts were further screened and abstract selection was carried out in line with the objectives of this study. Thirdly, only the selected abstracts that had full text in English language were eventually included for the literature review. The summary of the procedure followed in the literature search is presented in the flow chart in Figure 5.
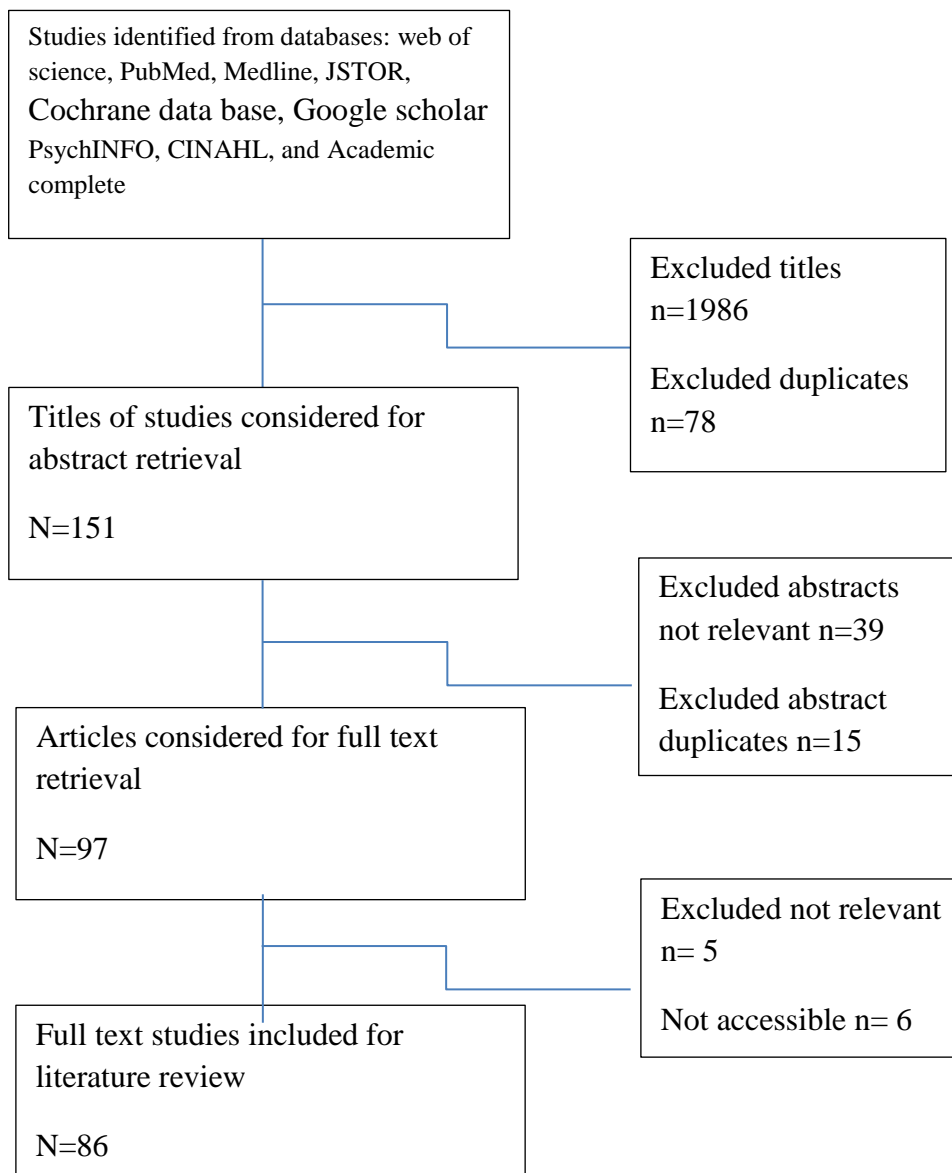
Figure 5: Flow chart diagram for the literature review

4.4 The structure of the literature review

The literature search is divided into two broad groups

a. Studies on selected social determinants of tuberculosis relevant to this study

b. Studies on spatial distribution and determinants of TB relevant to this study

4.5.**Social determinants of Tuberculosis**

This section will review non-spatial studies on the social determinants of TB in the literature that are relevant to this study. Rasanathan et al. (2011) described health inequities in TB as the differences that occur in risk exposure, vulnerability and the ability to recover after being ill with TB and that these are differentially distributed both within and among countries due to the differences in socioeconomic status and other structural factors. Table 3 summarises the studies on the social determinants of TB that were reviewed. This is followed by a critical review of the socioeconomic determinants of TB, including: overcrowding, housing conditions, access to public transportation, urban residence, population density and the health system.

Table 3: Summary of studies on the social determinants of TB

Author(s), Date, Country	Type of study	Method of analysis	Major findings/ Outcomes
Suk et al. (2009) Europe	Ecological	Regression analysis	Inverse relationship between TB rates and the public wealth index
Ploubidis et al. (2012) Europe	Ecological (prospective study)	Quintile Regression analysis	TB was associated with both absolute and relative socioeconomic disadvantage.
Olson et al. (2012)	Ecological ZIP code-level	Generalized estimating equation approach	Higher TB rate was associated with low SES among US - born and foreign born persons
Clark, Riben, & Nowgesic (2002) Canada	Ecological	Multiple logistic regression analyses	Inverse relationship between socioeconomic status and TB. TB rates increased with higher housing density
Córdoba-Doña et al, 2012 Spain	Ecological census tract level	Multilevel analysis	Inverse relationship between socioeconomic status and TB
Dye et al. (2009) Multi-country (134 countries)	Ecological census tract level	Regression analysis	Inverse relationship between TB and Human Development index, lower child mortality and access to improved sanitation.

Harling, Ehrlich, and Myer (2008) South Africa	Ecological	Multi-level analysis	Self-reported TB had an inverse relationship with SES. However, Gini coefficient was not associated with an increase in the odds of TB. Household crowding, urban residence were significantly associated with lower odds of TB.
Cramm et al. (2011) Eastern Cape South Africa,	Ecological	Multi-level analysis	No significant association between self-reported TB incidence and income. However, higher social capital was associated with lower TB rates
Gonçalves, Leon, & Penna, 2009 Brazil	Ecological	Multi-level analysis	Municipalities with high socioeconomic status had a corresponding low TB rates
Leung et al. (2004) Hong Kong	Ecological	Pearson's correlation coefficient & General linear model	TB was associated with high proportion of households living in one room apartment. However no association between TB and Household crowding
Muniyandi et al., (2007) India	Cross sectional	Conditional logistic regression was	Lower standard of living index (SLI) was significantly associated with TB prevalence. TB was associated with poor housing conditions (houses with walls built with mud without a ceiling and a floor built with earth)
Oxlade and Murray (2012) India	Cross sectional	Mediation analysis using Principal Components Analysis and Regression	Self-reported-TB prevalence was higher among households in the poorest wealth quintile
Shetty et al. (2006) Bangalore, India	Case control	Multivariate analysis	No significant association between TB and household income and living in a single room apartment
Baker, et al. (2008) New Zealand	Ecological study	Negative binomial regression model	Household overcrowding was significantly associated with TB incidence

Boccia et al., 2009 Zambia	Case-control	Univariate and multivariate logistic regression analysis.	TB infection was associated with higher household socioeconomic position (SEP)
Boccia et al., 2011 Zambia	Case-control	Conditional logistic regression analysis.	Higher TB prevalence was associated with low household SEP. However no association between TB and Household crowding
Glynn et al. (2000) Northern Malawi	Cross-sectional	Univariable and multivariable	A positive relationship was observed between TB and SES. Better housing' condition was associated with higher risk of TB. High population density was not associated with TB
Lienhardt et al., (2005) multi-country study (Guinea, Guinea Bissau and the Gambia)	Case control	Multivariate analysis.	Income and ownership of selected items was not associated with TB in multivariate analysis
Boccia et al., (2013)	Nested case-control study	Principal component analysis	Inverse relationship between household SEP and prevalent TB
Odone et al. (2013) Malawi	Case control	Univariable and multivariable logistic regression modelling	Better housing (houses built with burnt bricks) was associated with increased odds of having TB
Hossain et al. (2012) Bangladesh	Cross sectional survey	Logistic regression analysis	TB rates was higher in individuals with low SEP among patients identified during the survey while higher TB rates were observed in individuals with upper SEP among patients identified during routine TB surveillance system

Kistemann, Munzinger, and Dangendorf (2002) Germany	Ecological study	Poisson regression model	High TB notification rates in the densely populated inner-urban areas. Poor housing conditions had little effect on TB rates
Gustafson et al., 2004 Guinea-Bissau	Prospective community study	Multivariate analysis	Adult crowding, population density, were independent significant factors for TB
Hill et al. (2006) The Gambia	Case control study	Univariable and multivariable	TB disease was associated with household overcrowding
Myers et al. (2006), California USA	Ecological study	Negative binomial regression analysis	Crowding was protective of TB
Feske et al. (2011) USA	Ecological study	Pearson's chi-square analysis	Weekly bus ridership of public transportation was associated with high TB risk
Harling and Castro (2014) Brazil	Ecological study	Generalised linear regression model	Population density, urban residence, number of health facilities per capita, no of doctors per capita were predictors of high tuberculosis
Chan-Yeung et al., (2005) Hong Kong	Ecological study	Pearson correlation analyses	No association between high TB rates and population density

4.5.1. Tuberculosis and socioeconomic status (SES)

Socioeconomic status can be measured both at the individual, household and community levels. Composite area-level socioeconomic indices have increasingly been used to examine the relationship between TB and area socioeconomic status especially in developing countries because of the lack of data on income and expenditure at the individual and household level (Boccia et al., 2013).

Though the incidence and prevalence of TB is on the decline in developed countries (WHO, 2014b), there is still evidence linking poor socioeconomic status to increase in TB rates in Europe and other developed countries. Suk et al. (2009) in an

ecological study on the relationship between the Public Wealth Index and tuberculosis rates in Europe, observed an inverse relationship between TB prevalence rates and the public wealth index (PWI) derived from the division between the gross domestic product (GDP) in purchasing power standards and measures of social cohesion. The study found that with increasing PWI among countries, the proportion of TB among foreign-born populations increased. Despite some limitations in classification of foreign born populations in the study, it brought to the fore the apparent inequality in TB incidence both within and among countries in Europe. Furthermore, another study in Europe conducted by Ploubidis et al. (2012) found that about 50% of the country-level variation in TB among the countries in Europe is explained by the National income levels per capita and income inequality (measured by Gini coefficient). TB was also associated with both absolute and relative socioeconomic disadvantage. Wealthier nations have more resources to provide basic sanitation and health promotion programmes while at the individual level more wealth translates to better housing conditions, healthier food, safer environment and a better access to health care.   Olson et al. (2012), explored the relationship between TB incidence and ZIP code-level measures of socioeconomic status (SES) over a 10-year period (1996-2005), in the USA. The SES was derived from four variables namely crowding, unemployment, education and income. Higher TB rate was associated with low SES among US - born and foreign born persons. There was a 5-fold and 1.3 fold increase in TB rates among the US born and foreign born persons respectively between the highest and the lowest SES quartiles. The study however concluded that SES alone may not be sufficient to explain the TB epidemiology among foreign born persons in the country. Clark, Riben, & Nowgesic (2002) in an ecological study in Canadian First Nation communities found an inverse relationship between socioeconomic status

and TB. However, a higher incidence of TB was observed in some isolated communities with higher income which was probably mediated by household crowding. A similar inverse relationship was established between TB and a socioeconomic index based on percentage of unemployment, low educational level and unskilled labour at the census tract level in a multilevel analysis of two urban municipalities in Spain between 1997 and 2007 (Córdoba-Doña et al, 2012). Moreover, Dye et al. (2009) conducted a regression analysis on the trend of TB incidence and their determinants in 134 countries and found a significant inverse relationship between TB incidence and Human Development index, lower child mortality and access to improved sanitation.

Studies carried out in some emerging economies like India and Brazil have also reported similar inverse relationships between SES and TB. Muniyandi et al., (2007) in a cross sectional TB prevalence survey in rural area of South India found that a lower standard of living index (SLI) was significantly associated with TB prevalence. The SLI scores was computed from variables such as housing quality, basic sanitation and safe water, ownership of durable goods, ownership of agricultural land and livestock. Households with lower SLI had a higher TB prevalence (57%) compared with households with medium (28%) and high SLI (15%). Also, TB prevalence was higher in individuals that lived below the poverty line compared with individuals who lived above the poverty line. Oxlade and Murray (2012) in their analysis of the 2006 Demographic and Health Survey (DHS) in India observed that self-reported TB prevalence was 5.5 fold higher among households in the poorest wealth quintile compared with the households with the highest wealth quintile. However, Shetty et al. (2006) observed in Bangalore, India that there was no significant association between household income and TB in a multivariate analysis

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of a case control study of 189 new TB patients attending an outpatient clinic at St Johns Medical College in South India. In a multilevel study on the relationship between TB and socioeconomic status (based on the percentage of households with low income), it was found that municipalities with high socioeconomic status in Brazil had corresponding low TB rates and vice-versa (Gonçalves, Leon, & Penna, 2009).

There is mixed evidence on the relationship between TB rates and socioeconomic indices in Africa. Harling, Ehrlich, and Myer (2008) in South Africa found that self-reported TB had an inverse relationship with socioeconomic status at the individual, household and community level. In addition, high community level income inequality was independently associated with higher prevalence of TB. However, the Gini coefficient was not associated with an increase in the odds of having a recent or lifetime TB disease. In another household survey by Cramm et al. (2011) in Grahamstown, Eastern Cape South Africa, there was however, no significant association between self-reported TB incidence and income in a multi-level logistic regression analysis of the survey. Nevertheless, higher social capital was found to be significantly associated with lower household TB possibly due to the diffusion of TB related knowledge through the social networks that may have necessitated the adoption of healthy and TB preventive behaviours. This relationship between social capital and TB however requires further evaluation.

In a nested case-control study of 106 prevalent TB cases and 318 controls in Zambia between 2005 and 2006, TB infection was erroneously positively associated with a higher household socioeconomic position (SEP). The SEP was constructed from household human resources, household food availability and vulnerability, housing quality and ownership, and access to community services and infrastructure

(Boccia et al., 2009). The plausible reason was that the study was conducted in a high density urban area with a high prevalence of HIV. The generalization of the study results was limited due to the relatively small sample size. In a follow up study among 52 culture confirmed TB cases and 318 controls in Zambia between 2006 and 2007, high TB prevalence was associated with low household socioeconomic position defined from four socioeconomic domains namely household human resources, household food availability and vulnerability, housing quality and asset ownership and access to community services/infrastructure (Boccia, et al. 2011). The strength of the household SEP odds ratio was however reduced when food intake related variables (such as less than twice a day meal and the number of meals with protein per week) and TB exposure variables (such as known contact of a TB case, attending a video club, bar or hairdressing shop) were included into the model. The study found that the food related variables were the mediators of the observed significant association between SEP and prevalent TB. The authors concluded that the differences in the two studies may be related to the different outcome variable. The outcome variable of the earlier study was TB infection while the later study was prevalent TB disease. Households in the lowest SEP were more likely to progress from infection to disease and as such the effect of SEP was more pronounced in the later study that had TB disease as the outcome variable. Households with higher SEP were more likely to be infected with TB because of their increased human interaction and movement which may increase their contact and exposure to TB but because of their high SEP, they are not likely to progress from TB infection to TB disease probably as a result of good nutrition and a high immunity.

Glynn et al. (2000) conducted a cross-sectional TB prevalence survey in Northern Malawi between 1981-1984 and 1986-1989. The occupation of the head of

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household was used as a measure of household socioeconomic status. A positive relationship was observed between TB and socioeconomic status. The reasons suggested for this finding was that a higher socioeconomic status may provide an opportunity for an increase in exposure to TB through increased volume of travels which may increase the probability of contact with an individual with active TB disease. In addition, individuals with a higher socioeconomic status were more likely to have access to TB diagnosis. Similarly, Lienhardt et al., (2005) in a multi-country case control study of three West African countries (Guinea, Guinea Bissau and the Gambia) from 1999 to 2001 reported that socioeconomic indices such as income and ownership of selected items showed some degree of association with TB during univariate analysis but the relationship was not sustained in multivariate analysis.

The conflicting conclusions from these studies in low income countries brings to question whether indicators used in assessing socioeconomic status in the developed countries were appropriate for the sub-Saharan African countries. Boccia et al., (2013) argued that though asset based composite indices have become available and widely used in socioeconomic inequality studies, there may be inherent biases in using these composite indices to measure socioeconomic status or positions. Firstly, some of the variables used for the computation of these composite indices were in themselves known risk factors for TB such as overcrowding, housing quality or food availability which could lead to overestimation of health inequalities. Secondly, composite indices that used ownership of some asset items tend to rate urban areas as having a higher socioeconomic status compared to rural areas and because TB tends to be more easily diagnosed in urban areas, this could lead to a wrong conclusion that TB is more prevalent in areas of high socioeconomic status. Boccia et al., (2013) compared four different combinations of asset based socioeconomic composite

indices and TB. The first Index (referent index or index 0) was an asset based index derived from principal component analysis (PCA). The second (Index 1) accounted for the potential urban-rural bias and the third (Index 2) accounted for the effect of the inclusion of the food related variables in index 0. The fourth (Index 3) used asset based index derived from regression analysis instead of a PCA which accounted for a different weights allocated to the individual variables. The study found a strong inverse relationship between household SEP and prevalent TB in all the four composite indices derived in the study though the magnitude varied across the composite socioeconomic index used. However, there was no association when single economic variables were used for the analysis. Odone et al. (2013) however stated that the difference observed in the studies on SEP in Africa compared with high income countries may be a reflection of the dynamics of three inter-related factors: increased opportunities for infection, higher susceptibility for infection and the higher likelihood of diagnosis. They argued against the use of occupation as a proxy for SEP since the majority of people in low income countries work in the informal sector outside formal employment where occupation may not be an accurate reflection of SEP. They however suggested an asset index that include housing quality specific to the local settings may be a better reflection of SEP in Africa.

Harling, Ehrlich, and Myer (2008) highlighted the limitation of studies assessing the relationship between socioeconomic indices and TB case notification rates. They pointed out that socioeconomic factors could affect the three stages in the pathogenesis of TB from latent infection through progression to disease and the eventual diagnosis and reporting of such cases by the health facility to national authorities. Individuals with low SEP were more likely to live in densely populated areas with poor quality housing which predisposes to TB; they were usually

malnourished and more likely to have compromised immune defence system which facilitates the progression of latent TB infection to active disease; and that poor individuals were less likely to afford or reach a health facility where they could be promptly diagnosed. Therefore, poverty can lead to underreporting of TB cases and hence TB case notification rates may not be an accurate reflection of the true TB prevalence rates. Nevertheless, TB case notification rates still remain a useful tool in epidemiological studies in many countries as they are the only available epidemiological measure of TB at the sub-national level and a careful analysis can provide valuable information that can be useful to inform policy decisions in the control of TB at the sub-national level (Wong et al., 2013; WHO 2013).

Hossain et al. (2012) compared the SEP (determined by asset score based on ownership of household items and dwelling characteristics such as availability of sanitation, drinking water and materials used in building) of 33 active TB patients identified during the prevalence survey and 240 TB patients that were captured by the routine TB surveillance system in Bangladesh between 2007-2009. The study found that of the 240 TB cases identified from routine surveillance 57% were in the two uppermost SEP quartile while only 2.1% were in the lowest quartile while 75% of the TB patients detected during the survey were from the lower two quartile and only 24.2% were from the uppermost quartile. Also, the majority of TB cases notified were from urban population with relatively high SEP while majority of TB cases identified (85%) during the prevalence survey were in rural areas. The study showed that a large proportion of TB patients in the rural areas remained undiagnosed by the routine TB surveillance system largely because of lack of access to health care services. Consequently, TB patients sought alternative care from non-licensed providers, pharmacies and private practitioners.

4.5.2. **Tuberculosis and Housing conditions**

Muniyandi et al. (2007), in a cross sectional TB prevalence survey in rural India found that TB was associated with poor housing conditions. Individuals that lived in houses with walls built with mud without a ceiling and a floor built with earth (katcha) have increase odds of about 2.5 times of being infected with TB. However, Odone et al. (2013) in rural Malawi found that better housing (houses built with burnt bricks) was associated with increased odds of having TB. The authors explained that houses termed 'better housing' had less ventilation because of the solid materials and solid glass windows used in their construction. Furthermore, residents in these 'better housing' stayed indoors more because of the comfort of such houses and this may attract dependants from the countryside that may harbour TB. Consequently, the poor ventilation coupled with overcrowding may predispose individuals living in such houses to TB. Similarly, Glynn et al. (2000) found that 'better housing' condition was associated with higher risk of TB. The so called 'better housing' was found mainly in urban slums that had compromised ventilation which may facilitate and predispose occupants to TB. Kistemann, Munzinger, and Dangendorf (2002) however, found that poor housing conditions had little effect on TB incidence rates in Germany possibly because there was less segregation in housing quality between the rich and the poor.

Furthermore, Leung et al. (2004) in the study of the ecological analysis of socioeconomic factors and TB in Hong Kong found that high TB standardised notification rate was significantly associated with a high proportion of households living in one room apartment or "bedsits" compared with those living in an independent housing units or flats. However, there was no significant association between TB and households living in public housing and those in temporary lodgings. Single room apartments were more likely to be poorly ventilated and sometimes

overcrowded which predispose occupants to TB. Shetty et al. (2006) however, found no association between TB and living in a single room apartment compared with those living in flat apartments.

4.5.3. **Tuberculosis and Household Crowding**

Harling, Ehrlich, and Myer (2008) in a multilevel in South Africa found that household crowding was associated only with recent TB and not life time risk of TB. The increased risk is possibly as a result of prolonged contact with an index TB case if present within the household. Furthermore, it was observed in a prospective urban community study in Bissau, Guinea Bissau that adult crowding is an independent significant factor for TB. Each additional adult in the household increases the risk of TB by 5% (Gustafson et al., 2004). Similarly, Hill et al. (2006) in a case control study in the Gambia found that the strongest risk factor for TB disease is household overcrowding. However, Boccia et al. (2011) and Leung et al., (2004) did not find an association between higher TB rates and household overcrowding.

Overcrowding still remains a risk factor for TB in high income countries. Baker, et al. (2008) in New Zealand in an ecological analysis at the census area unit of 1898 notified TB cases for 2000-2004 found that household overcrowding was significantly associated with TB incidence with a relative risk of 1.05 within the total population and 1.08 among New Zealand-born population under 40 years of age. Clark et al. (2002) also reported that TB incidence rates increased with higher housing density in Canada. The TB rate was 18.9/100,000 in communities with a housing density of 0.4-0.6. The TB rates increased to 113/100,000 in communities with average density of 1.0-1.2 and to 225/100,000 in communities with average density of 1.3. An increase of 0.1 in the average number of persons per room in a community was associated with a 40% increase in the risk of more than 2 TB cases in the

community. Myers et al. (2006) found that crowding was protective of TB in California USA possibly as a result of increased social capital due to interwoven social network among the study population. There is need for more research to examine the effect of social capital on TB incidence.

4.5.4. Tuberculosis and access to transportation

Odone et al. (2013) and Glynn et al., (2000) in Malawi suggested that occupations that require increased volume of travel especially in crowded mini buses in Africa could increase the risk of exposure to TB transmission in low income countries. Though the effect of access to transportation on TB was not quantified or evaluated in their study other studies from developed countries have also described the potential for the transmission of TB in public transportation especially in poorer regions where there is a high TB burden (Edelson & Phypers, 2011; Mohr et al., 2012; Mohr, Schink, Eckmanns, & Krause, 2015). Feske et al. (2011) however found that weekly bus ridership of public transportation was associated with high TB risk. Bagchi et al. (2010) in Mumbia, India found that travel related problems such as long distance to DOTs treatment centres and loss of time during travel and transportation cost were significantly associated with access to TB services and non-adherence to TB treatment.

4.5.5. Tuberculosis and place of residence (urban or rural)

Harling and Castro (2014) in Brazil found that urban residence was a predictor of high tuberculosis rates irrespective of poverty though the effect of urban residence may be partially mediated by higher AIDS cases in urban municipalities. The urban areas compared to rural areas were usually wealthier and have high TB rates because of the presence of risk factors such as overcrowding, high population density, poor environmental conditions which facilitate transmission of TB. Furthermore, urban

dwellers were more likely to report TB cases because of better access to health care services. This situation may suggest that low socioeconomic status appear to be protective of TB due to a strong negative confounding effect of urban residence on poverty. However, Harling, Ehrlich, and Myer (2008) found that urban residence was significantly associated with lower odds of having a lifetime TB risk in South Africa. Hossain et al. (2012) in a comparative study of TB patients notified under routine TB surveillance by the National Tuberculosis Programme (NTP) and TB patents detected during a population based prevalence survey in Bangladesh. The study found that majority of TB cases identified from routine NTP surveillance were from urban areas thereby raising the question of access of rural dwellers to health care services. Rural residence had also been identified as an important risk factor for delay in the diagnosis of TB mainly due to issues of poor access to health care facility, poor training of lower cadre staff, and lack of supervision of health staff at the periphery (Lienhardt et al., 2005). In Canada, Clark et al. (2002) found that isolated communities with limited access to radio, telephone and poor road access had increased rates of TB. The finding may be as a result of a robust and accurate surveillance system to detect TB cases in rural areas in developed countries compared to low income countries where many of the TB in rural areas remain undiagnosed because of poor access to health facilities.

4.5.6. **Tuberculosis and population density**

Harling and Castro (2014) found that population density was a predictor of high tuberculosis rates regardless of poverty and urban residence which may be partially mediated by higher rates of AIDS cases in the densely populated municipalities. Gonçalves et al. (2009) also found a positive relationship between high TB rates and population density. Similarly, Kistemann et al. (2002) detected high TB notification

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rates in the densely populated inner-urban areas of Cologne, Germany. However, Glynn et al. (2000) in Malawi and Chan-Yeung et al., (2005) in Hong Kong found no association between high TB rates and population density respectively. High population density is associated with an increase in contact between persons which can facilitate the transmission of TB.

4.5.7. **Tuberculosis and Health Systems**

Maciel et al. (2010) in Brazil observed that poor access to health care and poor quality of the TB services provided in areas of low socioeconomic status may create barriers for early diagnosis of TB and adequate treatment. In addition, distance to the health facility and long travel time to the township health centre were significantly associated with delay in seeking care in a study in Shandong Province China (Cheng et al., 2013). Similarly, a systematic review of factors associated with delay in TB diagnosis and treatment also found that distance and travel time to a health facility were responsible for delay and that this made patients who had symptoms of TB to seek alternative care from traditional healers while some resorted to self-treatment (Finnie et al., 2011).

Although most of the 22 high burden countries provide sputum microscopy and first line anti-TB medication free of cost in the public health system, TB patients were required to pay for other TB related diagnostic test such as x-rays, sputum culture and drug susceptibility tests (Lönnroth et al., 2009). Ukwaja, Alobu, lgwenyi, & Hopewell (2013) in their study in Nigeria estimate the sum of direct and indirect costs for a TB patient to be $528. The out of pocket expenditures borne by individual and households and the loss of income and time during sickness from TB poses enormous financial burdens resulting in further impoverishment of households and families. They further observed that only one-tenth of TB patients initially visited a

public health facility after the onset of symptoms. Therefore, the majority of patients especially the poor were left with no choice but to patronise private and alternative health practitioners. TB patients who could access TB services from private care providers payed out of pocket to obtain health services such as hospitalization, diagnosis, treatment and care. Barter, Agboola, Murray, & Bärnighausen (2012) in a systematic review on TB and poverty in sub Saharan Africa stressed that the TB patients often have to spend more than 10% of their income on TB care. This enormous patient cost has negative implications for health seeking behaviour that can lead to delays in accessing TB services, deterioration in the clinical condition of patients and the continuous spread of infection in the community. Furthermore, the financial burden on patients can lead to poor adherence to treatment and poor treatment outcomes with a potential for the spread of multidrug resistant tuberculosis in the community (Barter et al., 2012).

Harling and Castro (2014) found that the number of health facilities (number of hospital per 100,000 populations) and health man-power resources (doctors/100,000 population) were associated with higher TB rates in South Africa. Touray et al. (2010) detected high rates of TB in densely populated areas with a high concentration of TB diagnostic facilities owned by both government and private health care providers in The Gambia. The presence of increased health resources may result in increased detection and reporting of TB in the districts or municipalities.

4.6 Spatial epidemiology of tuberculosis

The application of spatial analysis to the study of infectious diseases has led to the understanding that certain factors such as physical, environmental, cultural, genetic and economic factors that drive the non-uniform distribution of disease incidence and prevalence in certain geographical areas. These factors may indeed be spatially

distributed and influence the intensity and extent of certain diseases. The monitoring of the evolution of these factors can be helpful in the design and implementation of appropriate health interventions that can mitigate the development of disease (Elliott & Wartenberg, 2004; Ostfeld et al., 2005).

Tuberculosis like many infectious diseases is prone to spatial aggregation or clustering. Thus spatial data analysis of TB can help to understand the spatial distribution of the disease, risk factors that cause the uneven occurrence of the disease in space, predict outbreaks in areas where such risk factors predominate, identify population at risk and therefore help in targeting mitigation efforts and channel scarce health resources to areas of greatest need (Saidu, 2014; Woldeyohannes & Abera, 2015).

The section below will review studies on spatial distribution of tuberculosis along the different methods employed in conducting spatial data analysis and review literatures from outside Africa, within Africa and end with local studies conducted in Nigeria.

4.7 International evidence on the spatial distribution of TB

Studies on the spatial distribution of TB have utilised different methods and approaches in the analysis of spatial variation of TB and its relationship with socioeconomic factors ranging from explorative techniques to spatial modelling. Table 4 provides an overview of international studies on the spatial distribution of TB. This review attempts to group studies on spatial analysis of TB according to the complexity of the spatial analytical technique used.

Table 4 Summary of international studies on the spatial distribution of TB

Author(s), Date, Country	Type of analysis	Method/tool of analysis	Major findings/ Outcomes
Moonan et al., (2004) USA	Spatial analysis	SaTScan technique	TB was clustered around a homeless shelter, among ethnic minorities, persons who abuse substance, and males
Bastida et al., (2012) Mexico, Mexico	Spatial analysis	SaTScan technique	TB clusters were observed in urban zones located close to and around Mexico City.
Onozuka & Hagihara (2007) Fukuoka , Japan	Spatial analysis (spatial and space-time analysis)	SaTScan technique	TB clusters were observed in coal mining areas, industrial areas and the urban area of Fukuoka
Li et al., (2011) Beijing, China	Spatial analysis (spatial and space-time analysis)	SaTScan technique	High TB rates were found in areas of high population density of migrants
Tiwari et al. (2006) Almora, India	Spatial analysis	SaTScan technique	High rates of TB in the hilly Uttaranchal region
Gomez-Barroso et al. (2013) Barcelona, Spain	Spatial analysis (spatial and space-time analysis)	SaTScan technique	High TB rates observed in Greater Barcelona
Couceiro, Santana, & Nunes (2011) Portugal	Spatial analysis (spatial and space-time analysis)	SaTScan technique	High TB rates in metropolitan areas (Port and Lisbon). TB associated with overcrowding, unemployment, non-standardized housing and the prison.
Areias, Briz, & Nunes (2015) Portugal	Spatial analysis (spatial and space-time analysis)	SaTScan technique	High TB rates in metropolitan areas with high HIV and high immigration rates
Nunes (2007) Portugal	Spatial analysis	SaTScan technique Semi-variogram technique	High TB rates Port and Lisbon with an additional critical cluster (Fundao) identified

Higgs, Mohtashemi, Grinsdale, & Kawamura, (2007) San Francisco, USA	Space-time permutation scan statistics	SaTScan technique	Identified areas of TB outbreaks in San Francisco
Rodrigues, Ruffino-Netto, & de Castilho (2006) Sao Paulo, Brazil	Spatial analysis	Generalized weighted least square method (conventional kriging)	TB was clustered in the eastern region of the state with a high population density and high HIV/AIDS incidence
Venkatesan & Srinivasan (2010) Chennai, India	Spatial analysis	Spatial variogram	High rates of TB in urban slum areas
Li, et al. (2014) People's Republic of China	Spatial analysis	kriging and Co-kriging method	TB was higher in Western and South-western China with lower Human Development Index.
Tsai (2011) Taiwan	Spatial analysis	Geographically weighted regression (GWR)	High TB rates among aboriginal communities associated with low income and alcoholism
Sun et al. (2015) People's Republic of China	Spatial analysis	Geographically weighted regression (GWR)	TB was clustered in regions of high altitude and lower latitudes and in relatively hot regions with high humidity
Li et al. (2014) People's Republic of China	Spatial analysis	Geographically weighted regression (GWR)	Provinces with higher investment in TB control detected more TB cases while the provinces that were more economically advanced had lower prevalence of TB.
Feske, Teeter, Musser, & Graviss (2011) Harris County, Houston USA	Spatial analysis	Kernel density estimation	Risk factors associated with high TB risk were weekly bus ridership of public transportation, homelessness, history of substance abuse, poverty, black race, foreign birth and age

Venâncio, Tuan, & Nascimento (2015) Brazil	Spatial analysis	Kernel density estimation	High TB rates were in cities with better socioeconomic conditions and better access to education.
Goswami et al., (2012) Wake County, North Carolina USA	Spatial analysis	Kernel density estimation	Identified two areas designated as "hot spots" for TB in the country
Ribeiro et al. (2015) Vitoria, Brazil	Spatial analysis	Kernel density estimation	Detected clusters of recent on-going active transmission of TB The risk factors for TB transmission were young age, positive smear test and lower index of the quality of urban municipality.
Chan-Yeung et al., (2005) Hong Kong	Spatial and non-spatial analysis	GIS tools Multivariate analysis	A significant correlation was observed between TB and low education, elderly and low-income. Population density and unemployment were not associated with TB.
Pang, Leung, and Lee (2010)	Spatial and non-spatial analysis	GIS tools Multivariate analysis	TB was associated with low household income, being single and non-Hong Kong-born
Souza, et al. (2005) Brazil	Spatial and non-spatial analysis	GIS tools Multivariate analysis	TB was associated with household size, families with more than one case of TB and the presence of TB retreatment cases
Maciel et al., (2010) Vitoria, Brazil	Exploratory Spatial analysis	Global and Local Moran's I statistics and Getis Ord Gi*	A significant positive spatial autocorrelation of TB was observed
Erazo et al., (2014) Salvador, Brazil	Exploratory Spatial analysis	Global Moran's index and LISA	The study identified areas of significant TB clusters in areas associated with low living conditions

QueirogaI et al., (2012) Campina Grande, Brazil	Exploratory Spatial analysis	Global Moran's index and LISA	Significant positive autocorrelation for TB was observed. TB rates were higher in neighbourhoods with worse socioeconomic indices
Jia et al., (2008) Beijing, China	Exploratory Spatial analysis	Global Moran's *I* and Getis Gi* statistics	Hot spots for TB were identified among the migrant population
Wang et al. (2012) Linyi city, China	Exploratory Spatial analysis	Global Moran's *I* and Getis Gi* statistics	Five significant clusters (hotspots) in the city
Ng, Wen, Wang, & Fang, (2012) Taiwan	Spatial analysis	Global Moran's *I* statistics, GeoDa Regression analysis	TB incidence in a township was found to be significantly affected by TB incidence in the surrounding neighbours.
Izumi et al. (2015) Japan	Spatial analysis	Global Moran's *I* and Getis Ord Gi*.	Hot spot for TB was identified in areas of higher population density, high business/commercial activities and in areas where a large proportion of foreign-born reside.
Alvarez-Hernández et al. (2010) Hermosillo, Sonora state Mexico	Exploratory Spatial analysis	Global Moran's *I* index, LISA Besag and Newell method	TB was clustered in areas of high social deprivation
Pereira et al. (2015) Rio de Janeiro, Brazil	Spatial and non-spatial analysis	Global Moran's *I* index, LISA Multivariate analysis	TB was associated with poor households, people living alone in the neighbourhoods and households with more than 2 people per bedroom .
Venkatesan, Srinivasan, & Dharuman (2012) India	Spatial regression analysis	Bayesian conditional auto regression (CAR) model in Win BUGS software	Higher risk of TB in states in the North-eastern region compared with other regions

Roza, Caccia-Bava, & Martinez (2012) Ribeirao Preto, Sao Paulo, Brazil	Spatial regression analysis	Bayesian conditional auto regression (CAR) model in Win BUGS software	High TB incidence was found in the west and southern regions of the city. TB was associated with low income, low education and increased social vulnerability
Souza et al. (2007) Olinda, Brazil	Spatial regression analysis	Bayesian conditional auto regression (CAR) model in Win BUGS software	TB associated with household size, low income and low education
Harling & Castro (2014)	Spatial regression analysis	Bayesian conditional auto regression (CAR) model in R statistical software	TB associated with household overcrowding, low income and low education

One of the most common approaches in spatial analysis of TB is the use of SaTScan software developed by Martin Kulldorff. The software performs spatial, temporal and spatio-temporal analysis of TB using spatial, temporal and space-time scan statistics to detect significant disease clusters (Kulldorff, 2015). Moonan et al., (2004) employed the SaTScan technique in combination with routine epidemiological surveillance and identified areas of *Mycobacterium tuberculosis* genotype clustered in a nationally representative study in the United States of America. The study observed that recent TB transmission was clustered around a homeless shelter in an urban area of Texas, among ethnic minorities, persons who abuse substance, and males. These marginalized groups have poor access to routine health screening services which led to delay in diagnosis and increased transmission of TB in the community. The study demonstrated that spatial analysis could be an effective tool superior to standard contact tracing methods in identifying areas of high tuberculosis transmission and incidence in the USA. Bastida et al., (2012) used SaTScan spatial statistics and

described spatial analysis of tuberculosis cases in Mexico between 2006 and 2010. The spatial analysis identified clusters in urban zones located close to and around Mexico City. The study however, did not assess the relationship between the identified hotspots and the socioeconomic indices. Onozuka & Hagihara (2007) carried out spatial and space-time analysis of TB in Fukuoka Japan using SaTScan statistics and found clusters of TB in a coal mining area in Chikuho, industrial area in Kita-Kyushu and the urban area of Fukuoka. The northern part of Fukuoka was identified as the most likely significant cluster for TB. The two methods identified clusters in the northern part of Fukuoka in the year 2000 in an area of significant coal mining activity that may predispose the community to TB. After the year 2000, no significant cluster was detected possibly due to the intensified public health efforts to control TB carried out by the Ministry of Health and Welfare in 1999 when it declared TB an emergency. Li et al., (2011) further described the impact of new migrant population in 2005-2006 on the spatial distribution of TB in Beijing using similar methods but at a much smaller scale using the town instead of district. High TB rates were found in areas of high population density of migrants and areas with a rapid increase in the number of migrants. The four central areas with high TB rates were also the areas with higher levels of education, good living conditions, improved health care and areas where the people had a good sense of self-care. The two new spatial clusters were related to the redistribution of migrant population in Beijing. Similarly, Tiwari et al. (2006) also used SaTScan statistics and geographic information systems in the analysis of the spatial pattern of tuberculosis in Almora district of Uttaranchal, India between 2003 and 2005. The spatial and space–time analysis identified two statistically significant spatial clusters with high TB case notification at Almora, India. The study however was limited to only one district in

Uttaranchal and the study was based on hospital records of patients without information on the socioeconomic status of the patients. The possible reasons for the high occurrence of TB in the hilly Uttaranchal region were poor socioeconomic status, indoor air pollution due to smoke from firewood, high intake of alcohol and a high HIV rate possibly due to a large migrant population. The effects of these factors on TB however were not objectively quantified and evaluated.

Gomez-Barroso et al. (2013) described the spatial analysis of tuberculosis cases in Spain between 2008-2010 using SaTScan spatial statistics. The spatial analysis detected 28 significant clusters while the most likely cluster consisted of seven municipalities in the Greater Barcelona Area. The space-time analysis detected 20 significant clusters while the most likely cluster consisted of three municipalities in Greater Barcelona Area. The Greater Barcelona Area has an intense ongoing industrial activity and a high immigration rate though the extent of the influence of these variables on the spatial distribution of TB was not accounted for in the analysis. The authors believed that SaTScan statistics were superior to other methods such as Knox, Mantel or Moran's *I* index in that they adjust for confounders and population density, and produced a single p-value despite taking multiple testing's into consideration and that there is no selection bias since no prior hypothesis as to where the location, size or period of the cluster will be. Nonetheless, the study did not assess the effect of socioeconomic and other environmental factors on the high TB case notification.

Couceiro, Santana, & Nunes (2011) performed a cluster analysis of tuberculosis incidence at the municipality level in Portugal between 2004-2006 using SaTScan. Major clusters of TB were in Porto and Lisbon (including the Setubal Peninsula located south of Lisbon) metropolitan areas which coincided with areas of

high HIV/AIDS incidence and high immigration rates. Other socioeconomic factors associated with high TB rates in Portugal include overcrowding, unemployment, non-standard accommodation and the prison population. Similar clusters in Portugal were identified using space-time cluster analysis on the updated TB data from 2000 to 2010 by Areias, Briz, & Nunes (2015). Nunes (2007) suggested that the semi-variogram approach may be more sensitive than SaTScan analysis of tuberculosis in Portugal by the identification of an additional critical cluster (Fundao) to Port and Lisbon earlier identified. These studies did not assess the influence of the environmental and predictors variables on TB risk.

Space-time permutation scan statistics were used to detect TB outbreaks in San Francisco, USA (Higgs et al., 2007). The study used exact coordinates of individual addresses rather than census tract or zip codes. The study found that the detection, sensitivity and timeliness of TB outbreak improved when individual addresses were used instead of area zip codes and concluded that there needs to be a trade-off between using individual level data, the concern of maintaining patient confidentiality and improving public health disease surveillance.

Some studies have used kriging in the study of spatial distribution of tuberculosis. Kriging is a spatial analysis technique that can be used to perform exploratory analysis, variogram modelling and exploration of variance surface (Samarasundera et al., 2012). The technique considers measured values in a location and uses it to extrapolate to unmeasured locations and takes into consideration the spatial relationships among the measured values around the unmeasured locations. Rodrigues, Ruffino-Netto, & de Castilho (2006) studied the spatial pattern of TB incidence among HIV/AIDS patients in 24 administrative health regions in São Paulo State, Brazil using the generalised weighted least square method ("conventional

kriging") to estimate the risk of TB among HIV/AIDS patients. The R statistical software was used for the geo-statistical analysis using a model of spatial continuity of event with a semi-variogram function for the analysis of association between space and disease incidence. The model presumed that the distances from each of the municipality to the central locations acted as the weights. Spatial autocorrelation was observed in the eastern region of the state where the capital Sao Paulo is located with a high population density and high HIV/AIDS incidence. Similarly, Venkatesan & Srinivasan (2010) found high rates of TB in slum areas in Chennai, India with the use of spatial variogram. In another spatial exploratory study using the kriging and cokriging method in People's Republic of China, Li, et al. (2014) found that TB was higher in Western and South-western China with lower Human Development Index.

Another method utilised for the study of spatial heterogeneity of tuberculosis is geographically weighted regression (GWR). The GWR approach allowed the exploration of local spatial pattern rather than global parameter estimates that may uncover underlying local factors responsible for the spatial heterogeneity of TB. Tsai (2011) found higher TB rates in areas with a high proportion of aboriginal communities using GWR in Taiwan which is possibly as a result of environmental, social (low income) and behavioural factors such as alcoholism in the region. Similarly, Sun et al. (2015) explored the local relationship between TB and latent risk factors such as population density, climatic, economic, health service, altitude and air quality factors. The GWR was analysed with various combinations of fixed and adaptive bandwidth and Gaussian kernels to build the model. TB was clustered in regions of high altitude and lower latitudes and in relatively hot regions with high humidity. In addition, Li et al. (2014) used GWR model and found a significant spatial variation in TB prevalence across the regions especially in the Western and

South-western regions of the People's Republic of China. The investment in the prevention and control of TB had the highest impact on TB prevalence where the provinces with higher investment in TB control detected more TB cases. In addition, provinces that were more economically advanced had lower prevalence of TB. Climatic factors, air pollution and geographic factors were also associated with a high TB prevalence. The GWR however is sensitive to small sample size which can result in collinearity and estimation of local coefficients can be counter-intuitive (Páez, Farber, & Wheeler, 2011). The bias in GWR may be due to user-defined bandwidth selection used to determine the level of influence by the neighbouring observations on the local value. Feske, Teeter, Musser, & Graviss (2011) in Harris County, Houston used kernel density estimation to map average incidence of TB. The risk factors associated with high TB risk were weekly bus ridership of public transportation, homelessness, history of substance abuse, poverty, black race, foreign birth and age. Venâncio, Tuan, & Nascimento (2015) in Brazil used kernel density estimation in a study of TB between 2001 and 2010. There was no significant spatial autocorrelation in the first period (2001-2005) though 10 cities were identified as priority areas for intervention. However in the second period (2006-2010), there was significant autocorrelation of TB among children in Sao Paulo. The cities with high TB rates were interestingly the cities with better socioeconomic conditions and better access to education. The reason postulated was better access to health care services in the cities which facilitated prompt and correct diagnosis as a result of the availability of experienced and qualified health care workers who have high index of suspicion for TB in children. In a related study in Wake County in North Carolina USA, kernel density estimation was used to analyse geocoded addresses of incident TB, HIV and syphilis cases. The study identified two areas designated as "hot spots" which were

stable over the four year period of study. The study observed that the integration of geospatial approach to screening programmes provided an additional benefit compared to traditional clinic based screening alone (Goswami et al., 2012). Similarly, Ribeiro et al. (2015) combined the genotype data and spatial analysis using kernel density estimation to detect clusters of recent on-going active transmission of TB in Vitoria, Brazil. The risk factors for TB transmission were young age, positive smear test and lower index of quality of urban municipality. The main limitation of kernel density estimation method is the relative arbitrary selection of bandwidth limits. A bandwidth that is too small can lead to under smoothing while bandwidth that are too large can result in over smoothing of the original data and have a major impact on the estimate of the relationship between the risk factors and TB (Carlos, Shi, Sargent, Tanski, & Berke, 2010).

Other studies have utilised GIS tools such as ArcView to map the spatial distribution of TB. Chan-Yeung et al., (2005) used GIS to map significant spatial TB patterns in Hong Kong. The study assessed five socio-demographic indicators at the large street block groups (LSBGs) level and found strong correlations between TB and low educational attainment, elderly population and low-income households. However, population density and unemployment were not associated with higher TB risk. The five socio-demographic indicators in this study were not related to recent transmission of TB. Also in Hong Kong, Pang, Leung, and Lee (2010) mapped significant pattern of TB Standardized Notification Ratio using GIS. The study observed that TB was not evenly distributed and is independently associated with low household income, being single and non-Hong Kong-born in a multivariate analysis using Spearman's correlation. Similarly, Souza, et al. (2005) in Brazil mapped TB

using GIS and found a strong association between TB and average household size, families with more than one case of TB and the presence of TB retreatment cases.

Other studies have used exploratory spatial techniques such as Global Moran's *I* statistics and local indicators of spatial autocorrelation (LISA), to identify significant clusters of TB. Maciel et al., (2010) conducted a spatial analysis of the pattern of TB and its relationship with socioeconomic status in Vitoria, Brazil between 2002 and 2006. A significant spatial autocorrelation was observed in TB using Global Moran's *I* test while Local indicator of spatial autocorrelation (LISA) and Getis Ord Gi* statistics identified four significant areas with high TB transmission. A similar study in Salvador, Brazil by Erazo et al., (2014) also identified areas of significant clusters using Global Moran's index and LISA. The relationship between TB and living condition index (LCI) derived from income, education, crowding, sanitation and slum population were also explored. The areas of increased TB risk were in the central and North-west region of the city from 1995-1996 and in the central west and south west region of the city from 2004-2005. The areas of the city with very low living conditions had an inverse significant effect on TB in 1995-1996 but this association was not sustained in the period 2004-2005 possibly due to general improvement in the living conditions and the activities of the TB control programme. QueirogaI et al., (2012) in the city of Campina Grande, Brazil geo-referenced TB cases to the patient's residential address and observed significant positive autocorrelation for the years 2004, 2006 and 2007 but not for the year 2005 using Global Moran's *I* test. The study concluded that TB rates were higher in neighbourhoods with worse socioeconomic indices. Nevertheless, there were neighbourhoods with high socioeconomic condition that also had high TB rates and this is attributed to better access to health care service, the heterogeneous nature of the inhabitants in the city, high population density,

increased means of transportation and opportunities for increased contact in the cities. Jia et al., (2008) conducted spatial data analysis of TB among migrant population and permanent residents from 2000 to 2006 in Beijing, China and identified hot spots of TB among the migrant population in the 4 central districts in Beijing using Global Moran's I statistics and the Getis Gi* statistics. However, TB was randomly distributed among the permanent residents. In order to bring TB under control in Beijing concerted effort needs to be targeted at the migrant population. Wang et al. (2012) assessed the spatial distribution of TB in Linyi city, China between 2005 and 2010. A significant Global Moran's I was observed for the TB incidence rates while the local G* identified five significant clusters (hotspots) that suggests that TB was not randomly distributed in Linyi city, China. Also, Ng, Wen, Wang, & Fang, (2012) used Global Moran's I statistics and a model that incorporated a spatially lagged dependent variable to identify spatial dependence. The relationships between TB and socioeconomic variables were analysed using a stepwise regression model while spatial analysis was carried out with GeoDa (*www.geodacenter.asu.edu*). The study showed that the TB incidence in a township was significantly affected by the TB incidence in the surrounding neighbours which suggests that recent transmission may play an important role in TB incidence in Taiwan. High income was significantly associated with lower TB rates and TB was 3-5 times higher among aborigines compared to non-aborigines in Taiwan. The areas where aboriginals reside were characterised by lower socioeconomic status, low health status and a poor compliance with TB treatment with prolonged period of infectiousness and increased TB transmission within the community. Izumi et al. (2015) identified hot spots for TB transmission at the census tract level in Japan using Global Moran's I and Getis Ord Gi*. The hot spots were areas of higher population density during the day time, near

proximity to the railway station where there is high business and commercial activities and in areas where a large proportion of foreign-born resides. Alvarez-Hernández et al. (2010) used Moran's *I* index to study the distribution of TB at the census tract or basic geostatistical area (BGA) in the city of Hermosillo, Sonora state Mexico. There was no significant spatial autocorrelation in TB rates with the use of both the Global and local Moran's *I* statistics. However, the Besag and Newell method (Besag & Newell, 1991) identified 24 clusters in the North West, Central East and South West areas of the city. Generally, TB was clustered in areas of high social deprivation which suggests that TB is unequally distributed according to the underlying immediate social context irrespective of the country's general or global socioeconomic index. However, it was also noted that some BGAs with very high socioeconomic deprivation had very low TB rates. This was attributed to underreporting of TB cases due to limited access to health care services. An ecological study by Pereira et al. (2015) in Rio de Janeiro, Brazil assessed the association between TB incidence rates and socioeconomic determinants using Moran's *I* statistic In the final model, the standardised TB incidence rate was significantly associated with poor households, people living alone in the neighbourhoods and households with more than 2 people per bedroom.

The use of crude standardised incidence or mortality ratio for disease mapping may be misleading especially for small areas and or rare diseases because of unstable risk estimates. The risk estimates can also be misleading if the spatial autocorrelation that exists within spatial data is ignored whereby areas that are close to each other tend to have similar disease rates. In addition, the use of spatial autocorrelation techniques is only exploratory and will require the use of more rigorous spatial regression techniques to determine accurate estimates of disease risk. Bayesian

methods are particularly useful to determine actual rates of disease and minimise bias by providing estimates which are weighted average of disease rates from neighbouring areas rather than areas far away thus smoothening local rates towards local neighbouring values (Srinivasan & Venkatesan, 2015).

Few studies have utilized Bayesian spatial methods in the analysis of spatial pattern of tuberculosis. Venkatesan, Srinivasan, & Dharuman (2012) employed Bayesian conditional auto regression (CAR) model in Win BUGS software to assess the spatial pattern of TB in India. The study observed that states in the North-eastern region had a higher risk of tuberculosis compared with other regions. The Bayesian CAR model in addition provided a smoothed map of the Standardised Incidence Ratio (SIR) that had fewer extreme relative risk values compared with the raw unsmoothed SIR values. Similarly, Roza, Caccia-Bava, & Martinez (2012) used Markov Chain Monte Carlo (MCMC) method in the GeoBUGS module of the WinBUGS software to determine the spatio-temporal pattern of tuberculosis between 2006 and 2009 in Ribeirao Preto, Sao Paulo, Brazil. The true amount of spatial dependencies and their associated patterns was quantified in the study, areas of elevated disease risk were identified and the associated social and environmental factors that may be responsible for the spatial heterogeneity were explored using Bayesian CAR model. The study also found significantly high TB incidence in the west and southern regions of the city. High TB incidence was associated with low income, low education and increased social vulnerability. Furthermore, Souza et al. (2007) explored the ecological spatial relationship between socioeconomic factors (such as inhabitants per households, income and schooling) and factors related to transmission of diseases (retreatment and more than one case of TB per household) in Olinda, a city in north-east of Brazil between 1996-2000. The WinBUGS software package was used for the Bayesian

analysis and Markov Chain Monte Carlo (MCMC) was used to estimate the parameters. The study found that an increase in the household size by one person doubled the risk of TB while low income was associated with increased risk of TB. However, low level of education was not associated with higher risk of TB.

Harling & Castro (2014) conducted spatial data analysis of TB in Brazil and found a significant global spatial autocorrelation of TB for each individual year (2002-2009). A significant cluster of TB was observed in municipalities along the land boarders and in major coastal areas in the Central West, Northern, North-Eastern and Southern regions. The study produced disease risk maps using the conditional auto regression model and observed that explanatory variables such as household overcrowding, population density, number of hospitals/100,000 population, number of AIDS cases and household poverty were positively associated with the age standardized tuberculosis notification rates in Brazil.

4.8 **Spatial distribution of tuberculosis in Africa**

Though spatial analysis tool possesses an inherent potential for the understanding of the spatial variation of disease and its associated underlying risk factors in Africa, it has largely been under-utilised due to factors such as lack of capacity, lack of suitable spatial data sets and the lack of appreciation of the potential value that spatial analysis can contribute to health by key players and policy makers (Tanser & Le Sueur, 2002). In spite of these challenges, some studies have been conducted in Africa using spatial analytic techniques in the study of tuberculosis. Table 5 provides an overview of studies on spatial distribution of TB conducted in Africa.

Table 5: Summary of studies on spatial distribution of TB in Africa

Author(s), Date, Country	Type of analysis	Method/Tool of analysis	Major findings/ Outcomes
Uthman et al. (2009), Multi-country, Africa	Spatial analysis	Global and local Moran *I* statistics	Significant clusters of TB/HIV deaths in the Southern and Eastern Africa
Munch et al. (2003), Cape Town, South Africa	Spatial analysis	Point pattern analysis	TB associated with unemployment and number of shebeens per area
Fredrick, (2014), Kitui County, Kenya	Spatial analysis	SaTScan Technique	High TB rates in major towns and roads and in areas with high HIV rates
Touray et al. (2010) Greater Banjul, The Gambia	Spatial analysis	SaTScan Technique	TB clusters identified in densely populated areas with a large concentration of TB diagnostic facilities
Yakam et al., (2014) Douala, Cameroon	Spatial analysis	SaTScan Technique	TB clusters identified in areas of high population density.
Dangisso et al., (2015), Sidama Zone, Southern Ethiopia,	Spatial analysis (spatial and space-time analysis)	SaTScan technique, Global Moran's *I* and Getis Ordi (Gi*)	TB was spatially auto correlate. TB clusters were in urban areas with high population density
Tadesse et al. (2013), Dabat, Ethiopia	Spatial analysis (spatial and space-time analysis)	SaTScan Technique	TB clusters in two districts
Randremanana et al. (2009) Antananarivo, Madagascar	Spatial analysis (spatial and space-time analysis)	SaTScan Technique	High TB risk in neighbourhoods with a higher proportion of households that own houses with ceiling and television. TB risk was higher in households that have patient lost to follow up, have more than one TB case and those that reside far away from the TB treatment centre.

Rakotosamimanana et al., (2014) Antananarivo city, Madagascar	Spatial analysis	SaTScan Technique	TB was spatially aggregated. Diagnosed patients tend to hide their disease because of stigma
Randremanana et al. (2010), Antananarivo city, Madagascar	Spatial analysis	Bayesian hierarchical modelling approach with the use of Markov Chain Monte Carlo (MCMC) in Win BUGS software	TB was associated with households with more than one TB case and households who had a TB patient that had been lost to follow-up
Musenge, Chirwa, Kahn, & Vounatsou, (2013) South Africa	Bayesian spatio-temporal analysis	Bayesian hierarchical modelling approach with the use of INLA package in R software	Childhood TB/HIV mortality was associated with lower socioeconomic status
Kipruto et al., (2015) Kenya	Bayesian spatio-temporal analysis	Bayesian Hierarchical generalized linear mixed model in the INLA package in R software	Identified TB hot-spots in 11 counties. TB was associated with age, gender and HIV

Uthman et al. (2009) in a multi-country study in sub-Saharan Africa observed spatial dependence with global and local Moran I test in the distribution of TB/HIV deaths with evidence of significant clusters in the Southern and some parts of Eastern Africa. Munch et al. (2003) in South Africa used point pattern analysis and spatial statistics to demonstrate clusters of TB cases in the southern and western areas around a clinic in an urban area of Cape Town. TB was significantly associated with unemployment, overcrowding and the number of shebeens (local drinking places) per sub-district. A strong association was observed between TB and unemployment, and shebeens per area which suggested an increased transmission of TB outside the households as a

result of the long hours unemployed individuals spend socialising in the shebeens. Another study by Fredrick, (2014) in Kitui County, Kenya from five TB management units found a higher prevalence of TB in most of the major towns and roads. There appeared to be a relationship between the number of reported TB cases and the HIV rates in the county but the strength of the association was not evaluated.

Most of the studies on spatial analysis of tuberculosis in Africa utilised the SaTScan technique as described above. Touray et al. (2010) used SaTScan to detect the presence of TB clusters in the greater Banjul area of The Gambia. The study identified four primary significant TB clusters and a secondary cluster which is located in one of the most densely populated areas with a high concentration of TB diagnostic facilities owned by both government and private health care providers which suggest that access to TB diagnostic services could lead to an increase in TB diagnosis and notification. Similarly, Yakam et al., (2014) identified areas of high TB clusters in New-Bell, Nylon, Sodiko and Bonassama which were areas of high population density and areas where there was high social contact and exchanges in Douala, Cameroon using SaTScan. For example these areas hosted the largest ethnic community (Bamilike) living in Douala for routine social meetings which may suggest opportunities for increased social interaction and exposure to TB outside the household. Furthermore, TB patients generally had a lower socioeconomic score compared with the general population but a linear relationship was not demonstrated between mean SES and TB incidence.

Dangisso, Datiko, & Lindtjorn, (2015) used a combination of SaTScan, Global Moran's I and Getis Ordi (Gi*) statistics to analyse TB case notification rate over 10 years in 192 kebeles (which is the lowest administrative unit within the district), in eight districts in Sidama Zone, Southern Ethiopia. The Global Moran's I statistic

showed significant spatial autocorrelation for each year. The study observed significant clusters of TB in the north-western and east central districts. The significant clusters were mostly in urban areas which were capitals of the district, rural areas with a high population density and areas close to major towns or road networks. In addition, space-time statistics and the Gi* statistics used in the spatial analysis identified similar clusters of TB in the same location. This may suggest that the disease persisted in the same places over the years in spite of the various country wide interventions carried out which may not have specifically targeted these high risk areas. The study however did not assess the socioeconomic factors that may affect TB rates in the districts. Similarly, Tadesse et al. (2013) in Dabat, Ethiopia identified significant smear positive TB clustering in two districts using purely spatial and space-time analysis. Both methods identified significantly high clusters of TB in the same districts.

Randremanana et al. (2009) used spatial scan statistics to determine spatial clusters of TB cases in three of the six arrondissements (districts) of Antananarivo city in Madagascar. The study took place in two time frames between August 2004 and July 2005 while the second was between August 2005 and July 2006. There was a decrease in the number of clusters in the second period compared with the first period which was attributed to better quality of TB care provided by the TB treatment centres. The study found that the risk of TB increased in neighbourhoods with a higher proportion of households that own houses with ceiling and television, have a TB patient lost to follow up, have more than one TB case and households who reside far away from the TB treatment centre. TB risk however was lower in households with higher proportion of hard walls, tap water, radio, and in households where TB patients were undergoing treatment.

Few studies have used the Bayesian hierarchical modelling approach in spatial analysis of tuberculosis in Africa. Randremanana et al. (2010) in Antananarivo city, Madagascar used a combination of a Bayesian approach and generalised linear mixed model to assess spatial variation of TB and to investigate some explanatory variables associated with TB. The Bayesian spatial modelling approach in Markov Chain Monte Carlo (MCMC) used the Win BUGS software to detect clusters of TB. Tuberculosis was associated with households with more than one TB case and households who had a TB patient that had been lost to follow-up. In comparing the two approaches (the spatial scan statistics and the Bayesian approach) in Antananarivo city, Madagascar, it was observed that the spatial scan method detected general regions with significantly high risk for TB. However, the spatial scan method generated larger clusters than expected thus had more high false positive areas than the Bayesian approach. The Bayesian approach on the other hand identified neighbourhoods that significantly contributed to the scan statistics circle but with a lower false positive rate (Randremanana et al. 2010). Similarly, Rakotosamimanana et al., (2014) investigated the role of knowledge, attitude and practice of tuberculosis on the spatial aggregation of TB in Antananarivo and found that diagnosed TB patients do not share information about their illness and therefore tend to hide their disease status as a result of stigma. This resulted in delayed diagnosis, continued transmission of TB which may be responsible for the observed significant clusters in some districts.

As described above few studies have used the Bayesian approach in spatial analysis, yet only a handful of studies have used R statistical software in the Bayesian spatial analysis of TB in Africa. The Bayesian technique in R statistical software (R-INLA) has some advantages over the commonly used Markov Chain Monte Carlo (MCMC) in that it provides accurate approximation of the posterior marginals of the

latent effects and it is more efficient in that it greatly reduces the computational burden and time of analysis especially with a large sample size (Rue & Martino, 2009). Musenge, Chirwa, Kahn, & Vounatsou, (2013) conducted Bayesian spatio-temporal analysis using the INLA package in R software in the study of childhood TB/HIV mortality in South Africa. The study identified three hotspots areas in the central, south easterly and south westerly regions. The factors protective of childhood mortality were number of adults in the household, number of antenatal clinic attendance and mother being alive. Households with a higher socioeconomic status had significantly lower childhood deaths compared with poorer households.

Kipruto et al., (2015) undertook a spatio-temporal modelling of tuberculosis in the 47 counties in Kenya using the Bayesian Hierarchical generalized linear mixed model in the INLA package in R software (Rue & Martino, 2009). The study identified TB hot-spots in 11 counties namely Nairobi, Mombasa, Marsabit, Isiolo, Lamu, Machakos, Kajiado, Makueni, Kisumu, Siaya and Homabay. In addition the study found a significant association between TB and risk factors such as age, gender and HIV. The study however was done at the first administrative level of the country which had population ranging from 224,000 to about 3.2 million people. The study did not examine the role of socioeconomic and health care related factors such as access to and utilisation of health services on TB rates.

4.9 Spatial distribution of tuberculosis in Nigeria

Few studies on the spatial distribution of TB in Nigeria were retrieved during the literature search. Table 6 provides an overview of the limited studies conducted in Nigeria on the spatial distribution of TB.

Table 6: Summary of studies on the spatial distribution of TB in Nigeria

Author(s), Date, Country	Type of analysis	Method/Tool of analysis	Major findings/ Outcomes
Cadmus, Akingbogun, and Adesokan (2010) Oyo State, Nigeria	Exploratory spatial analysis	GIS techniques Nearest neighbour distance analysis	Identified significant TB clusters in overcrowded areas
Igu et al., (2013) Enugu state, Nigeria	Non-spatial analysis	No specific spatial technique	High TB rates in urban areas
Gulma (2011), Kebbi State, Nigeria	Spatial analysis	kernel density	Detected significant TB clusters in 4 LGAs
Ibrahim et al. (2015), Kebbi State, Nigeria	Spatial analysis	Global Moran's I Gestid Ord (Gi*)	Detected significant TB clusters in 4 LGAs

Cadmus, Akingbogun, and Adesokan (2010) used GIS techniques to analyse routine TB surveillance data around a university community in Ibadan, Oyo State, Nigeria. The study identified significant TB clusters in overcrowded areas with the use of nearest neighbour distance analysis. Also in Ibadan, Oloyede-Kosoko and Akinkogun (2013) used nearest neighbour distance analysis to detect clusters of TB cases in the inner city of five Local government areas in Oyo state, namely Ibadan North West, Ibadan North East, Ibadan North, Ibadan South East and Ibadan South West. These studies however did not evaluate the interaction of TB with any explanatory variables and no robust statistical analyses were done. Igu et al., (2013) studied the variation in TB cases notified in the 17 LGAs in Enugu state and concluded that TB case notification was associated with urban residence. The LGAs classified as more urban were Enugu North, Nsukka and Igbo-eze which had high TB incidence while Nkanu West and Nkanu East classified as a rural LGA had the lowest TB incidence. The study had several limitations including the fact that cumulative absolute TB case

count was used for the analysis without any reference to the population of the LGAs and no specific spatial analysis was carried out. Gulma (2011) used kernel density analysis to map the trend of TB cases notified in Kebbi state, Nigeria between 2008 and 2011. There was significant TB clusters in four LGAs namely Yauri, Gwandu, Argungu and Zuru. Similarly, Ibrahim et al. (2015) also studied the spatial distribution of TB in the 21 LGAs in Kebbi state. The Global Moran's *I* did not detect any TB cluster but Getis Ord (Gi*) detected some clusters especially in the data for 2010. However, these studies did not include analysis on socioeconomic factors that may be responsible for the observed spatial pattern of TB in the state.

4.10   Conclusion of literature review and research gaps

After a thorough search of the literatures it is evident that several studies have been conducted on TB and socioeconomic factors in the global north and in some countries in South America, especially Brazil. However, very few studies have been done on the spatial distribution of TB in sub-Saharan Africa. The studies done on socioeconomic factors and TB in Africa were mostly individual level case-control studies of a relatively small sample size of TB patients and controls. The national study by Harling, Ehrlich, and Myer (2008) in South Africa made use of self-reported TB disease as the outcome variable which was prone to recall bias. In addition, the contextual effect of geographic space on TB risk was not taken into consideration in their analysis. The other national study in Kenya by Kipruto et al., (2015) considered spatial analysis of TB using R-INLA but did not assess the effect of socioeconomic and health-related determinants of TB. The majority of studies in Africa used SaTScan technique which was limited in scope to one province, district/city or township area and the effects of socioeconomic factors on TB were not measured (Randremanana et al., 2009; Touray et al., 2010; Yakam et al., 2014).

The studies on the spatial distribution of TB conducted in Nigeria were largely limited to one LGA or at most one of the 37 states of the federation. There has been no study on TB in Nigeria on a national scale that has included all the 774 LGAs which are the lowest administrative level of government in the country. In addition no study in Nigeria has yet looked at the relationship between TB and socioeconomic, demographic and health related explanatory variables or applied advanced spatial analytic techniques to identify areas of high TB risk in the country.

This study is therefore designed to conduct a spatial analysis of TB in Nigeria and to investigate the contribution of area-level socioeconomic, demographic and health-related covariates using Bayesian conditional auto regression modelling. It is expected that the study will contribute to the existing body of knowledge on the on-going debate of whether socioeconomic factors in sub-Saharan Africa are positively or inversely associated with tuberculosis. The study will develop an asset-based composite socioeconomic index for the LGAs and analyse its effects on TB in the country. Furthermore, the R- statistical software will be used for the data analysis of both the non-spatial and spatial analysis. The Global and Local Moran's statistic will be used for the initial exploration of the data while Bayesian conditional auto regression model will be conducted in R-INLA with the capacity to produce maps for exploration of disease patterns, detection of clustering and identification of risk factors for TB and the detection of LGAs with high risk of TB which can be helpful to decision makers to make informed decisions in planning effective targeted local specific control measures to the identified priority high risk LGAs.

In conclusion, a review of the literatures on the social determinant of tuberculosis have been conducted with an emphasis on socioeconomic status and the material living standards such as housing quality, overcrowding, place of residence, population

density and the health systems. This review provides the stage for the selection of key explanatory variables that will be used in this study. These are: composite socioeconomic status, mean household size, access to public transportation, percentage of households living in a single room, percentage of households living in urban residence, population density and health related variables such as number of microscopy centre per capita, number of DOTs treatment centres per capita and the total number of health facilities per capita in each LGA.

CHAPTER 5: Methodology

This chapter describes the methodology employed in this study which includes the study design, ethical issues, data sources, data elements and variables utilised and the processes employed in the analysis of data in this study.

5.1 Study Design:

The study is an ecological retrospective spatial study of TB case notification rates in Nigeria in 2013 and the associated socioeconomic, demographic and health related risk factors.

5.2 Ethical issues

The study utilised secondary data obtained by permission from the National Tuberculosis and Leprosy Control Programme (NTBLCP) in Nigeria. The population data and the core welfare questionnaire survey used to derive the composite asset based socioeconomic index were obtained from the websites of the National Population Commission (NPC) and the National Bureau of Statistics (NBS) respectively. The data for this study were aggregated at the local government areas (LGAs) without any individual personal identifiers. Data were stored as encrypted files in a secured computer that were password protected. Hard copies of data obtained from the various sources were kept in a safe locked cabinet from unauthorized access. The ownerships of data used for this study were duly acknowledged.

Ethical approval was obtained from the ethics board of the Olabisi Onabanjo University Teaching Hospital Research Ethics Committee Ogun State, Nigeria and the Faculty of Medical and Health Research Committee Lancaster University, United Kingdom.

5.3 Data Sources

The study utilised a combination of data from a variety of data sources: this included LGA level data on Tuberculosis which was obtained from the National TB and leprosy Control Programme in Nigeria (NTBLCP); the Nigerian population census information was obtained from the National Population Commission, Nigeria; health service data on the number of TB diagnostic and treatment centres in the country was also obtained from the NTBLCP while the total number of health facilities in each LGA was retrieved from the directory of health facilities in Nigeria, published by the Federal Ministry of Health in 2012. The shape file for the second administrative level (LGAs) in Nigeria was downloaded from the global administrative areas database at www.gadm.org; the socioeconomic variables were derived from the Core Welfare Indicator Questionnaire (CWIQ) survey of 2006, obtained online by permission from the NBS in Nigeria.

The following sections provide a detailed description of each of these data sources.

a. **Tuberculosis Data in Nigeria**

TB count data for the 774 LGAs for 2013 were obtained with permission from the National TB and Leprosy Control Programme. The NTBLCP established a system of data collection from over 5000 TB treatment facilities scattered around the country in the 774 LGAs. The TB programme in Nigeria has a robust system for the collection, collation, analysis, interpretation and reporting of TB data from the health facility within each Local Government Area (LGA) up to the Central Unit of the NTBLCP (FMoH, 2010; WHO, 2014a). The TB programme in Nigeria utilizes passive case finding strategy in the detection of TB cases. This means that individuals with signs and symptoms of TB come to a health facility where they are identified as presumptive TB cases. These patients are referred to the TB microscopy centre for

laboratory investigation and diagnosis of tuberculosis. A TB patient is defined according to the National TB guideline as one who has at least two AFB positive sputum smear (sputum smear positive TB), or a person whose sputum smear is negative but based on other ancillary investigations is confirmed by a trained medical officer as having clinical tuberculosis (Sputum smear negative pulmonary TB) or a patient with signs and symptoms suggestive of TB outside the lung (Extra pulmonary TB). TB patients in any of the aforementioned three categories are classified as a TB case. After diagnosis, relevant demographic and clinical information of the patient are obtained and recorded into the TB treatment cards. The patient information in the TB treatment cards are transferred into the TB facility treatment register for all patients receiving treatment in that facility. The policy of the NTBLCP is that patients receive treatment at the facility closest to where they reside irrespective of where diagnosis is made. The Local Government TB and Leprosy Supervisor (LGTBLS) visit health facilities within the LGA monthly to validate and update patient information into the LGA TB central register. At the end of each quarter, the LGTBLS summarises the data for the LGA in the quarterly recording and reporting forms and transmits the information within the first week of the month following the end of a quarter to the State TB and Leprosy Control Programme (STBLCP). The STBLCP collates the data from each of the LGAs during a two-day quarterly review meeting on the second or third week of the month following the end of the quarter under review and summarises the state data into the state quarterly recording and reporting form which is transmitted to the zone. A zonal meeting usually holds before the end of the third or fourth week of the month following the quarter to collate the data from the states within each of the six geopolitical zones of the country. A zonal summary from the six zones is then forwarded to the Central Unit

of the NTBLCP where an annual national summary is compiled for the country and transmitted to the epidemiological unit of the Federal Ministry of Health and the World Health Organization. The monitoring and evaluation system of the NTBLCP has an in-built mechanism for data validation and data quality checks during the review meetings at all levels in addition to the quarterly supportive supervisory activities carried out at all levels to ensure compliance with the national guidelines and ensure data quality. The NTBLCP organises standardized trainings at the National TB training centre in Zaria for all the 774 LGA TB supervisors and staff of the TB laboratory and DOTs treatment centres. However, TB cases can still be missed by routine notification because of the passive strategy employed by the programme if people with TB do not seek care at designated health facilities or laboratories or when they seek care but remain undiagnosed due to lack of high index of suspicion or are picked up by general health care workers but lost during referral to the laboratory or are diagnosed by health facilities who do not report such patients to the NTBLCP. This may introduce some potential bias if the rate of reporting is spatially distributed. The age and sex distribution of the TB data is not available and so the case notification rates is not standardised by age and sex. Consequently, the analysis uses total counts for each LGA.

b. Population data

The National Population Census of 2006 for each 774 LGAs was projected for 2013 at the current national annual inter-census growth rate of 2.8% (UNDP, 2015). The projected population for 2013 provided the denominator to calculate the TB case notification rates/100,000 population for each LGA.

c. Health service data.

The health service data included indices of access to health services generally and to the diagnosis and treatment of TB specifically as described by Odone et al., (2013) , Harling & Castro, (2014) and Randremanana et al., (2010) Consequently, the health service related factors in this study were:

i. Total number of health facilities in each LGA: The data includes all health facilities in the LGA namely primary, secondary and tertiary health care facilities irrespective of ownership status (whether public or private). This data was obtained from the directory of health facilities in Nigeria (FMoH, 2012)

ii. Total number of DOTS treatment centres in each LGA for 2013: The data on the number of TB treatment centres were obtained from the NTBLCP. A TB treatment centres is a designated health facility where there is a trained DOTS staff with the availability of the NTBLCP recording and reporting tools and anti-TB drugs to initiate TB treatment. The facility can be a primary, secondary or tertiary health care facility.

iii. Total number of Acid Fast Bacilli (AFB) microscopy centres in each LGA in 2013: This data was obtained from the NTBLCP and it included designated laboratories with a laboratory staff trained to carry out sputum smear microscopy for AFB. The *Mycobacterium tuberculosis* is an acid fast bacillus (which means the organism appears as rod-like bright red bacillus against a blue background when stained with the Ziehl-Neelsen stain). After diagnosis, the results of the examination were forwarded to the referring DOTs treatment centre for further action.

d. Digitized map of Nigeria:

A digitized map of the country at the lowest administrative unit (LGAs) is freely available and was downloaded from the global administrative areas data base website at www.gadm.org.

e. Socioeconomic variables:

The socioeconomic variables were retrieved from the Core Welfare Indicator Questionnaire (CWIQ) survey, 2006 (National Bureau of Statistics, 2006). The proxy variables for socioeconomic status at the LGAs were:

i.   Single room: Percentage of households who live in a single room in the LGA. This variable was selected in line with the observation by Leung et al., (2004) that the variable is associated with poor ventilation which is identified as a significant correlate for TB.

ii. Mean household size: Mean household size in the LGA was selected as a surrogate for household crowding. Household crowding was observed as a significant determinant of TB by several studies (Gustafson et al., 2004; Harling et al., 2008; Hill et al., 2006).

iii. Access to transportation: This is the percentage of households who take less than 30 minutes to the nearest public transportation. Increased volume of travel especially in crowded transportation in rural Africa has been suggested as a potential risk factor for transmission of TB (Glynn et al., 2000; Odone et al., 2013) but Feske et al., (2011) found that weekly bus ridership of public transportation is significantly associated with high TB risk.

iv. Urban residence: This is the percentage of households in urban areas within the LGA. Several studies have found urban residence to be a significant risk factor for TB (Harling & Castro, 2014; Harling et al., 2008).

v. Population density: This is calculated as the population of the LGA divided by the area in Km^2. Population density is identified as a risk factor for TB by Gonçalves et al., (2009) and (Harling & Castro, 2014).

5.4 Dependent and independent variables

The dependent (outcome) variable is the TB case notification rate/100,000 population which is the total TB cases notified by the LGAs divided by the 2013 projected total population of the LGA. In the Poisson and spatial regression analysis, the TB counts for 2013 represented the dependent variable while the Standardised Notification Ratio (SNR) is the dependent variable in the spatial regression analysis in R-INLA. The final set of independent or explanatory variables were divided into socioeconomic (standardised composite socioeconomic index, mean household size, percentage of households living in single room and access to public transportation); demographic (percentage of households living in urban areas and population density) and health related (total number of facilities/100,000 population, number of Acid fast bacilli TB microscopy centres/100,000 population and the number of DOTS TB treatment centres/100,000 population) variables.

Construction of a composite socioeconomic index: A composite standardised asset based socioeconomic index was developed for each of the 774 LGA with the use of the variables listed in Table 7 from the Core Welfare Indicator Questionnaire (CWIQ) survey, 2006 (National Bureau of Statistics, 2006). These variables had been used in similar studies in Africa for constructing area based socioeconomic index as a proxy for socioeconomic status (Montgomery, Gragnolati, Burke, & Paredes, 2000; Vyas & Kumaranayake, 2006). The variables were initially entered individually as independent variables into the regression model to assess if they had any relationship with TB, but none of them showed a significant relationship. These variables were

then used to construct an area-based socioeconomic index for each LGA. The index provided an area-level contextual socioeconomic risk factor that served as an alternative to household income or consumption data which is not available in the country at the time of this study.

Similar studies in Africa have demonstrated the usefulness of area-based socioeconomic index as a relative measure of socioeconomic status that can be used in comparing inequality across different geographical locations (Montgomery et al., 2000; Vyas & Kumaranayake, 2006).

Table 7: Variables used for the construction of composite socioeconomic index

S/N	Variables	Variable description
1.	Safe sanitation	Percentage of households using flush toilets ventilated improved pit latrines or covered pit latrines.
2.	Ownership of personal computers	Percentage of households with ownership of personal computers.
3.	Ownership of a house	Percentage of households that own their dwelling house.
4.	Ownership of mobile phone	Percentage of households with ownership of mobile phone.
5.	Safe water	Percentage of households with safe water source defined as households using treated pipe water, borehole/hand pump or protected well.
6.	Access to water	Percentage of households with access to water defined as households with a water source less than 30 minutes away.
7	Building wall type	Percentage of households where the material of the walls of the house is cement or sandcrete.
8	Ownership of Motor cycle	Percentage of households with ownership of motorcycle.
9.	Electricity	Percentage of households who have access to electricity from the national grid or rural electrification.
10	Ownership of a vehicle	Percentage of households with ownership of vehicle.
11	Ownership of land	Percentage of households that own more than 6 hectare of land.

The composite socioeconomic index was constructed with the approach described by Krishnan, (2010).The choice of variables for the Principal Component Analysis (PCA) was based on similar studies in Africa (Boccia et al., 2013; Montgomery et al., 2000; Vyas & Kumaranayake, 2006; Yakam et al., 2014). The variables used for the PCA included asset ownership, housing quality and access to basic infrastructure such as electricity and water. The data frame containing these variables for each of the LGAs was explored with SPSS to check individual variables for normality and skewness by carefully examining the histograms, Q-Q plots, 5% trimmed mean and

kurtosis, steam and leaf plots, and the skewness score in the descriptive analysis. Skewness is said to occur when the skewness value in the descriptive analysis is greater than -1 or +1. The skewed variables were transformed using natural logarithm or $\log_{10}$ and square root depending on the nature of skewness. The Kaiser-Meyer-Olkin (KMO) value of 0.858 was observed and a KMO value close to 1 is considered optimal for factor analysis to proceed. The Bartlett's test of Sphericity is also checked to test the strength of the relationship and correlation among variables. This also indicated that the factor analysis could proceed (Krishnan, 2010).

Factor analysis was carried out on the eleven selected variables. The correlation matrix and the scree plot of the eigenvalues were used to determine the number of factors to be considered. Two factors were eventually extracted from the result of the scree plot which explained a cumulative variance of 60.62% (47.75% for factor 1 and 12.87% for factor 2). The variables that contributed to factor 1 were ownership of house, phone, vehicle, computer, motorcycle, house built with sancrete, safe water supply and sanitation while two variables contribute to factor 2: access to water and ownership of land. The proportion of the variances contributed by the two factors to the overall variance was used as the weights for each of the selected variables. The first factor described the extraction of a set of variables that captured the largest possible variation in the original data set while the second factor explained additional dimension in the data but less variation compared to the first factor. The weights (indicated by the eigenvectors of the correlation matrix) for each factor signified the relative importance of the variables in the data set. The procedure of using the weights in principal components analysis (PCA) to derive a SES index has been found to have a reasonable agreement with estimates from household consumption expenditures (Filmer & Pritchett, 2001; Gwatkin, Rutstein, Johnson , Suliman ,

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Wagstaff , 2000; Vyas & Kumaranayake, 2006) compared with the approach by Montgomery et al., (2000) where the number of assets in households were simply summed. This assumes that all assets are equally weighted and this assumption has been described as arbitrary and lacking in objectivity (Filmer & Pritchett, 2001).

The non-standardized socioeconomic index (NSSEI) for each LGA comprised of the addition of the weights of both factors as described by Krishnan (2010).

NSSEI = weight of factor 1(factors 1) + weight of factor 2 (factors 2) …………(1)

Therefore, the NSSEI for this study is as follows:

NSSEI = (0.788)*(COMPUTER)+(0.788) *(SANITATION) + (0.788) *(OWN HOUSE) + (0.788)*(ELECTRIC) + (0.788) *(VEHICLE)+(0.788) *(CEMENT) + (0.788)*(PHONE) + (0.788) *(WATER) + (0.788) *(MOTORCYCLE) + (0.212) * (LAND) + (0.212) *(ACCESS WATER).

Since the value of the index can be positive or negative, the score for each LGA is standardized so that the range of values of the socioeconomic index score for the LGAs varied between 0 to a maximum of 100. The higher the score of the standardized socioeconomic index (i.e. close to 100), the more socioeconomically advanced the LGA is. The formula is expressed thus:

Standardized socioeconomic index (SSEI) $= \frac{(NSSEI\ of\ LGAs - Min\ NSSEI)}{(Max\ NSSEI - Min\ NSSEI)}\ X\ 100$ ......*(2)*

5.5 Data Analysis

5.5.1 Data cleaning and diagnostic analysis

The data frame was constructed from the dependent variable and the 9 explanatory variables in Microsoft Excel. The data were checked for errors and out of range values. Initial data exploration was done with SPSS to check for normality by using the descriptive analysis function and by plotting histogram, QQ plots and the stem and leaf plots of all variables. Frequency distributions were generated for categorical

variables with the minimum and maximum values while for continuous variables, the mean, median, standard deviation, interquartile range, minimum and maximum values were determined. In addition, scatter plots were conducted for all variables to check for outliers. The data for Kuje LGA in the Federal Capital Territory were excluded from further analysis because of the extreme value of TB CNR which was above 1500/100,000 population. The TB CNR for Kuje LGA constituted a major outlier and therefore likely to have a distorting effect on the result of the analysis. The reason for the extremely high CNR may be partly due to the migration of people to the capital city of Nigeria (Federal Capital Territory) and because of the high cost of living in the city centre, Kuje LGA provides a ready place of residence for low income earners (Ebhota & Opoola, 2014). All variables finally included for analysis were checked for multi-collinearity, though no significant collinearity was observed.

The R statistical package version Ri3863.1.2 was used for the analysis of both non-spatial and spatial analysis (Brunsdon & Comber, 2015). The value of statistical significance for the entire statistical test performed in this study was taken at p≤0.05.

5.5.2 Descriptive statistical analysis

Descriptive statistics were conducted for all the variables finally selected for analysis. During the diagnostic analysis, it was observed that most of the variables were not normally distributed; therefore the median and the interquartile range (IQR) were computed for all variables in addition to the mean and standard deviation as presented in Table 8.

Table 8: Definition and summary statistics of dependent and explanatory variables

Variable name	Definition	Mean (S.D)	Median (IQR)	Range
TB	TB cases notified	128.32(183.09)	58.00 (29.00-143.0)	0.00-1451
CNR	Case Notification rate per 100,000	55.59 (71.87)	31.04 (15.70-65.64)	0.00-592.38
SNR	Standardised Notification Ratio	97.76 (126.51)	54.47(27.37-115.62)	0.00-1042.68
Population	Population of LGAs	220398.34 (123937)	191705 (146825-258488)	38440-1603156
Socioeconomic factors				
SEI	Composite standardised Socioeconomic index	44.29 (17.36)	42.39(32.38-54.47)	0.00-99.99
Crowding index	Mean household size in each LGA.	4.88(1.11)	4.76(4.04-5.70)	2.58-10.98
Access public to transportation	Percentage of households who take less than 30 minutes to the nearest public transportation	65.04 (24.133)	68.00(47.40-85.30)	0.00-100
Ventilation index	Percentage of households living in one room apartment	66.11(27.87)	70.80(47.00-91.65)	0.00-100
Demographic factors				
Urban	Percentage of households living in an urban area	22.75(30.96)	10.00(0.00-30.00)	0.00-100
Population density	Population Density per km^2	1276.10 (4714.95)	277.69 (125.97-640.02)	11.58-67613.39
Health/Medical Factors				
Health facility	Number of health facilities per 100,000 pop	21.95 (17.11)	18.99(13.21-26.63)	2.75-336.22
DOTS treatment facility per capita	Number of DOTS treatment facilities per 100,000	3.51(2.81)	2.84(1.92-4.26)	0.00-22.61
Microscopy per capita	Number of AFB microscopic facilities per 100,000	0.94(0.63)	0.80(0.53-1.25)	0.00-4.14

5.5.3   Non-spatial analysis (multivariate analysis)

The data was fitted into a non-spatial generalised linear model (GLM) to explore the relationship between explanatory variables and TB count with the assumption that the TB cases were spatially independent of each other.

The number of TB cases in each *of the LGAs (i= 1, ...774)*, Y_1 ......Y_n is defined as an independent Poisson random variable with a mean of μ_i (μ_1....μ_n). The mean (μ_i) was stated as the multiplication of the expected number of TB cases (ε_i) and the relative risk of TB (λ_i) in each LGA_i i.e. $\mu_i = \varepsilon_{i \ x} \lambda_I$ (Randremanana et al., 2010; Souza et al., 2007). Therefore, the logarithms form of the expression is:

$$log\ (\mu_i) = log(\varepsilon_i) + log(\lambda_i)\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots.(3)$$

Theoretically, the relative risk of TB in each LGA_i (λ_i) = $\frac{\mu i}{\varepsilon i}$ is a function of the k covariates X_k which described the differences in the incidence of TB. Thus the Poisson regression model as was reported by Souza et al. (2007) is expressed as:

$$\lambda_i = exp(\beta_0 + \beta_{1i}X_{1i} + \beta_{2i}X_{2i} + \beta_{3i}X_{3i} + \dots\dots\dots\dots + \beta_{ki}X_{ki})\dots\dots\dots\dots\dots.(4)$$

X_{ki} is defined as the area based covariates, β_{ki} are the vectors of the parameters that describes the covariates (X_{ki}) effects on TB and β_0 is the intercept parameter.

Poisson regression analysis was carried out to assess the relationship between the explanatory variable and TB. Initially, the explanatory variables were entered individually into the model, thereafter all the explanatory variables were entered into the multivariate model. The output of the regression model consisted of regression coefficients, the standard error, 95% confidence interval and p-values. The assumption of the Poisson regression model is that the conditional variance is equal to the conditional mean. The degree of dispersion calculated from the standardised residual deviance divided by the degree of freedom produced a value of 12.16 which is greater than 1 and thereby signified substantial over-dispersion in the data. As a

result of the over-dispersion in the Poisson regression analysis, a quasi-Poisson regression model was fitted to the data (Ver Hoef & Boveng, 2013). The quasi-Poisson maximum likelihood estimate coefficients were the same as the Poisson regression model, however the standard errors were more robust and gave more accurate estimates than the Poisson regression. The coefficient estimate was exponentiated to produce an incidence rate ratio (IRR) which is a measure of the risk associated with the covariates. A one unit change in the explanatory variable will increase the relative risk of TB by the exponentiated regression coefficients estimate provided that all other explanatory variables in the model were held constant.

5.5.4   Spatial data analysis: Global Spatial autocorrelation

Global spatial autocorrelation was performed with the GISTool in R. The data frame in Microsoft Excel was merged with the Nigerian shape file at the second administrative level (LGA) in R. The contiguity-based neighbour is defined as first-order queen's contiguity, such that only LGAs sharing borders with each another were considered neighbours. The row standardized weight matrix is created and the Moran's *I* test for global spatial autocorrelation is determined at p ≤0.05. The Global Moran's *I* statistic is used to test the null hypothesis that the spatial autocorrelation of the TB Case notification rate is zero. If this hypothesis is rejected, then TB is spatially auto correlated. The Global Moran's *I* is defined as:

$$I = \frac{N}{\Sigma_i \Sigma_j \omega_{ij}} \ \frac{\Sigma_i \Sigma_j \omega_{ij} \left(X_i - \bar{X} \right) \left(X_j - \bar{X} \right)}{\Sigma_i \left(X_i - \bar{X} \right)^2} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (5)$$

Where N is the number of spatial units indexed by i and j; X is the variable of interest, $\bar{X}$ is the mean of X; and W_{ij} is an element of a matrix of spatial weights.

The Global Moran's *I* test was carried out under different assumptions: under randomization, normality and Monte Carlo simulation (Brunsdon & Comber, 2015).

The value of the Global Moran's *I* ranged from -1 to +1. A value close or equal to +1 indicated a positive spatial correlation while a value close to or equal to -1 showed a negative spatial autocorrelation while a value of '0' signified no spatial autocorrelation. The output of the Global Moran's *I* test also computes the Z-score and the P- value associated with the Moran's *I* statistics against the null hypothesis. Significant global spatial autocorrelation occurred when the p value is less than 0.05. A scatter plot between TB CNR and the spatial lag of TB CNR (computed by averaging the values of TB CNR from all the neighbouring LGAs) was done. The slope of the regression line in the scatter plot is the Global Moran's *I* test statistic value.

5.5.5   Spatial data analysis: Local indicators of spatial association

Anselin (1995), proposed the use of Local indicators of spatial association (LISA) for a localised form of exploratory spatial analysis. The importance of the LISA test was to detect or identify regions of spatial clustering around an observation. The local Moran's *I* test statistics is expressed in the equation below.

$$I_i = z_i \sum_j \omega_{ij} z_j \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(6)$$

Where the z_i is the original variable x_i in standardized form and w_{ij} is the spatial weight.

The advantage of Local spatial autocorrelation was that it can identify spatial clusters at a more local spatial unit rather than relying on Global Moran *I* statistics which is a single global autocorrelation measure. Local spatial autocorrelation is presented as choropleth thematic map of the false discovery rate (FDR) adjusted local Moran's *I* p values for each LGAs. A p-value of ≤ 0.05 was regarded as statistically significant.

LISA allows for identification of four different types of spatial clusters (Cromley & McLafferty, 2012). A positive LISA statistic identifies a spatial concentration of LGAs with similar values of TB CNR. These are:

    i. High-High clusters (or hotspot): these are LGAs with significantly high TB CNR surrounded by LGAs with high TB CNR

    ii. Low-Low clusters (or cold spot) these are LGAs with significantly low TB CNR surrounded by LGAs that have low TB CNR.

A negative LISA statistic is indicated by a spatial pattern where the values of TB CNR were dissimilar. These are:

    iii. High-Low clusters: these are LGAs with high TB CNR surrounded by LGAs that have low TB CNR (spatial outliers)

    iv. Low-High clusters: these are LGAs with low TB CNR surrounded by LGAs with high TB CNR (spatial outliers).

The LGAs designated as insignificant were LGAs with a P value greater than 0.05

5.5.6 Spatial auto-regression modelling

A spatial auto regression analysis is considered because from the previous analysis, TB showed significant residual spatial dependence which may be due to confounding or a neighbourhood effect (the behaviour of one area being affected by that of a neighbouring area) coupled with the fact that substantial over dispersion was also observed in the Poisson regression analysis. Consequently, random effects were introduced into the Poisson model in a Bayesian analysis to account for the unobserved spatial heterogeneity in the data and adjust TB rates towards the mean of the neighbouring rates in other to produce a more reliable rate estimates for geographic areas with unstable rates. The Bayesian approach provided a valid inference where there was over dispersion due to the fact that the disease risk of

neighbouring areas tend to be positively correlated as they share a number of spatially varying characteristics. The Bayesian analysis was carried out using the R-INLA package in R statistical software

The Bayesian hierarchical Conditional Autoregressive model accounted for the unobserved spatial heterogeneity and allowed for the spatial correlation between observations in the data. Initially, the observed TB count in each LGAi is modelled as a function of area level disease risk. The Bayesian hierarchical Conditional Autoregressive (CAR) model, developed by Besag, York, & Mollie, (1991) for disease mapping model allowed for the smoothing of the disease risk in each LGA towards the mean risk of the neighbouring LGA and reduced the extra variability. Thus, it provided a more precise estimate of both mean and variance compared with using unsmoothed Standardized Notification Ratio (SNR). The equation is represented as:

$$Y_i \sim Poisson\ (\lambda_i \varepsilon_i) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\ (7)$$

Where Y_i is defined as the number of observed TB count in LGA_i in 2013, λ_i is the risk in LGA_i and is the observed number of TB cases divided by the expected number of TB cases in each LGA in 2013 and ε_i is the expected TB count based on population size of the LGA_i which is estimated from the mean rate of the national TB count multiplied by the population of each LGA.

In the Bayesian framework, the observed TB counts $Yi = (Y_{1,\dots\dots}Y_n)$ in each LGA "i" (i=1,2,……..n) was taken as non-independent Poisson random variables with a mean of μ_i ($\mu_1\dots,\mu_n$). The mean (μ_i) can also be stated as the multiplication of the expected number of TB cases (ε_i) and the relative risk of TB (λ_i) in each LGA_i i.e. $\mu_i = \varepsilon_i \times \lambda_i$. Therefore in logarithm form of the expression is the same equation described earlier in equation 3: $\log\ (\mu_i) = \log(\varepsilon_i) + log(\lambda_i)$.

The next stage was the specification of the collection of the risks as a function of the explanatory variables. The log risk is modelled by the equation:

$$\lambda_i = exp(\beta_0 + \beta_{1i} X_{1i} + \beta_{2i} X_{2i} + \beta_{3i} X_{3i} + \ldots\ldots\ldots + \beta_{ki} X_{ki} + v_i + u_i)\ldots\ldots\ldots(8)$$

Equation 8 is the same equation that is described in equation 4 with the addition of the unstructured and the structured spatial random effects v_i and u_i. The uncorrelated or non-spatial heterogeneity or unstructured random effect is designated as v_I while the correlated spatial heterogeneity or spatially structured random effect is labelled as u_i. The Bayesian analysis usually specified a prior (assumed) distribution to the parameter (TB CNR) to adjust for uncertainty. The specified prior distribution was a consequence of previous studies or background knowledge and It utilises observed data to inform prior knowledge (Rezaeian, Dunn, Leger, & Appleby, 2007). The Bayesian analysis assumed a prior distribution for the spatial random effects which took into consideration the neighbourhood (spatial) correlation structure of the LGAs. A non-informative Gaussian prior distribution was specified for β's with a mean of zero, a variance of 1000 and a precision of 1×10^{-5}, while a uniform prior distribution was assigned for β_0 (Best, Richardson, & Thomson, 2005; Wakefield, Best, & Waller, 2000).

The non-spatially structured random effects between LGAs $v_i = (v_1\ldots\ldots v_n)$, were independent of one another and it is assumed to have an independent Gaussian distribution with a mean of zero and a variance $\sigma^2 v_i$. This non-spatial extra-Poisson variation was assigned to follow an inverse Gamma distribution of $1/\sigma^2 v_i \sim$ gamma $(0.5, 5 \times 10^{-4})$ as suggested by Best et al., (2005) and Wakefield et al., (2000). The model usually included the variance ($\sigma^2 v_i$) to compensate for the extra-Poisson variation as a result of important covariates that were not measured by the model but which could influence the relative risk of TB (Best et al., 2005; Randremanana et al.,

2010; Souza et al., 2007). The spatially structured random effects, $u_i = (u_1 \ldots u_n)$ accounted for spatial correlation between the spatial unit and contiguous adjacent spatial units or neighbouring areas. The term "neighbourhood" is defined as adjacent LGAs with simple binary adjacency weights. Though the adjacency matrix or weight matrix structure was defined in this study as two regions that share a boundary (adjacency based neighbourhood structure), another method of defining neighbourhood structure is the distance-based neighbourhood spatial weight approach where the distances between the centroids of the polygons or areas are used as weights. Best, Cockings, Bennett, & Wakefield, (2001) compared both methods in their analysis of benzene emissions and the incidence of leukaemia in Greater London. They found that adjacency-based neighbourhood spatial weights provided a better fit to their data compared to a distance-based neighbourhood structure. Though the adjacency method has the advantage that the distances that define neighbourhood do not need to be defined, the method is limited if the spatial areas differ significantly in size or shape in which case some areas only share boundaries with a few neighbours. Earnest et al., (2007) found that the distance-based models performed better when the aim of a study is the identification of areas of elevated risk or when the aim is to explain the spatial relationship in the relative risk estimates. However, the study suggested that adjacency-based approach may be preferable if the aim of the study is to preserve the spatial structure of the relative risk and examine the relationship between covariates that are spatially structured. Therefore this study used the adjacency method to examine the relationship between covariates which were spatially structured.

The relative risks of adjacent LGAs were more similar than the risk for more distant LGAs. The mean value for ui is the weighted average of the neighbouring

random effects and the variance σ^2_{ui} is the spatial extra-Poisson variation which controlled the strength of this local spatial dependence. The Gaussian intrinsic conditional auto regression (CAR) model proposed by Besag et al., (1991) was used to specify the spatial correlation term u_i:

$$\rho(u_i \ / \ u_{j, \ j \neq i}) \sim N\left(\frac{\Sigma j \neq i \ Wij \ ui}{\Sigma j \neq i \ Wij}, \frac{\sigma 2ui}{\Sigma j \neq i \ Wij}\right)\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (9)$$

W_{ij} is defined as 1 if LGAs i and j share a common boundary *and* $W_{ij} = 0$ if otherwise. The spatial extra-Poisson variation is assumed to follow a similar inverse Gamma distribution of $1/\sigma^2 \nu_i \sim$ gamma (0.5, 5 x 10^{-4}) as proposed by Wakefield et al, (2000). The spatial variance ratio, described by Harling & Castro (2014) and Best et al. (2005) is the ratio of

$$\frac{spatial \ variance}{spatial \ variance + non-spatial \ effect} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (10)$$

It is a measure of the relative contribution of the spatial and non-spatial effects to the total variance in the data. If the value of the spatial variance ratio was close to unity (1) then the spatial random effects dominates the total variation in the data while a value close to zero showed that the spatial variation in the data was insignificant (Best et al., 2005).

5.5.7 Integrated Nested Laplace Approximation (INLA) analysis

The first model fitted in INLA is the spatially unstructured heterogeneity model which reflects the simple random effect term (Model 0). Model 1, termed the convolution model is specified by adding a spatially structured intrinsic conditional auto regression term to the spatially unstructured heterogeneity random effect term in Model 0. Model 2 involved the addition of the composite socioeconomic index to the convolution model. The addition of all the socioeconomic covariates such as

household size, living in single room and access to transport to the convolution model constituted Model 3. Model 4 was the addition of demographic covariates (urban residence and population density) to Model 3. The full model (Model 5) consisted of the addition of all covariates into a convolution model while Model 6 was the full Model 5 fitted with only spatially unstructured random effects to ascertain if the data fits better than the full model with all covariates in Model 5.

The output of the models included the Deviance Information Criterion (DIC) and effective parameter (pD) and a fixed effect intercept. Also, the exponentiated posterior mean of the covariates is interpreted as the residual risks for TB with a 95% Credible Interval (CrI) after the covariates has been accounted for. The spatial variance ratio is the ratio of the variance explained by structured spatial (CAR) component divided by the unstructured spatial variance. The result of the final spatial model containing all explanatory variables is mapped to display the overall risk, spatial risk and the associated spatial exceedance or the level of uncertainty associated with the spatial risk greater than 1.

The goodness of fit of the Bayesian models is determined by DIC values and number of effective parameters (P_D). The model with the lowest DIC values represented a better fit model while the model with the lowest value of the number of effective parameter (P_D) is the most parsimonious model. Models with a DIC value of within 1-2 of the 'best' model were regarded as strongly supported by the data while a DIC value of between 3-7 from the 'best' model were weakly supported and a DIC of more than 7 from the 'best' model showed a poorer model compared with the 'best' model (Spiegelhalter, Best, Carlin, & van der Linde, 2002).

CHAPTER 6: Results

This chapter presents the results of the analysis conducted. This is divided into four sections which are descriptive analysis, non-spatial analysis with the use of Poisson and quasi-Poisson regression models, exploratory spatial analysis with the use of global and local Moran I test and the spatial regression analysis with the use of Bayesian conditional auto regression analysis in R-INLA.

6.1   Descriptive analysis

The histogram of TB case notification rate in Nigeria, 2013 is outlined in Figure 6 which reveals a skewed distribution typical of count data. The TB CNR ranged from 0-592/100,000. The majority of the LGAs had a TB CNR that was less than 100/100,000 pop. Similarly, Figure 7 presents the map of the case notification rate in Nigeria in 2013 with the highest rates in the north central and the north east geopolitical zones.
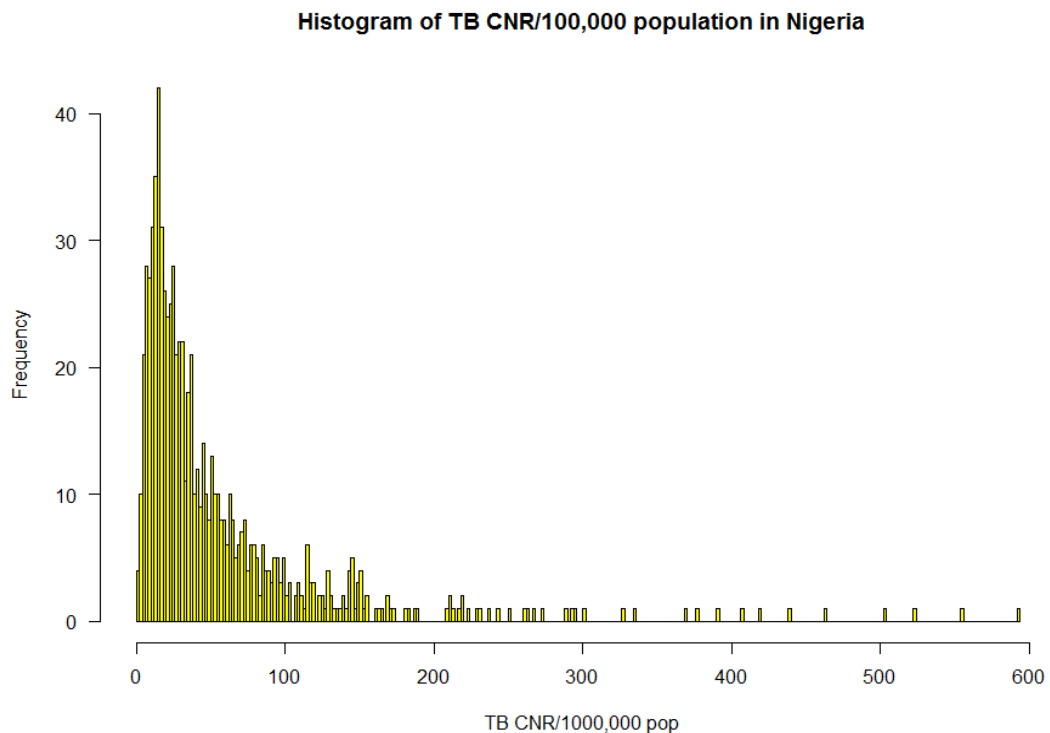

Figure 6: Histogram of TB Case notification rates in Nigeria, 2013
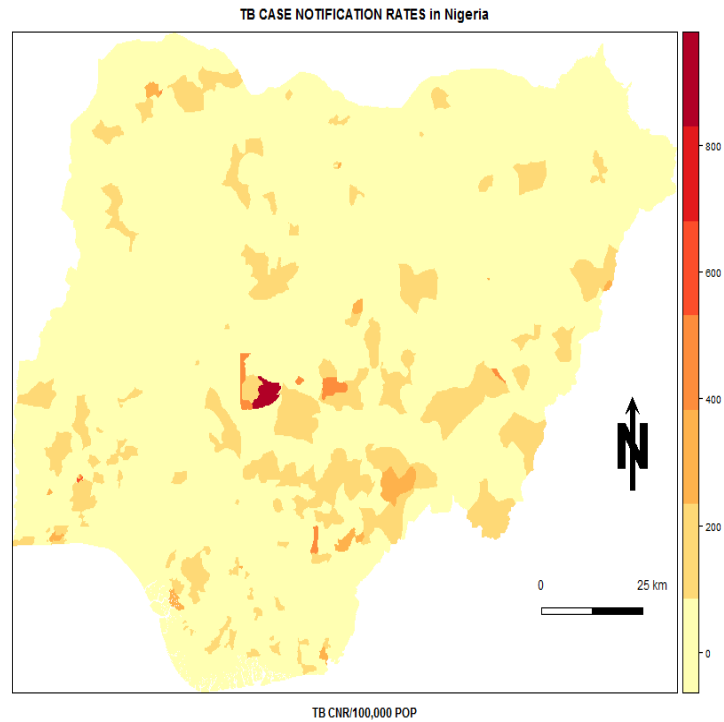
Figure 7: TB case notification rates in Nigeria, 2013

Figure 8 and 9 displays the histogram and the map of the raw unsmoothed Standardized Notification Ratio (SNR) for TB in Nigeria, 2013. The SNR is the ratio between the observed TB counts divided by the expected TB counts multiplied by 100 for each LGA. It estimates the risk of TB relative to the average risk of the entire LGAs in the country. It highlights the LGAs with high risk of TB greater than the national average of 100. The SNR ranged from 0-1042. The majority of the LGAs had a TB SNR below 100. A total of 227(29.3%) LGAs have an unsmoothed relative risk (SNR) above 100. The LGAs with the highest SNR are located in the north central, the north east, south west and south-south geopolitical zones.
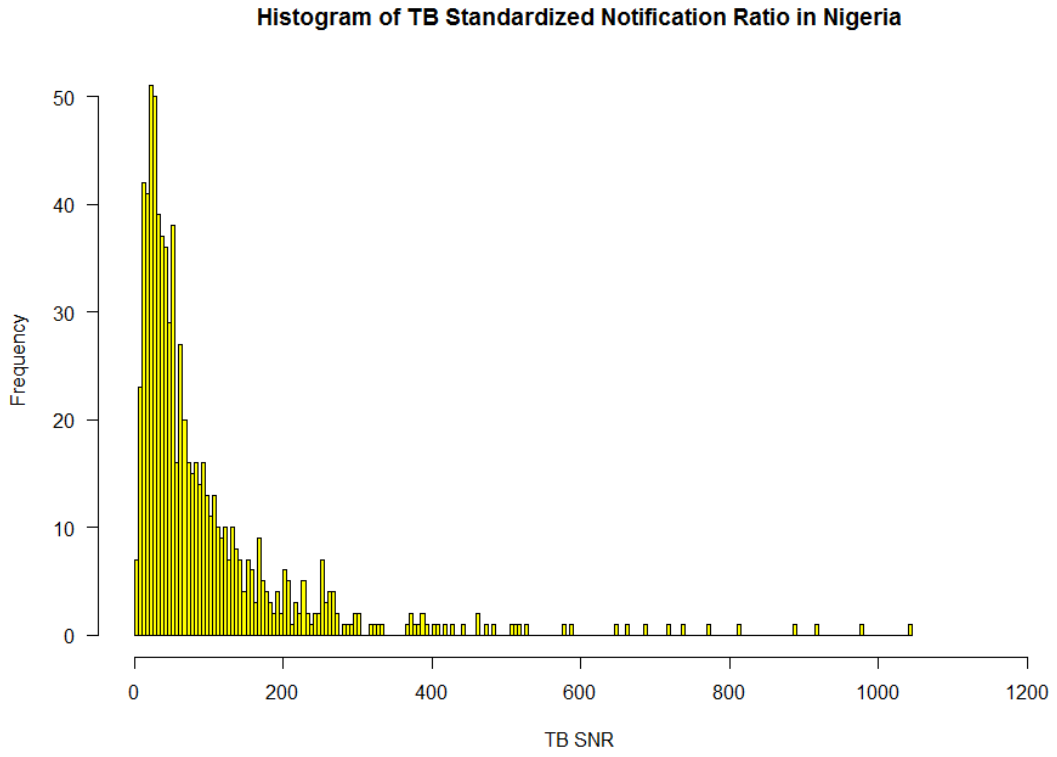
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Histogram of TB Standardized Notification Ratio in Nigeria

Figure 8: Histogram of the standardized notification ratio for TB in Nigeria, 2013.
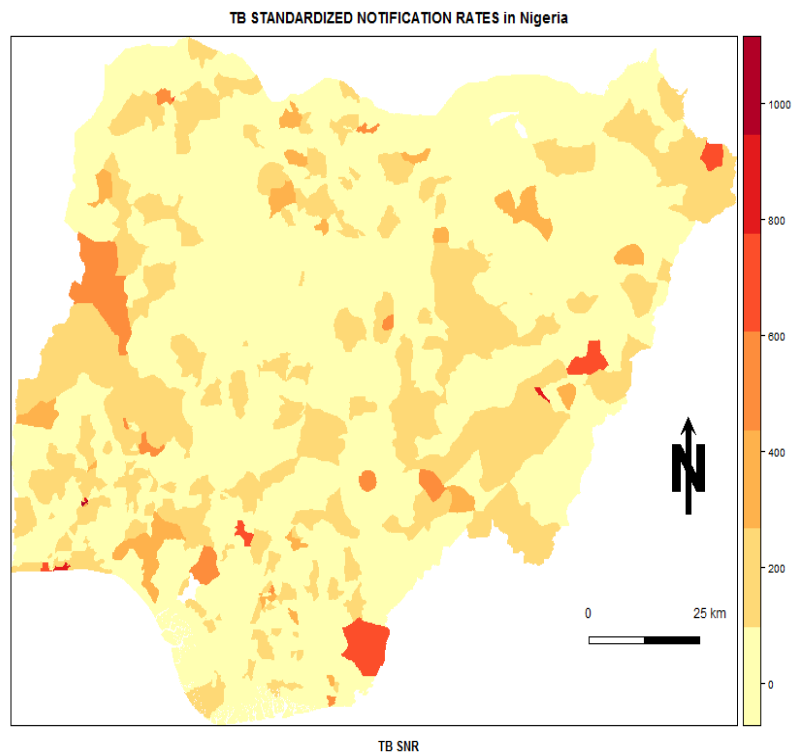

Figure 9: Standardized notification ratio for TB in Nigeria, 2013.

Variation in the standardized socioeconomic index (SSEI) in Nigeria is mapped in Figure 10. The closer the value of the SSEI is to 100, the more affluent the LGAs. Generally LGAs in the south are more affluent compared with LGAs in the north.
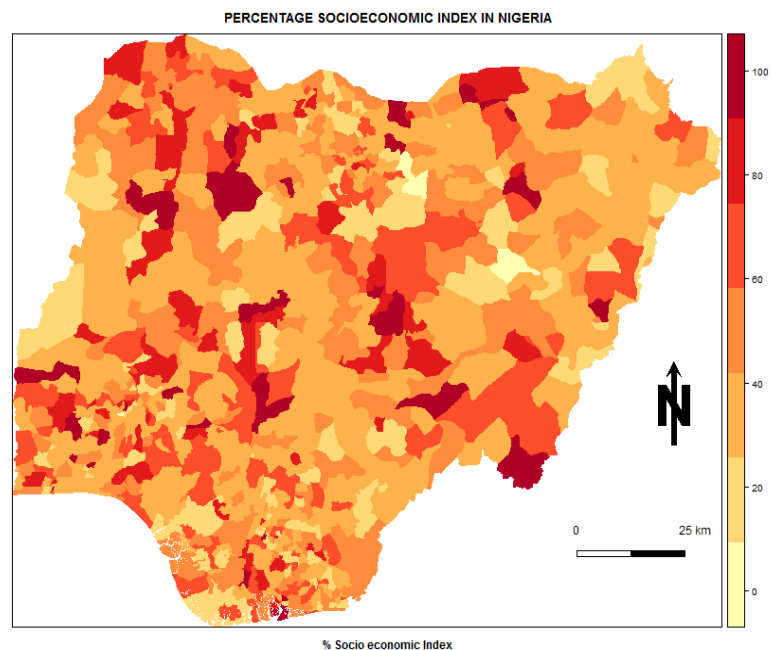

Figure 10: Standardized socioeconomic index of LGAs in Nigeria

Access to transportation (Figure 11) is better in the south compared to the northern part of the country while living in urban residence (Figure 12) is generally more in the south than the north. The northern part of the country generally has a higher mean household size (Figure 13) and households living in a single room (Figure 14) compared with the southern part of the country. The distribution of AFB microscopy centres (Figure 15) were more in the LGAs in the North Central and North East while TB treatment centres (Figure 16) were more in the south compared to the north. The total health facilities (Figure 17) in the country were more in the South West and North central geopolitical zone.
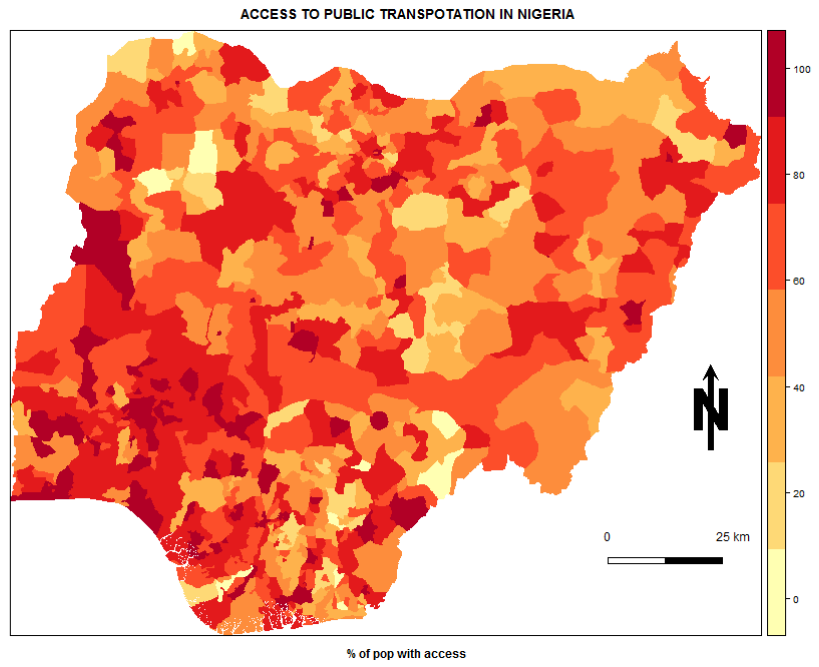
Figure 11: Access to public transportation in Nigeria
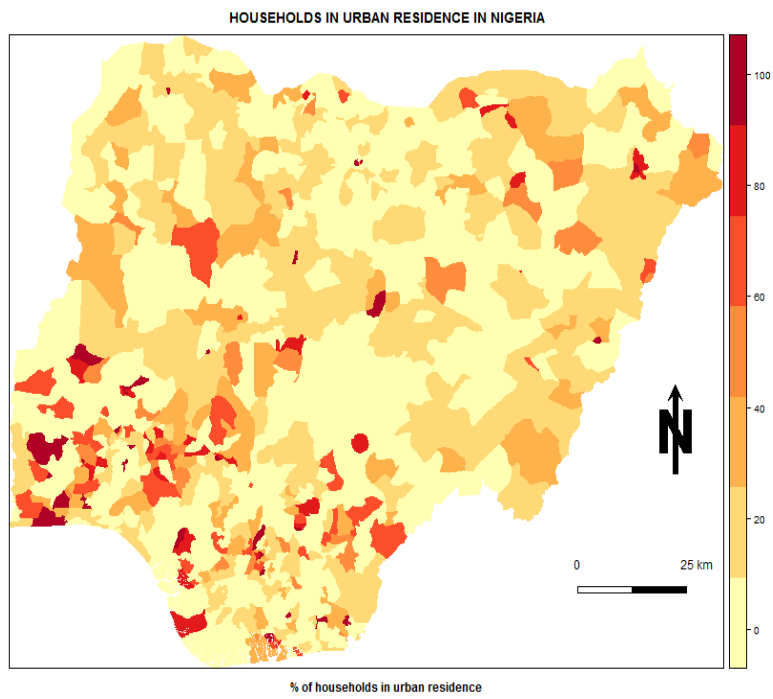

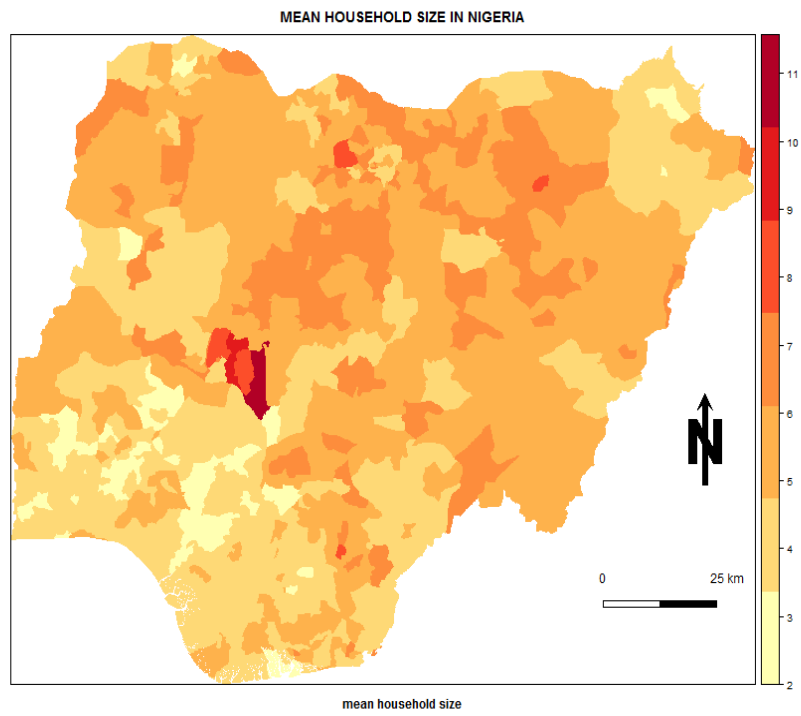**Figure 12:** Percentage of households that reside in urban areas in Nigeria

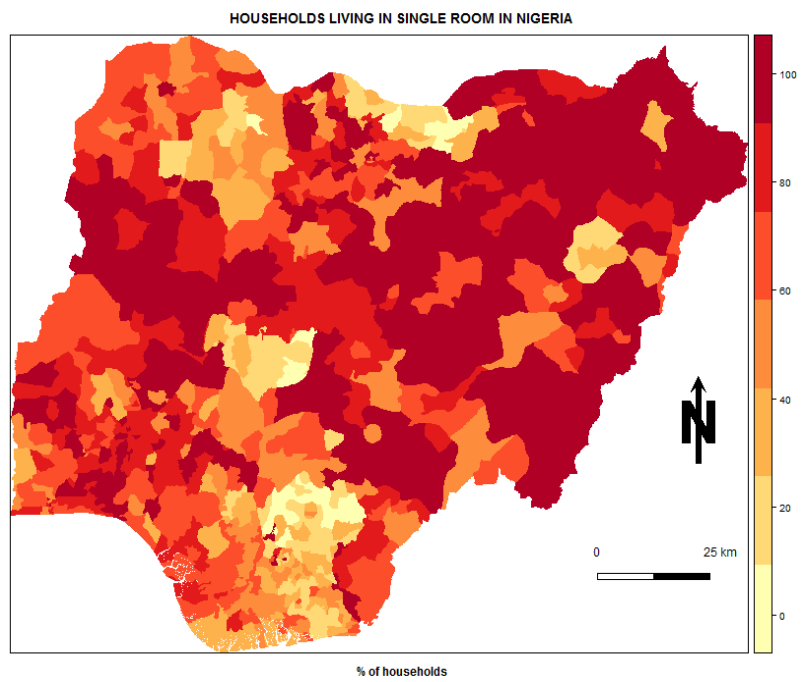**Figure 13:** Mean household size across the LGAs in Nigeria

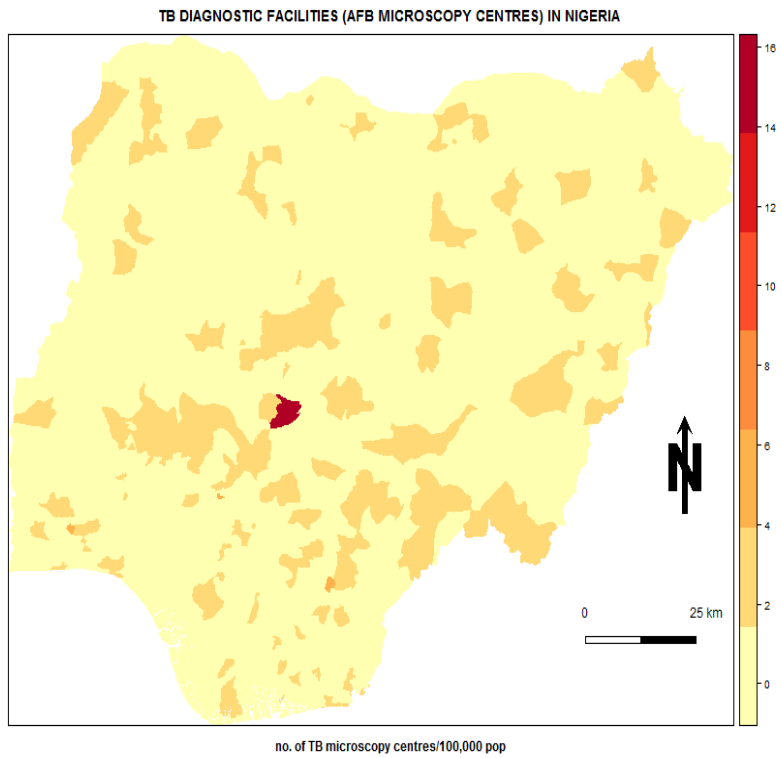**Figure 14:** Percentage of households living in a single room in Nigeria.

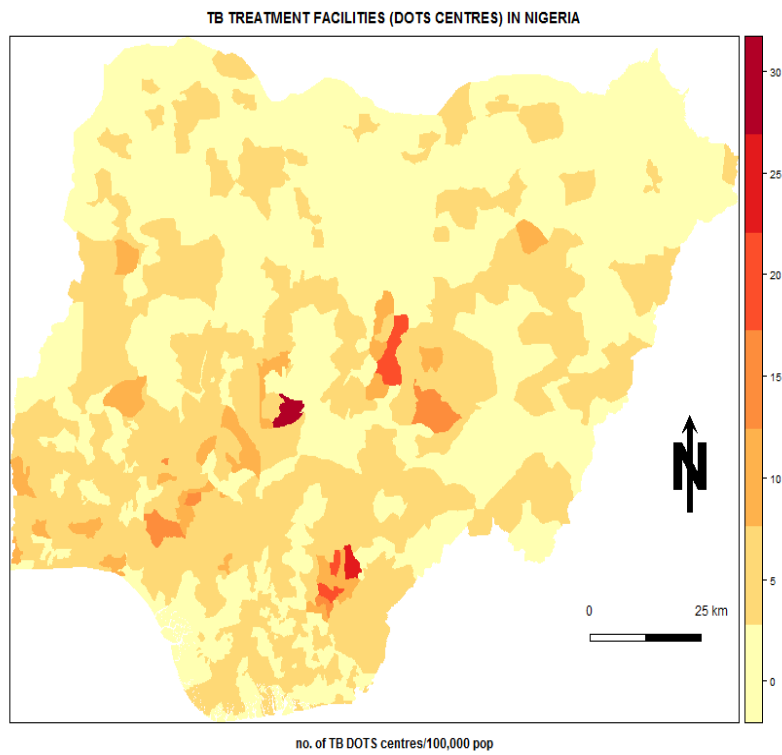**Figure 15:** TB diagnostic facilities per 100,000 population in Nigeria

Figure 16: TB treatment centres per 100,000 population in Nigeria

HEALTH FACILITIES IN NIGERIA

no. of health facilities/100,000 pop
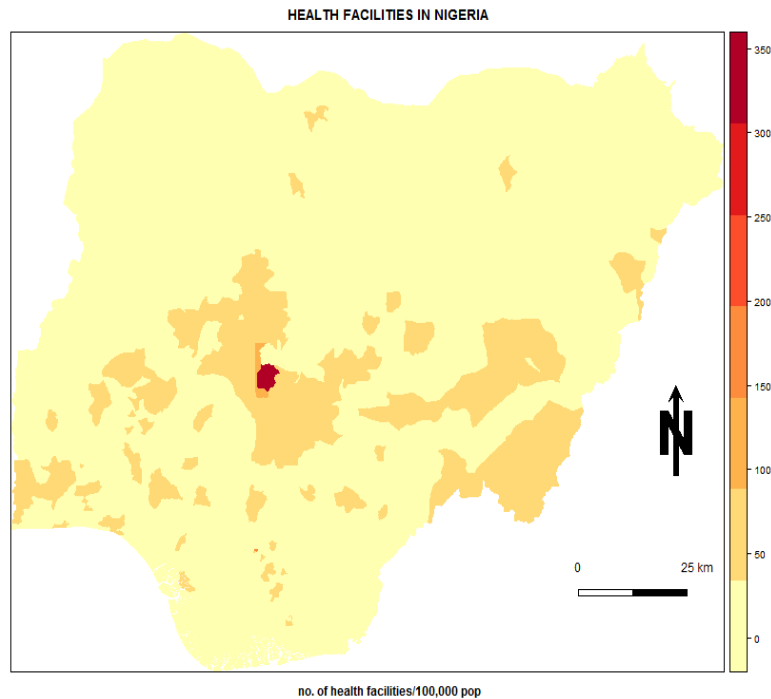
Figure 17: Total number of health facilities per 100,000 population in Nigeria

6.2 Non-spatial analysis of TB and explanatory variables

Poisson regression model is commonly used for the analysis of count data (Coxe, West, & Aiken, 2009). Therefore a Poisson regression model is fitted with TB count as the response variable. The outlier (Kuje LGA) was excluded before fitting the data into the Poisson regression model because of a very high TB CNR which may distort the results of the analysis. The covariates added to the model includes percentage of households living in a single room, percentage of households that have access to public transportation, number of microscopy per/100,000 population, number of TB treatment centres/100,000 population and the total number of health facilities/100,000 population. The output of the model is presented in Table 9. All the explanatory variables are significantly associated with TB. However, a strong interaction is observed between the composite socioeconomic index (SEI) and urban residence. When the interaction term (urban*SEI) is added to the model, the composite SEI no

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longer shows a statistically significant relationship and the coefficient estimate becomes negative (-0.0004127; p=0.123). There is substantial over-dispersion in the data considering that the residual variance is higher than the degree of freedom and therefore greater than one. This suggests that the standard errors of the estimates are incorrect. Consequently, the data is fitted into a quasi-Poisson regression model to correct the estimate and account for the unobserved variation among observations (Ver Hoef & Boveng, 2013). The output of the quasi-Poisson model is shown in Table 10. The coefficient estimates in Table 9 and 10 are the same but standard errors, Z-values and the P-values of Table 10 are significantly reduced compared to Table 9.

To assess the contribution of each of the statistically significant explanatory variable on TB, the coefficient estimates are exponentiated to produce an incidence rate ratio (IRR) which is a measure of the risk associated with the covariates. For example the coefficient estimate for urban residence was 0.0071 and the exponentiated value is 1.007, which means that a 1 percentage point increase in the proportion of household living in urban areas will lead to 0.7% increase in the risk of TB. Similarly, the exponentiated coefficient estimate for population density is 1.299 which indicates that a one unit increase in the population density will lead to a 30% increase in the relative risk of TB. A unit increase in mean household size will lead to a 17% increase in TB risk, while a one unit increase in AFB microscopic centre will lead to 31% increase in TB. On the other hand a one unit increase in DOTS treatment centre will lead to a decrease of 1.8% in the risk of TB, though this relationship is not statistically significant. In the quasi-Poisson regression model, the composite socioeconomic index, health facilities/100,000 population and the DOTS treatment centres/100,000 population are no longer significantly associated with TB compared to the standard Poisson regression model.

Table 9: Poisson regression model for TB and explanatory variables

Variable name	Estimate	Standard error	Z-value	P value	Sig. level
Intercept	1.7301	0.0301	35.68	<0.0001	Sig***
Composite Socioeconomic index	0.0027	0.0002	14.49	<0.0001	Sig***
Percentage of households living in urban area	0.0071	0.0001	60.08	<0.0001	Sig***
Population Density per km^2	0.2620	0.0026	100.60	<0.0001	Sig***
Mean household size	0.1585	0.0029	53.99	<0.0001	Sig***
Percentage of households living in one room apartment	0.0062	0.0001	47.20	<0.0001	Sig***
Access to public transportation	0.0053	0.0002	31.43	<0.0001	Sig***
AFB microscopic facilities per 100,000 pop.	0.2706	0.0051	52.70	<0.0001	Sig***
Health facilities per100,000 pop.	0.0023	0.0002	16.07	<0.0001	Sig***
DOTS treatment facilities per 100,000 pop.	-0.0186	0.0002	-12.46	<0.0001	Sig***

Residual deviance 80568 on 763 degree of freedom; AIC, 85225; Sig *** signifies   significant levels

at p<0.00001.

Table 10: Quasi-Poisson regression model for TB and explanatory variables

Variable name	Estimate	Standard error	t-value	P value	Sig. level
Intercept	1.0730	0.0366	2.933	0.0035	Sig**
Composite Socioeconomic index	0.0027	0.0023	1.191	0.2339	NS
Percentage of households living in urban area	0.0071	0.0014	4.939	<0.0001	Sig***
Population Density per km^2	0.2620	0.0316	8.270	<0.0001	Sig***
Mean household size	0.1585	0.0357	4.438	<0.0001	Sig***
Percentage of households living in one room apartment	0.00621	0.0016	3.880	<0.0001	Sig***
Access to public transportation	0.0053	0.0021	2.584	<0.01	Sig**
AFB microscopic facilities per 100,000 pop.	0.2705	0.0625	4.333	<0.0001	Sig***
Health facilities per100,000 pop.	0.0023	0.0021	1.321	0.1869	NS
DOTS treatment facilities per 100,000 pop.	-0.0186	0.0182	-1.024	0.3060	NS

Residual deviance 80568 on 763 degree of freedom; Sig *** signifies significant levels at p<0.0001;

Sig** P<0.01; NS not significant

6.3 Exploratory spatial analysis

The use of crude standardised incidence or notification ratio for disease mapping may be misleading especially for small areas and or rare diseases because of unstable risk estimates (Elliott & Wartenberg, 2004). In addition, the non-spatial analyses (Poisson and quasi-Poisson regression models) assume that variables are spatially independent which may also lead to incorrect estimates in the presence of spatial dependency in the data. To establish the presence of spatial autocorrelation, the Global and local Moran's I test statistics are used to explore spatial dependency in the data.

Table 11 shows the result of the Global Moran's I index in the three scenarios which are the Moran's I test under randomization, under normality and using Monte Carlo simulation. The Global Moran's test measures the degree to which LGAs with similar TB CNR are spatially close to each other. A positive Moran's I value of 0.109004 was obtained in the Moran's I test under randomization (with the assumption that Moran's I was normally distributed). This suggests that LGAs with above average values for TB CNR are near each other. The P value of $p < 0.00001$ for the Global Moran's I test is highly statistically significant implying the presence of some degree of global spatial dependency in the data. The Monte Carlo simulation approach is also used to calculate the Moran's I test with 1:10001 numbers of simulations. The value of 0.13 also suggests a positive spatial autocorrelation which indicates that TB CNR is similar among neighbouring LGAs compared to non-neighbouring LGAs.

Table 11: Global Moran's *I* statistic for spatial autocorrelation of TB case notification rate in Nigeria, 2013.

Characteristics	Moran's I test under randomization	Two directional Moran's I test under normality	Monte –Carlo simulation of Moran's I
Moran's *I* statistic	0.13	0.13	0.13
Expectation	-0.001	-0.001	
Variance	0.0005	0.0005	
P value	0.0001	0.0001	0.01

Figure 18 displays the Moran's scatterplot between TB CNR and the spatial lag of TB CNR. This is the correlation between TB CNR and spatial lag of the CNR (which is computed by averaging the values of TB CNR from all the neighbouring LGAs). The slope of the regression line is the Moran's *I* statistic which also shows a positive spatial autocorrelation.
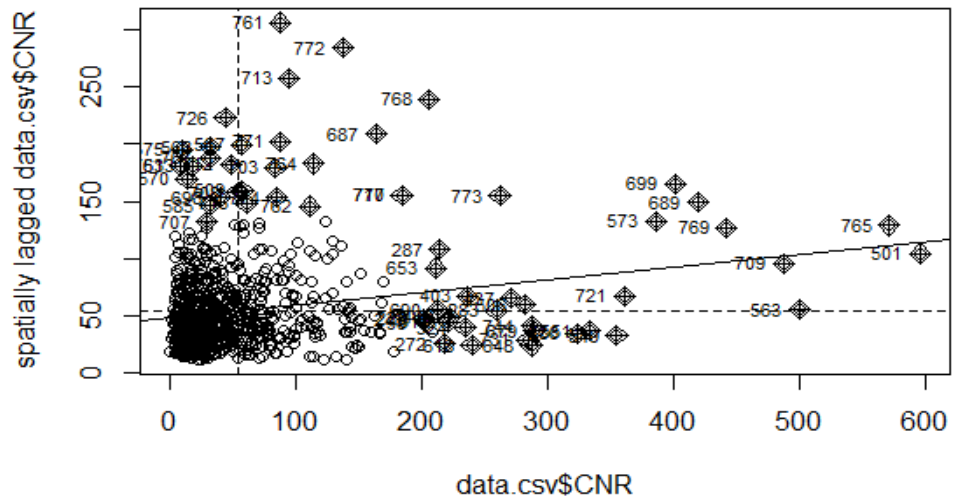
Figure 18: Moran's *1* scatterplot on TB case notification rate in Nigeria, 2013

Following a significant Global Moran test, the local indicator spatial autocorrelation (LISA) is utilised to explore local clustering of TB. Figure 19 shows the map of local spatial clustering of the dependent variable TB CNR. The map shows significant clustering of TB in 19 LGAs in the country. These LGAs are located in Lagos (Lagos Mainland), Oyo (Oluyole, Ibadan North, Ibadan North East, Ibadan North West, Ibadan South West, and Ibadan South East), Cross river (Calabar South), Benue (Ukum and Katsina Ala) Taraba (Ardo kola and Jalingo), Nasarawa (Nasarawa egon and Nasarawa) Federal Capital Territorry (Abaji, Kwali and Kuje) and Sokoto (Wamakko and Sokoto South) states. These LGAs are primarily urban, densely populated areas and in states with a high HIV prevalence rates.

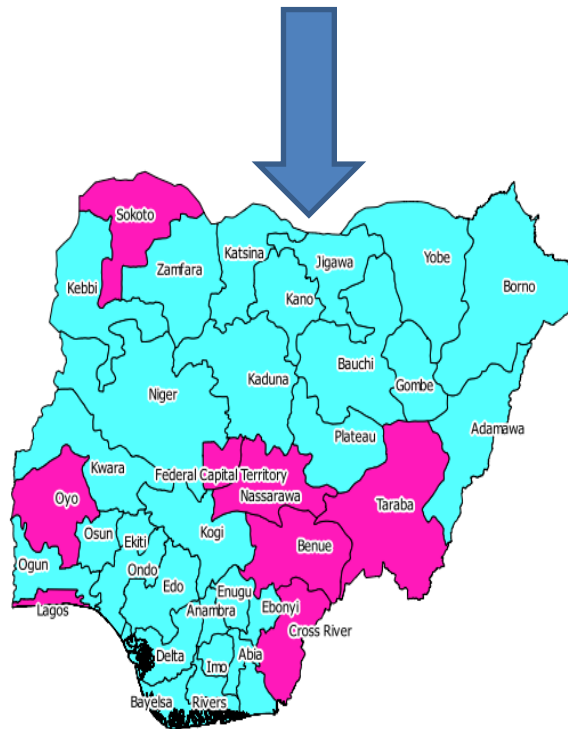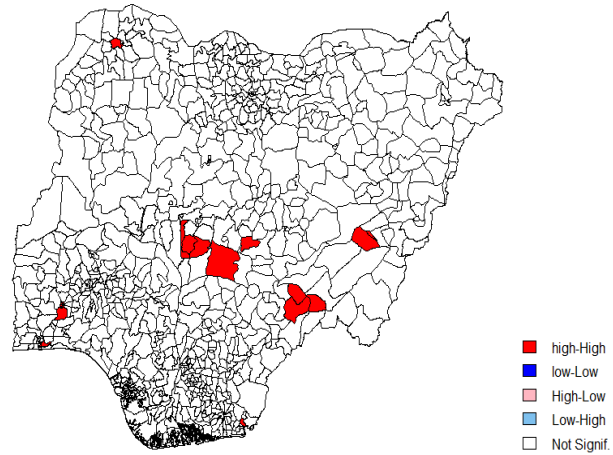LISA Cluster Map of TB CASE NOTIFICATION RATE IN NIGERIA

Figure 19: LGAs with significant clusters for TB CNR in Nigeria and the States where the LGAs are located.

6.4 Spatial regression analysis of TB

The analysis so far shows that some of the explanatory variables such as mean household size, living in one room apartment, having access to public transportation, living in urban area, population density and AFB microscopic facilities per 100,000 populations are significantly associated with TB in the non-spatial analysis. In addition, the global and local autocorrelation analysis reveals a spatial dependency in TB case notification rate in the country. In addition, the use of spatial autocorrelation techniques is only exploratory and will require the use of more rigorous spatial regression techniques to determine accurate estimates of disease risk. Consequently, a spatial regression model is developed that includes all the explanatory variables and incorporates spatial random effects to allow for spatial heterogeneity and spatial correlation in the data. A Bayesian hierarchical conditional auto regression model in R-INLA is used for this purpose with the added advantage that it can identify LGAs with increased risk of TB (DiMaggio, 2014; D. Lee, 2013).

The output of the Bayesian conditional auto regression model is shown in Table 12. The table is a summary of the posterior median, standard deviation and the 95% credible interval (CrI) of the covariate effects on TB in Nigeria, 2013. The table illustrates that household crowding, population density, urban residence and the number of TB diagnostic centres per capita are significant predictors of TB because the 95% credible interval did not cross zero. The composite socioeconomic index and the number of DOTS TB treatment facilities per capita are inversely related to TB CNR though the associations are not statistically significant. Conversely, the percentage of households living in a single room and the total number of health facilities are positively related but not significantly associated with TB CNR.

Table 12: Summary statistics of the posterior mean, posterior standard deviation, interquartile range and the 95% credible interval for the fixed effects of the convolution model with all covariates (Model 5).

Variable name	Mean (SD)	2.5%	50%	97.5%	Remark
intercept	0.8970 (0.3524)	0.2046	0.8971	1.5881	
Composite Socioeconomic index	-0.0007 (0.0019)	-0.0045	-0.0007	0.0030	NS
Percentage of households in urban residence	0.0066 (0.0014)	0.0039	0.0066	0.0094	Sig
Log (Population Density) per km^2	0.3328 (0.0396)	0.2551	0.3328	0.4106	Sig
Mean household size	0.0826 (0.0401)	0.0038	0.0826	0.1614	Sig
Percentage of households living in single room	0.0028 (0.0016)	-0.0002	0.0028	0.0059	NS
Access to public transportation	0.0074 (0.0017)	0.0040	0.0074	0.0108	Sig
Health facilities per100,000 pop.	0.0012 (0.0023)	-0.0032	0.0012	0.0056	NS
DOTS treatment facilities per 100,000 pop.	-0.0174 (0.0143)	-0.0455	-0.0174	0.0106	NS
AFB microscopic facilities per 100,000 pop.	0.2083 (0.0461)	0.1178	0.2083	0.2986	Sig

Sig = shows statistical significance NS = not statistically significant

Table 9, presents the exponentiated fixed effects of regression coefficient estimates of the explanatory variables in the Bayesian conditional auto regression model (Models 0-5) in INLA which are interpreted as the relative risk of TB for one standard deviation increase in each independent variable value. The different models in the spatial regression analysis are outlined in section 6.4.1 - 6.4.4 below. This procedure is well described in the literatures (Blangiardo, Cameletti, Baio, & Rue, 2013; DiMaggio, 2014; D. Lee, 2013)

6.4.1 The spatially unstructured heterogeneity model.

The baseline model (model 0) in Table 9 shows the simple random effect term or the spatially unstructured heterogeneity model without covariates. The DIC for the baseline model is 6179.19 and has an effective parameter (P_D) of 756.52. The output of the fixed model presents only the exponentiated mean of the intercept which is 64.86 ± 1.04 per 100,000 populations (95% CI 59.71-70.45). This is the average tuberculosis case notification rate across the country.

6.4.2 The Convolution or Besag York and Mollie (BYM) Model

The convolution or intrinsic conditional auto regression model (ICAR) or Model 1 in Table 9 is the null spatial random effects model which includes both spatial and non-spatial random effects but without the inclusion of covariates. The output also displays only one fixed effect which is the intercept. This also describes the average risk of TB across all LGAs in 2013. The DIC for the baseline convoluted model is 6173.30 (P_D751.79).

6.4.3 Addition of Covariates to the Convolution model

In Model 2, the composite socioeconomic index is added to the previous convolution (Model 1). The composite socioeconomic index did not exhibit a significant effect on TB case notification rate (1.000, 95% CrI 0.996 - 1.005). The DIC of 6173.33 (P_D751.83) is about the same with the convolution model.

In Model 3, three other socioeconomic variables are added to the composite socioeconomic index which are mean household size, households living in single room and access to public transportation. The addition of mean household size (1.063, 95% CrI 0.973-1.160) and the percentage of households living in one room apartment (1.002, 95% CrI 0.998-1.005) show no effect on the risk of TB and does not change the effect of socioeconomic index (1.001, 95% CI 0.996-1.005). However, there is a

positive significant association between access to public transportation and relative risk of TB (1.015, 95% CrI 1.012-1.019). The DIC of 6173.33 (P_D751.83) is about the same with the convolution model.

In Model 4, two demographic explanatory variables (households living in urban areas and the log of population density) are added to the model 3. There is a slight improvement in the DIC of 6172.97 with fewer effect parameters of 747.42. Urban residence (1.007, 95% CrI 1.004-1.010) and population density are significantly associated with TB (1.377, 95% CrI 1.274-1.488) while access to public transportation maintained a positive significant relationship with TB (1.008, 95% CrI 1.005-1.011). The addition of the demographic variables to model 3 changed the direction of the socioeconomic index 0.999 (95% CrI 0.995-1.003) suggesting that LGAs with a high socioeconomic index had a low TB risk. This relationship is however not statistically significant.

Model 5 is the addition of the health related explanatory variables which are number of TB microscopy services per 100,000 population, total number of health facilities (public and private) per 100,000 population and number of DOTS treatment centres to Model 4. The model shows that the mean household size (1.086, 95% CrI 1.004-1.175), access to public transportation (1.007, 95% CrI 1.004-1.011), household living in urban areas (1.007, 95% CrI 1.004-1.009), areas of high population density (1.395, 95% CrI 1.291-1.394), and the number of TB microscopy services per 100,000 populations (1.23195% CrI 1.125-1.348) are all important predictors of TB. The number of DOTS treatment centres shows a negative relationship with TB though the relationship is not significant (0.983, 95% CI 0.955-1.011) while the total number of health facilities (public and private) per 100,000 population in the LGA is positively related to TB CNR but the relationship is not statistically significant (1.001, (95% CrI

0.997-1.006). However, total health facilities per 100,000 pop and the percentage of households living in a single room apartment, which were significantly associated with TB in the non-spatial analysis, are no longer significant risk factors in the Bayesian spatial regression analysis.

Based on the DIC in Table 13, the best fit model is model 4 which has the lowest DIC of 6172.97. However, the difference in the DIC between models 2 to 5 when covariates are added to the conditional auto regression (CAR) model is quite small (less than 1). This suggests that models 2-5 are equally supported by the data and perform similarly in capturing the varying spatial risk.

The full model (Model 5) is selected for subsequent analysis because it contains all the explanatory variables for this study and it has the lowest number of effective parameters (746.21) compared to the other models. This model includes the convolution model with both spatially unstructured (random effect term) and the spatially structured (conditional auto regression term) in addition to the socioeconomic (composite socioeconomic index, percentage of household living in single room and mean household size), demographic (percentage of households living in urban and population density) and health related (number of AFB microscopy centres per capita, number of TB treatment centres per capita and total number of health facilities per capita) explanatory covariates.

In Model 5, a unit increase in the number of microscopes per 100,000 populations will increase the residual relative risk of TB by 23.1% if all other explanatory variables are held at zero. Also an increase in mean household size by one unit is estimated to increase the risk of TB by 9%. Furthermore, an increase of one unit in the percentage of households living in urban areas will increase TB risk by 1% while an increase in population density by one unit will increase relative risk of TB by 40%.

6.4.4   Addition of Covariates to the non-spatial random effect model

Model 6 is introduced to ascertain if the addition of only spatially unstructured random effects and all the covariates fits the data better than when both unstructured and structured spatial effects and all covariates are fitted into the model (Model 5). There is a general reduction in the relative risk estimates in Model 5 compared with Model 6 for all covariates. The DIC of Model 6 is 6181.42 which is higher than 6173.38 of Model 5. The difference is greater than 7 which suggest that Model 6 is inferior to Model 5. In addition Model 5 is more parsimonious than Model 6 because of a lower number of effective parameter (746.21) compared to Model 6 (751.79). Consequently, Model 5 was selected as the best model over Model 6 because it shows that after adjusting for the covariates, there is still some spatial heterogeneity in the data which might be captured by the spatial random effects. Subsequently, the introduction of spatial effects improves the model.

The range of the spatial variance ratio is 48.3% - 54.3% between Model 1 and Model 5 which signifies that total variation is fairly dominated by the spatial effects. There is a reduction in the spatial variance ratio from 54.3% in the null model (Model 1) to 48.3% in the full model (Model 5). There is also a reduction by about 32% in the spatial variance from 73.4% in the null spatial model (Model 1) to 50.2% in the full model (Model 5) when all the covariates are added to the model which indicates that between 50.2% - 73.4% of the variability in the model is explained by the spatial structure and therefore showed fairly strong spatial heterogeneity. The non-spatially structured effect also shows some reduction between Model 1 and Model 5 by 14% (0.6188 to 0.5366) which suggests that the inclusion of the covariates also explains part of the over dispersion in the data.

In summary, the inclusion of spatial effects into the model improves the model compared to the unstructured spatial and the non-spatial Poisson regression models. TB is significantly associated with household size, access to transportation, living in a single room, living in urban residence, population density and the number of AFB microscopy diagnostic centres in spatial regression analysis.

Table 13: Multivariable spatial regression analysis for TB and explanatory variables in Nigeria, 2013

Variable name	Model 0 RR (95% CrI)	Model 1 RR (95% CrI)	Model 2 RR (95% CrI)	Model 3 RR (95% CrI)	Model 4 RR (95% CrI)	Model 5 RR (95% CrI)	Model 6 RR (95% CrI)
Intercept	64.86 ±1.04 (59.71-70.45)	64.80 ±1.03 (61.22-68.57)	63.96 ±1.11 (52.36-78.12)	16.68 ±1.35 (9.29-29.92)	3.17 ±1.41 (1.62-6.17)	2.45 ±1.42 (1.23-4.89)	2.28 ±1.40 (1.17-4.44)
Socioeconomic factors							
Composite Socioeconomic index			1.000 (0.996-1.005)	0.999 (0.995-1.003)	0.999 (0.995-1.003)	0.999 (0.996-1.003)	1.001 (0.996-1.005)
Mean household size				1.063 (0.973-1.160)	1.081 (0.997-1.170)	**1.086 (1.004-1.175)**	**1.161 (1.086-1.242)**
Percentage of households living in single room				1.002 (0.998-1.005)	1.002 (0.999-1.005)	1.003 (0.999-1.006)	**1.007 (1.004-1.009)**
Access to public transportation				**1.015 (1.012-1.019)**	**1.008 (1.005-1.011)**	**1.007 (1.004-1.011)**	**1.005 (1.001-1.008)**
Demographic factors							
Percentage of households in urban residence					**1.007 (1.004-1.010)**	**1.007 (1.004-1.009)**	**1.009 (1.006-1.012)**
Log (Population Density) per km^2					**1.377 (1.274-1.488)**	**1.395 (1.291-1.494)**	**1.269 (1.190-1.395)**
Health/medical factors							
AFB microscopic facilities/100,000 pop.						**1.231 (1.125-1.348)**	**1.289 (1.166-1.425)**
Health facilities per 100,000 pop.						1.001 (0.997-1.006)	1.004 (0.999-1.009)
DOTS treatment facilities/100,000 pop.						0.983 (0.955-1.011)	0.982 (0.955-1.010)
Spatial structured variance		0.7343	0.7461	0.6568	0.5345	0.5020	-
LGA level unstructured variance		0.6188	0.6196	0.5864	0.5510	0.5366	-
Spatially variance ratio		0.5427	0.5430	0.5283	0.4924	0.4833	-
DIC (P$_D$)	6179.19 (756.52)	6173.30 (751.79)	6173.33 (751.83)	6173.25 (750.28)	6172.74 (746.74)	6173.38 (746.21)	6181.42 (751.79)
Maximum log-likelihood	-4460	-4262.08	-4271.64	-4262.44	-4208.08	-4220.80	-4416.87

CrI= Credible interval. Model 0=non- spatial random effect only; Model 1= intrinsic CAR model only; Model 2= intrinsic CAR + composite socioeconomic status; Model 3= Intrinsic CAR + 4 socioeconomic factors; Model 4= Intrinsic CAR + 4 socioeconomic factors + 2 demographic factors; Model 5= Intrinsic CAR + 4 socioeconomic factors + 2 demographic factors +3 health/medical factors; Model 6= non-spatial random effect + 4 socioeconomic factors + 2 demographic factors +3 health/medical factors.

The map of the Bayesian spatial CAR or Besag York Mollie (BYM) model of fitted Standardized Notification Ratio (SNR) estimates without covariates is presented in Figure 20. The SNR in this analysis is the ratio of the local fitted values predicted by the model and the expected counts. The map represents the spatial pattern of the observed relative risk of TB in all the LGAs and provides a more stable estimate of the pattern of underlying risk of tuberculosis by deriving information from neighbouring LGAs and thus smoothing the local SNR towards the values in neighbouring LGAs. The map reveals LGAs with higher or lower TB risk. The white coloured area (0.6-0.9) reveals LGAs that have between 10-40% risk for TB below the national average for Nigeria in 2013. This is followed by the LGAs shaded in light grey (0.9-1) which highlights LGAs that have 1-10% risk of TB below the national average for Nigeria in 2013. The dark-grey areas (1.0-1.1) represent LGAs where the risk of TB is between 1-10% greater than the national average for Nigeria in 2013 while the black areas (1.1-1.8) are LGAs which have between 10-80% risks of TB above the national average for 2013. About 13% (100) LGAs have a relative risk between 1-1.8 while 5% of LGAs have relative risk of TB between 1-1.1 and 2% of LGAs have relative risk of between 0.9-1. About 15.1% of LGAs have relative risk of between 0.6-0.9.

The posterior probability associated with the smoothed relative risk of TB SNR without covariates (Figure 21) based on the map of the conditional auto regression model in Figure 20, provides information on the strength of the evidence of the excess risk >1 for each LGA. The exceedance probability of an LGA is the posterior probability that the spatial risk is greater than 1. The black coloured areas display LGAs where there is more than 80% probability of the relative risk being higher than the national average. The LGAs coloured with dark grey colours (0.2-0.4) highlights

LGAs where the certainty of exceedance >1 is between 20-40% and the light grey areas are where there is no statistical certainty whether there is increase or decrease in relative risk. About 42% of the LGAs have a high posterior probability of greater than 80% that the TB SNR exceeds 1.

The spatially structured estimates or smoothed relative risk for TB Standardised Notification Ratio (SNR) after adjusting for the socioeconomic, demographic and health-related covariates in Nigeria, 2013 is presented in Figure 22. The adjustment for covariates produced noticeable changes in the spatial pattern of TB in the LGAs. About 138 (17%) LGAs have a relative risk of greater than 1.1 These LGAs are scattered around the country and not concentrated in any particular state or geopolitical zone. However some states have more TB high risk LGAs compared to others. The number of LGAs in states in the South West geopolitical zone includes: Osun (10), Oyo (8), Ogun (5), Lagos (2), Ekiti (2), Ondo (2); South East geopolitical zone: Enugu (4), Anambra (3), Abia (2), Ebonyi (2), Imo (2); South-South geopolitical zone: Akwa Ibom (10), Rivers (5), Delta (3), Cross river (3), Edo (2); North Central geopolitical zone: Benue (7), Kwara (6), Kogi (4), Plateau (4), Niger (3), Nasarawa (2), FCT (2); North West geopolitical zone: Kaduna (7), Kebbi (6), Kano (4), Jigawa (4), Sokoto (4), Katsina (3); North East geopolitical zone: Adamawa (8), Bauchi (3), Taraba (2), Borno (2), Yobe (2).

In summary, 29 LGAs have TB risk greater than 1 in South-West, 28 in North-Central, 27 in North West, 23 in South-South, 17 in North-East and 13 in the South East geopolitical zones. The reasons for the high TB risk in these LGAs are probably due to a variety of factors. The states in the North Central geopolitical zones (Nasarawa, Benue, FCT and Plateau) have high HIV prevalence. While states in the South-West geopolitical zone (Lagos, Oyo and Ogun) are industrial and commercial

states with a high rural-urban migration and the development of urban slum areas. In the South-South geopolitical zone (Akwa Ibom, Delta and Rivers) also have a high HIV prevalence in addition to a lot of petroleum exploration activities that may predispose to TB. The states in the North-west and Northeast geopolitical zone have the worst poverty indices in the country. Figure 23 presents the percentage of LGAs with TB SNR >1 in figure 22 in each of the states of the country. Akwa Ibom state has the highest percentage (58.8%) of high TB risk LGAs in the country followed by Adamawa (38.1%), Kwara (37.5%), Federal Capital Territory (33.3%), Osun (32.3%), Benue (30.4%) and Kaduna (30.4 %) states. Three states (Bayelsa, Gombe and Zamfara) have no LGA with a high risk of TB. The observed local patterns in this study can be further explored in subsequent studies with the of generalised weighted regression or a spatial model with varying rather than a constant regression coefficients over the LGAs assumed by the CAR model (Gelfand, Kim, Sirmans, & Banerjee, 2003).

The posterior probability of the SNR exceeding 1 in each LGA based on Figure 22 is presented in Figure 24. A posterior probability of 0.8 and above (black) signifies LGAs with a relatively high level of associated certainty (80%) with SNR exceeding 1 while the light areas (0-0.2) signifies LGAs with a wide level of uncertainty associated with the SNR exceeding 1. About 43% of LGAs have a posterior probability of 0.8 and above which signifies a relatively high level of associated certainty in the values of the SNR exceeding 1 in Figure 22.
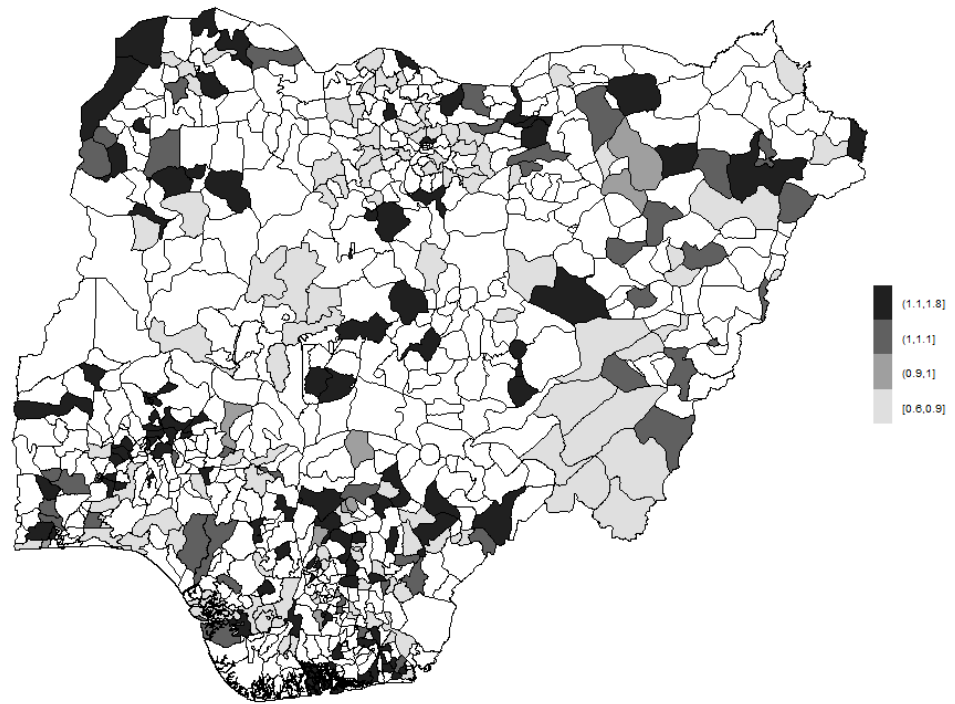
Figure 20: Spatially structured estimates for TB SNR without covariates

Posterior probability associated with the smoothed relative risk of TB SNR based on the CAR regression model without covariates
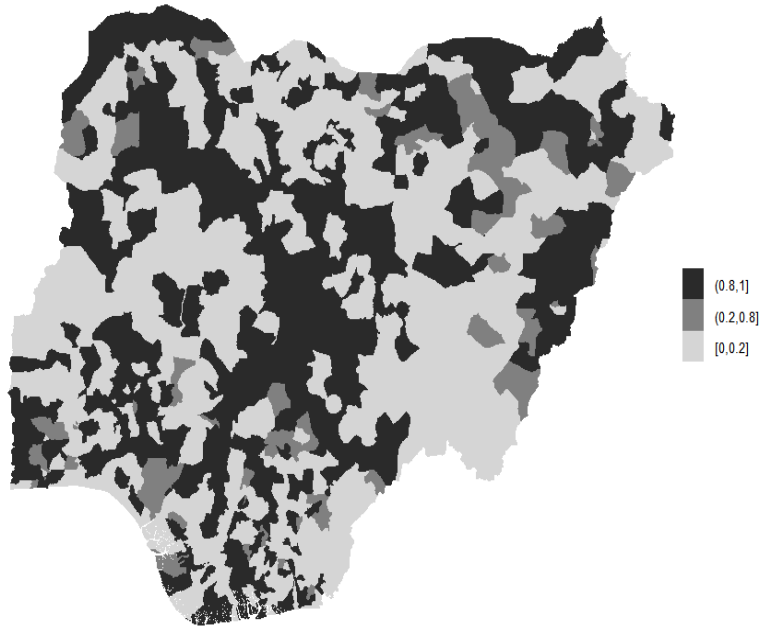
Figure 21: Posterior probability associated with the smoothed relative risk of TB SNR based on the CAR regression model without covariates

Figure 22: Spatially structured estimates for TB SNR after adjustment for the covariates, in Nigeria.

Figure 23: Percentage of LGAs with TB SNR >1 in the 37 States in Nigeria

Posterior probability of the TB SNR exceeding or >1 after adjustment for covariates, in Nigeria

(0.8,1]
(0.2,0.8]
[0,0.2]

Figure 24: Posterior probability of the TB SNR exceeding or >1 after adjustment for covariates, in Nigeria.
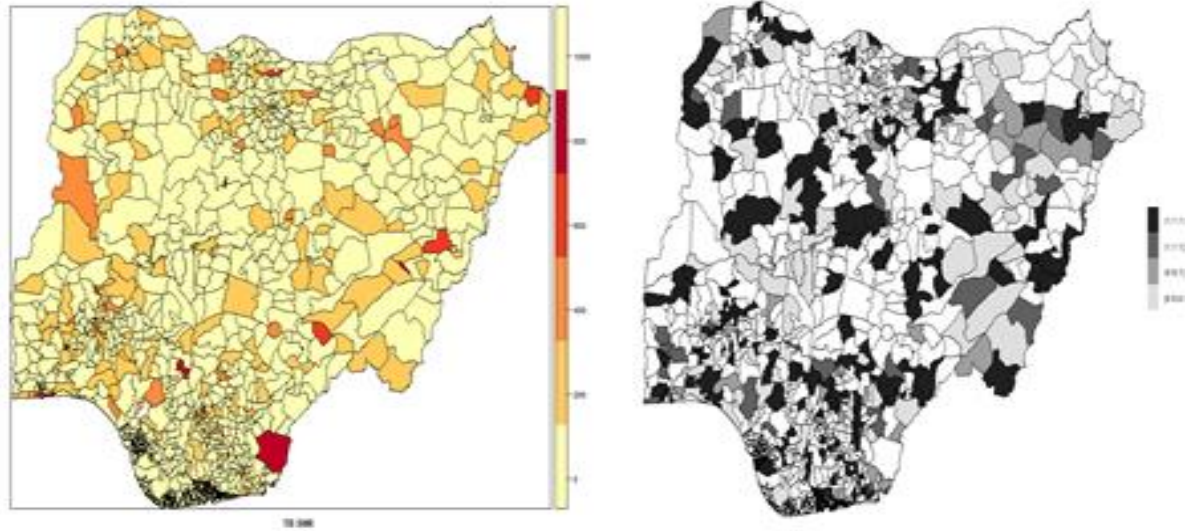
Figure 25: Comparative relative risk estimates for TB SNR for the unsmoothed (left) and the smoothed Besag York and Mollie model in INLA (right).
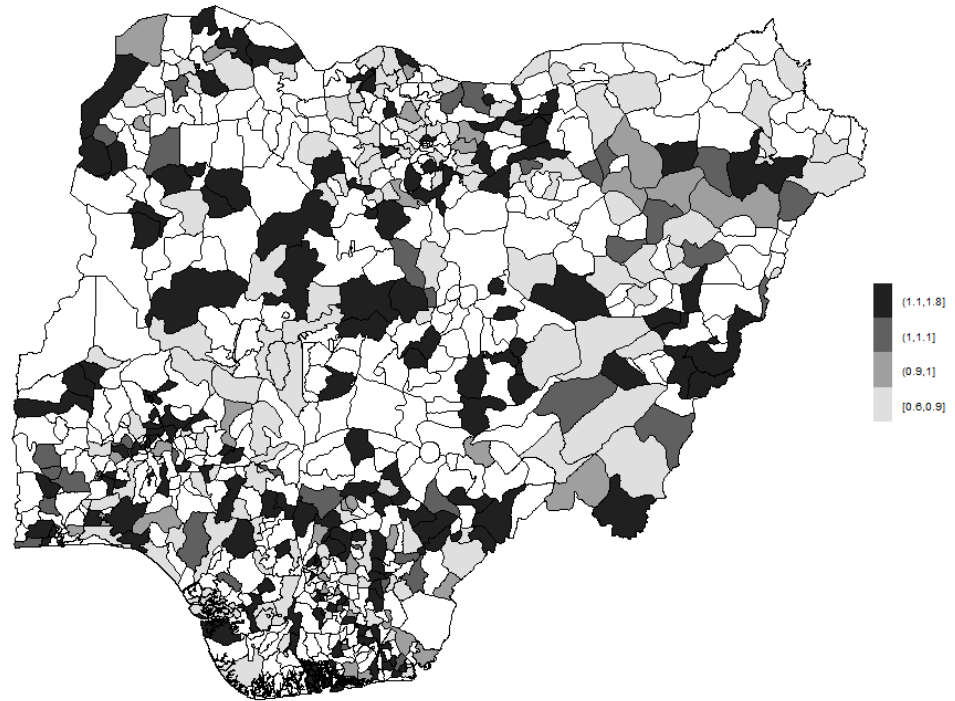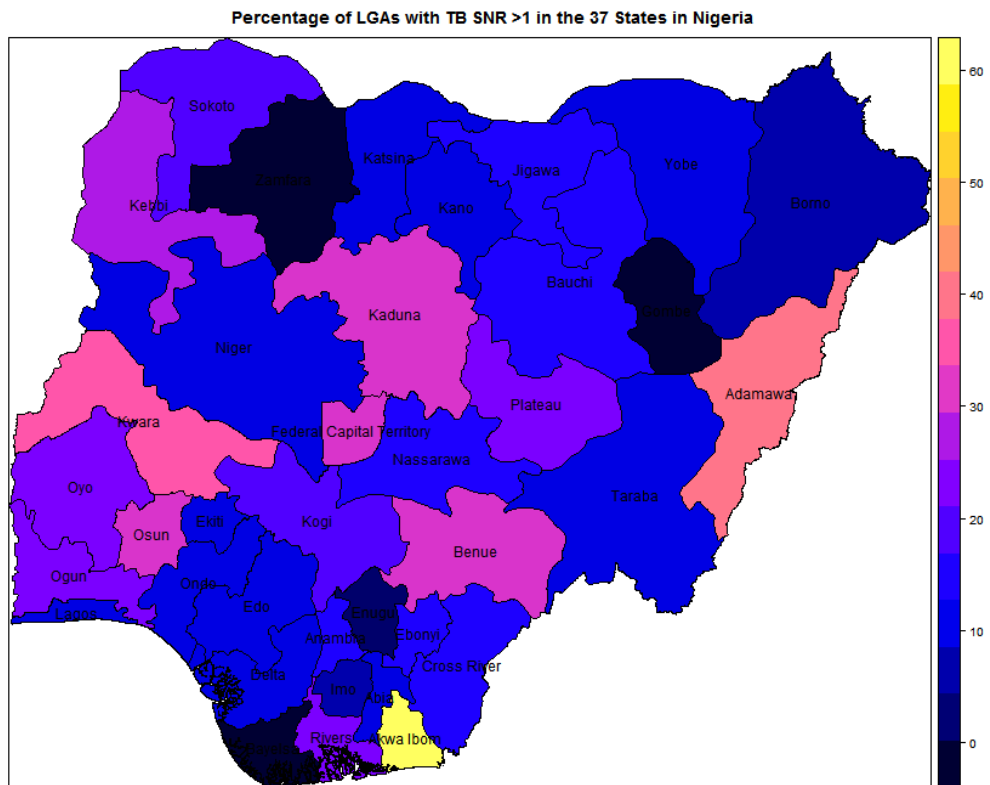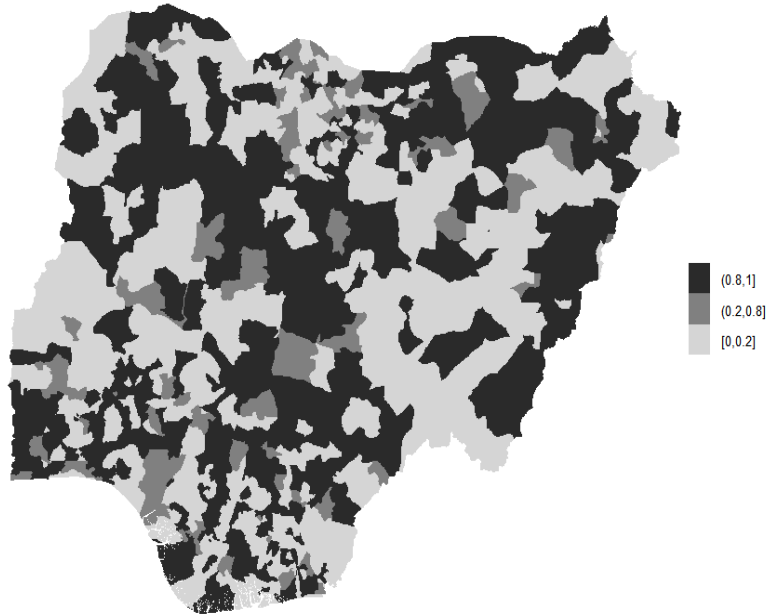
Figure 25 displays a comparative map of relative risk estimates for TB Standardized Notification Ratio (SNR) for the raw (unsmoothed) SNR on the left and the smoothed SNR estimate from the Besag York and Mollie (BYM) model in INLA on the right. The BYM map shows considerable smoothing of the SNR and provides a more reliable rate adjusted towards the mean of the neighbouring rates while the unsmoothed SNR may present a misleading picture especially in small geographic areas by producing unstable rates while in the BYM model only 17% of LGAs had a relative risk of more than 1 compared to 29.3% of LGAs in the unsmoothed SNR which suggests substantial shrinkage of the relative risk estimates to eliminate random noise and control for sampling variation. Some LGAs that have a high or low risk in the raw SNR now seems to have an average risk and some show unusually high risk.

The BYM model gives a more precise estimate and truly identifies LGA with high TB risk compared with the unsmooth SNR. In addition, it quantifies the risk and adjusts for the influence of covariates and spatial random effects in the data.

CHAPTER 7: Discussion

The conceptual underpinning in this study is that income inequality shaped by structural, political, and economic processes determines the observed health gradient in society through intermediary social factors or social determinants of health (SDH). The SDH are responsible for the differences that occur in risk exposure, vulnerability and the ability to recover after being ill with TB due to the socioeconomic position of individuals within the social hierarchy in society. This study was designed to assess the relationship between TB and area-based socioeconomic status and other proxy variables such as household size, access to public transportation, urban residence, population density, access to TB diagnostic centres, access to TB treatment services and access to health services generally.

This study was conducted on a national scale at the 774 LGAs and allowed for the first time the spatial visualisation, exploration and modelling of TB variation at the lowest administrative level in Nigeria. The result of this research showed that TB was spatially clustered in Nigeria and there were significant relationships between household size, access to public transportation, urban residence, population density, access to AFB microscopy diagnostic centres and tuberculosis. However, the composite asset-based socioeconomic index and the number of TB treatment centres and total health facilities per 100,000 populations were not significantly associated with TB.

This chapter will discuss the findings of this study in relation to the objectives of this research and conclude with the strengths and limitations of the study.

Non-spatial regression analysis of TB

The non-spatial analysis showed a significant relationship between TB and household size, access to transportation, living in a single room, living in urban residence,

population density, the number of AFB microscopy diagnostic centres. The asset-based socioeconomic index, the number of DOTS treatment centres and the total health facilities per 100,000 populations were not significantly associated with TB. The significant factors associated with TB during non-spatial analysis will be discussed in detail later on in this chapter.

Spatial autocorrelation of TB using Global and Local Moran's statistics

Initial exploratory spatial analysis was conducted with the Global Moran's *I* test and the local indicator of spatial autocorrelation (LISA). The analysis showed a positive global spatial autocorrelation and a local spatial dependence of TB in the country. Significant local spatial clustering of TB was observed in 19 LGAs within eight states (Lagos, Oyo, Cross River, Benue, Taraba, Nasarawa Sokoto and the Federal Capital Territory). The LGAs identified in Lagos and Oyo states were urban, densely populated industrial/commercial areas with a significant urban slum population (Olalekan, 2014). Cross River, Benue, Taraba, Nasarawa and FCT are states with high HIV prevalence rates above the national average (Djukpen, 2012) while Sokoto state has one of the highest poverty rates in the country (NBS, 2012). The presence of spatial dependency of TB during exploratory spatial analysis suggest the need for fitting a spatial regression model with covariates that will explain the spatial variation of TB and identify the factors significantly associated with the spatial variation of TB in Nigeria.

Spatial regression analysis of TB

The spatial regression model showed a true spatial heterogeneity of TB in Nigeria after controlling for the effects of the covariates included in the model. The addition of the covariates explained part of the spatial structure of TB and the over dispersion observed in the data, yet there was still unexplained variance attributed to important

risk factors related to TB that were not captured by our model. The smoothed map identified 138 (17%) LGAs with a high TB risk above the national average which involved all the six geopolitical zones and 34 of the 37 states. The LGAs with a high TB risk above the national average were concentrated in seven states which had over a third of their LGAs with SNR>1. These states were: Akwa Ibom (58.8%), Adamawa (38.1%), Kwara (37.5%), Federal Capital Territory (33.3%), Osun (32.3%), Benue (30.4%) and Kaduna (30.4 %). Fourteen states had less than a third of their LGAs with SNR>1 while three states (Bayelsa, Gombe and Zamfara) had no LGA with a high risk of TB.

The study revealed a more widespread TB pattern at the first administrative level in the country that was not localised to any particular state or geopolitical zone. However, earlier studies on spatial distribution of disease or health related events in the country have reported a more localised pattern such as the studies on the spatial distribution of childhood mortality (Uthman, Aiyedun, & Yahaya, 2012), childhood stunting (Adekanmbi, Uthman, & Mudasiru, 2013) and HIV prevalence (Djukpen, 2012; Oyediran & Cunningham, 2014) in Nigeria. The observed widespread pattern of TB in this study may be as a result of the spatial unit (LGAs) used in this study in contrast to the state-level analysis employed by other studies. This study is the first study on spatial analysis of health and health related event on a national scale at the LGA level in Nigeria and buttresses the point that the LGAs within a state are not homogenous entities but rather showed marked differences in economic, cultural, environmental and social characteristics that may determine the distribution of risk factors for the development of TB.

Spatial regression analysis showed that TB was significantly associated with household size, access to public transportation, urban residence, population density

and the number of AFB microscopy diagnostic centres per 100,000 populations while the composite asset-based socioeconomic index, proportion of households living in single rooms and the number of TB treatment centres and total health facilities per 100,000 populations were not significantly associated with TB.

TB and socioeconomic index

This study developed a composite asset-based socioeconomic index to measure area-based socioeconomic status at the LGAs with the use of principal component analysis (PCA). The PCA approach has been reported to have a reasonable agreement with household consumption expenditures (Filmer & Pritchett, 2001; Gwatkin, Rutstein, Johnson, Suliman, Wagstaff , 2000; Vyas & Kumaranayake, 2006) and has been utilised as a relative measure of socioeconomic status in studies comparing socioeconomic inequalities within and between countries in Africa (Montgomery et al., 2000; Vyas & Kumaranayake, 2006). The composite asset-based socioeconomic index showed an inverse relationship with TB although the relationship was not significant. This finding was in contrast to studies conducted in Africa (Boccia et al., 2013; Harling et al., 2008) and elsewhere (Harling & Castro, 2014; Souza et al., 2007; Roza et al., 2012; Muniyandi et al., 2007; Oxlade & Murray, 2012) that found a significant inverse relationship between TB and area-level socioeconomic status (SES). In addition, studies conducted at the individual level in Africa have also showed mixed evidence on the association between TB and SES. The study conducted in Zambia (Boccia et al., 2011) found an inverse association between TB and individual level SES while other studies found no significant relationship between TB and socioeconomic indices (Cramm et al., 2011; Lienhardt et al., 2005). Some studies indeed observed a positive relationship between high socioeconomic indices and high TB rates (Glynn et al., 2000; Boccia et al., 2009; Odone et al., 2013).

The lack of conclusive evidence on the traditional inverse relationship between TB and area-level socioeconomic indices as demonstrated in this study and elsewhere in Africa has brought into focus whether the indicators used to assess area-level socioeconomic status in high income countries were appropriate for countries in sub-Saharan Africa since there are differences in the social, economic and cultural characteristics between high and low income countries (Lienhardt et al., 2005). Boccia et al. (2013) also argued that there may be inherent bias in the composite indices used to compute the area-level based SES as some of the variables were in themselves risk factors associated with TB and therefore can lead to overestimation of SES especially in urban areas. Harling et al. (2008) were of the opinion that the increasing income inequality experienced in Africa and the interwoven nature of African society's, may have increased the likelihood of TB transmission between individuals with higher and lower SES as a result of increased contact, which may obliterate the expected inverse relationship between SES and TB. Hossain et al. (2012) found that TB patients captured by routine surveillance were more from higher SES because of access to TB diagnostic services while TB patients identified during a community based prevalence survey at the same time were more from the lower SES. The study concluded that data from routine surveillance may not be suitable to assess the effect of socioeconomic status on TB. There is therefore the need for the Federal Governments of Nigeria to invest in the collection of accurate household income and consumption expenditure data that reflects the actual economic situation in the country. In the short term, data on variables that capture standards of living conditions can be incorporated into ongoing surveys at little or no additional cost and this will provide information on the current economic reality in the country especially at the Local Governments Area level.

TB and household size

A positive relationship between household size and TB was observed in this study. Household crowding has been identified as a risk factor for the development of TB both in high income countries (Baker et al., 2008; Clark et al., 2002; Harling & Castro, 2014;Souza et al., 2007) and in Africa (Munch et al., 2003). However, Boccia et al. (2011) and Leung et al. (2004) did not find a significant association between TB and household overcrowding in Malawi and Hong Kong respectively. Household crowding increases the shared space among household members and the possibility of contact between infected TB patients and susceptible persons thereby increase the risk of exposure to TB infection and disease. This study documents a 9 percentage point increase in the risk of TB with a one unit increase in the average number of persons in a household. This is similar to the 11.4% increase by Harling & Castro (2014). However, Souza et al. (2007) reported a 94% risk of TB with an increase in household size by one person.

TB and public transportation

One interesting finding in this study was that TB was positively associated with access to public transportation. There are two competing hypotheses on the relationship between TB and public transportation that needs to be examined further: the first hypothesis is that public transportation increases the risk of exposure to TB through close contact in crowded poorly ventilated public transportation while the second is that better access to public transportation improve access to TB diagnostic services and therefore better notification. The potential for the transmission of TB in public transportation has been described in the literatures especially in regions with a high TB burden in Europe (Edelson & Phypers, 2011; Mohr et al., 2012; Oliver Mohr et al., 2015). Some studies in Africa have also suggested that crowded transportation

could be a potential risk factor for the transmission of TB (Glynn et al., 2000; Odone et al., 2013) though these claims are yet to be substantiated by empirical research. There is the need for further research to examine the role of public transportation in the transmission of TB.

The second hypothesis suggest that LGAs that had better access to public transportation were more likely to have better access to TB diagnostic services and therefore more likely for TB to be diagnosed and notified compared with LGAs that had poor access to public transportation. Hossain et al. (2012) observed that a large proportion of TB patients in rural areas remained undiagnosed because of lack of access to health care services which made them sought alternative care from non-licensed providers, pharmacies and private practitioners. In addition, the long distances travelled by patients seeking care together with the attendant transportation cost to health facilities may serve as barrier to TB diagnosis (Barter et al., 2012) which could lead to on-going transmission of TB in the community. Furthermore, there may be underreporting of TB cases in LGAs with many hard to reach communities with limited transportation as a result of the difficult terrain or poor road network to these communities (Lorent, Choun, Malhotra, & Koeut, 2015). These facilities in these hard to reach areas were usually poorly supervised, records poorly updated mainly because trained health care workers do not reside in these communities due to lack of basic infrastructure and amenities and because of the poor access to these facilities by road.

TB and microscopy diagnostic services

The study observed that TB was associated with the number of microscopy centres per capita (which suggests better access to TB diagnostic services). This finding may have confirmed by spatial regression analysis the earlier significant correlation found

between high TB rates and a high number of microscopy services in other studies (Dangisso, Datiko, & Lindtjørn, 2015; Obasanya et al., 2015). This study observed that a unit increase in the number of microscopy centre per capita will increase TB risk by 23%. The use of sputum smear microscopy has been the cornerstone of the National Tuberculosis Control Programme for TB diagnosis and is the most widely available means of TB diagnosis in the country (FMoH, 2010). However, issues have been raised concerning the sensitivity of sputum smear microscopy in the diagnosis of TB which has been shown to vary from 0-80% (Parsons et al., 2011). The sensitivity may be further reduced in HIV positive patients suspected of TB and in children due to low bacillary load in their sputum (Getahun, Harrington, O'Brien, & Nunn, 2007). This may lead to underestimation of the burden of TB especially in LGAs with a high HIV positivity rate. However, the use of more sensitive technologies such as Gene xpert MTB/Rif and LED microscopy recently being introduced as point of care diagnostics will improve the diagnosis of TB in the country (Parsons et al., 2011).

On the other hand, the low TB case notification rates in LGAs with low microscopy services may not reflect the true burden of disease in these LGAs. The current national guideline for TB diagnosis requires that sputum samples are collected over a minimum period of two days after which the patient is expected to visit the laboratory for collection of the result of the investigation. The patients are therefore required to make repeated visits at a cost that patients may not be able to afford. Ukwaja, Alobu, Nweke, & Onyenwe (2013) estimated a median of three visits to the health facility before the diagnosis of TB was made. Cambanis et al. (2005) found out that the major factors associated with delay in obtaining TB diagnosis were transportation cost, prolonged transport time, overnight travel especially for patients residing in rural areas. In addition, patients were also confronted with other costs

within the health care system that were not covered by the free diagnosis by sputum smear. Ukwaja et al. (2013) estimated that the median direct and indirect pre-diagnosis and diagnosis cost for TB in Nigeria is between $49 and $416 which constituted about 79% of total patient cost for TB. This economic barrier may be responsible for drop out of patients from TB diagnosis and this may lead to continuous spread of the disease within the community. Furthermore, as a result of this economic barrier, TB patients sought alternative care from traditional healers and non-qualified health care professionals and patent medicine vendors (Cambanis et al., 2005; Salaniponi et al., 2000) where inappropriate and inadequate treatment can cause TB complications including multidrug resistant TB.

TB and Urban residence

The study observed a significantly positive association between households living in urban areas and TB, although majority of Nigerians (55%) live in rural areas (National Population Commision, 2010). This finding is in agreement with the report from the first National TB prevalence survey in the country where TB prevalence was almost twice in urban compared to rural areas (FMoH Nigeria, 2012). Harling & Castro (2014) reported that urban residence was a strong predictor of TB irrespective of the effect of poverty or the interaction of poverty on urban residence but that the effect of urban residence on TB may be partially mediated by the higher HIV/AIDS rates in urban areas. This study however did not assess the effect of HIV/AIDS on TB for lack of HIV data at the LGA level. The urban poor tend to live in areas of cramped conditions which can increase the risk of TB. In addition, residents of urban areas are more likely to adopt risky lifestyle practices such as smoking, alcohol abuse, unsafe sex and unhealthy diet which are risk factors for TB (Lönnroth et al., 2009). Moreover, TB patients living in urban areas have better access to TB diagnostic

services and therefore more likely to report TB cases and be notified compared to patients living in rural areas where there is limited access to TB diagnostic services.

TB and Population density

The study also observed a high TB rates in areas of high population density. This is consistent with other studies (Gonçalves et al., 2009; Parslow et al., 2001; Lienhardt et al., 2003). Harling & Castro (2014) however, observed that population density was a predictor of high tuberculosis rates regardless of poverty and urban residence which was partially mediated by higher rates of HIV/AIDS rates in the municipalities. High population density is associated with outdoor residential crowding experienced in cities especially in urban slums and informal settlements characterized by lack of basic sanitation, poor housing and overcrowding, high levels of congestion and urban air pollution as a result of increased vehicular movements, industrial pollution, effluent from generating sets and household fuel combustion. These situations may contribute to increased respiratory illness including TB (McMichael, 2000).

TB and Living in single room

The percentage of households living in a single room was significantly associated with TB in the non-spatial analysis but this relationship was not sustained in the spatial regression analysis. This finding is however consistent with a similar study using non-spatial analysis in Hong Kong (Leung et al., 2004). The TB droplet nuclei could stay for a long time in the air of poorly ventilated rooms after a cough from an infectious TB patient and this could lead to increased exposure and transmission of TB among household contacts.

TB and DOTS treatment centres

There was a negative relationship between TB CNR and the number of DOTS treatment centres though this relationship was not statistically significant. The

provision of qualitative TB treatment services with a high treatment success has the potential over time to reduce overall TB rates in the community through the reduction in the pool of infectious TB patients (Frieden, 2002). The reduction in the overall burden of TB in the community would also lead to a lower number of TB cases reported by the LGAs. The NTBLCP, since inception pursued the expansion of TB diagnostic and DOTS treatment services nationally as part of the strategy to reach the TB case finding target of 70% of estimated TB cases and treatment success target of 85% (FMoH, 2010). The NTBLCP has been faced with major challenges in the continued expansion of TB services in the country especially expanding services within a weak and challenged health system. The health system in recent years has been through a lot of challenges including weak governance, inadequate health financing, dilapidated infrastructure, and shortage of qualified health work force, uncoordinated service delivery among others especially at the primary health care level. This has led to an inefficient health care delivery system that has poorly responded to the TB epidemic (Oyibocha et al., 2014). In addition, the perennial industrial strike action by health care workers of various categories and at different levels of the health care system has crippled the delivery of efficient health care especially in the face of a downward economic situation experienced lately by the county (Ukwaja & Onyedum, 2013).

TB and total number of health facilities

The total number of health facilities (both public and private) per capita in the LGAs was not associated with TB in this study. The majority of health care services in the country are provided by the public sector but sick individuals sought care more in the private health care system especially in rural areas as a result of the poor perception of the quality of care in the weak public health system (Onyeneho, Amazigo, Njepuome,

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Nwaorgu, & Okeibunor, 2016). Ukwaja et al. (2013) reported that only about one-tenth of TB patients initially visit a public health facility after the onset of symptoms especially in rural areas which meant that majority of patients in rural areas sought care more in private and alternative health care facilities. Some of these poor patients who may not be able to afford the services of private practitioners closest to them are therefore left to travel long distances to access TB treatment daily or weekly with its attendant high transportation cost. Ukwaja et al. (2013) estimated the sum of direct and indirect cost for treatment of a TB patient to be $528. This cost of treatment is usually borne by individuals and households and it poses enormous financial burden that result in further impoverishment of households and families.

Usefulness and limitation of Bayesian analysis in TB studies

Very few studies have used Bayesian approaches in the spatial analysis in the understanding of the distribution of TB (Harling & Castro, 2014; Roza et al., 2012; Souza et al., 2007; Venkatesan et al., 2012; Randremanana et al., 2010b; Kipruto et al., 2015). The Bayesian conditional auto regression model allowed for the smoothing of relative risk estimates in each region towards the mean risk in the neighbouring areas thereby produces a more reliable and precise estimate of the mean and variance and account for over-dispersion (Earnest et al., 2007). The Bayesian approach provides an opportunity to map and display smoothed relative risk estimates of the underlying factors (covariates) and its associated uncertainties to better understand the factors responsible for the observed spatial pattern. It also has the advantage to identify areas of higher or lower risk relative to other regions within the overall study area where scarce resources can be deployed for the control of tuberculosis.

Though Bayesian analysis is a useful analytical tool for the estimation of disease risk, identification of areas of high TB risk and provides insight into some of

the social determinants that may be responsible for the excess risk observed, yet this approach may not completely unravel the underlying social processes that generate the observed pattern of TB in this study. Some authors have criticised the ecological approach because it does not take into consideration the political economy which refers to how political, economic and social factors helps to establish, maintain and perpetuate inequality in the distribution of diseases within and between populations (Packard, 1989; Stack, 1980 ; Armelagos, Brown, & Turner, 2005; Dubos & Dubos, 1996). Farmer, (2003) buttressed the importance of structural violence or institutionalised harm often structured by historical antecedents and driven by economic forces in the production of diseases. These inequalities are created to serve and maintain the interest of the elite class in society and it contributes to the unhealthy environments, distribution of disease risk and the uneven pattern of disease among population groups (Poundstone, Strathdee, & Celentano, 2004). The proponents of the political economy approach advance the view that structural, economic and political processes create, impose and maintain social privileges and social inequality which are the root cause of social determinants of health and the socially produced geographic differences in disease rates (Krieger, 2001). Historically, many countries in Africa were at the receiving end of the distribution of power and economic resources during the long periods of colonial rule which entrenched social and economic inequality that predispose the citizenry especially the poor to disease and ill-health. In addition, the social inequalities and poorer health status in many African countries have been maintained by the unfavourable trade agreements, globalization, poor access to technological innovation, brain drain and by the elite few who control the political and economic resources to the detriment of the larger society (Eshetu & Woldesenbet, 2011). Gatrell & Elliott, (2015) reiterated that the political and

historical setting of a nation or country determines the health condition of a people. Thus the growing poverty and income inequality in Nigeria since 1970's, which was compounded by the Structural Adjustment Programme (SAP) of 1986 coupled with weak economy and weak governance have resulted in low investment to health and other sectors of the economy which has ultimately set the stage for increased vulnerability and exposure to TB especially in the more economically disadvantage segment of the population (Aigbokhan, 2000). On the other hand, TB affects the economically productive age group and thus has a negative impact on the economic growth and development of the country.

Limitations of study

This study presents some potential limitations. Firstly, the dependent variable is the TB case notification rate rather than the true TB prevalence in the LGAs. The information on the prevalence of TB is not available at the time of this study. The first National TB prevalence study conducted in 2012 did not include all the 774 LGAs. Therefore, some LGAs may have a relatively higher TB risk compared with what was reported in this study because of the current passive case finding approach utilised by the NTBLCP where individuals infected with TB need to seek care in health facilities before they are captured and notified by the NTBLCP surveillance system. Consequently, poor socioeconomic factors and lack of access to TB diagnostic and treatment services may serve as barriers to TB patients becoming notified by the National TB surveillance system. In addition, some TB patients could have been diagnosed by facilities and were not reported to the NTBLCP. In spite of this TB case notification remains the only reliable epidemiological data at the subnational level in many developing countries. In addition, there may be data management problems at the LGAs such as errors in transcribing and transmission of information from the TB

treatment facility to the central unit of the NTBLCP which may lead to underreporting of data in some LGAs. This situation can lead to a reduction in the risk of TB in some LGAs or the report of no TB risk where one actually exists. This study can however provide the lower bound estimate of the incidence of TB in the country.

Secondly, the population census figures used to calculate the denominator of TB CNR was projected from the last census conducted in 2006. This may not give an accurate reflection of the current population considering the fact that population growth may not be uniform across all LGAs in the country and many new neighbourhoods may have sprung up in some LGAs after the last population census. Similarly, the data used to develop the socioeconomic index (SEI) was collected in 2006 and it is unlikely that the economic situations of the LGAs have remained the same since 2006. Therefore the socioeconomic data may not adequately represent the present economic realities and the increasing income inequality in the country. However, the long duration between the data used to develop SEI and the data on TB provided some form of temporal association between the independent and dependent variables.

Thirdly, the findings from this study cannot be applied as a cause and effect relationship at the individual level as this may amount to committing ecological fallacy. Similarly, it was impossible to observe both the combination of the spatial and spatio-temporal changes in TB pattern because the study was done in a single year. However because TB is a chronic disease with a long incubation period, the study intentionally includes explanatory variables that may have some temporal relationship before the onset of TB diagnosis.

Fourthly, the study was conducted at the LGAs which is the lowest administrative level in the country with a median population of 191,705 (38,440 −

1,603,156). It is therefore unlikely that the LGAs are homogenous but rather there may be internal variation in both the distribution of the dependent and the explanatory variables measured at the LGAs. In addition, Nigeria has over 350 ethnic groups scattered all over the country and within a LGA there may be more than one ethnic group with variation in cultural, socioeconomic, environmental and demographic characteristics. Krieger et al., (2013) suggested that the impact of socioeconomic status (SES) varies according to the size of the community used for analysis. There is therefore the need for further studies at finer spatial scale (possibly the political wards) to elucidate the true effect of SES on TB in the country.

Fifthly, there is the possibility of migration across contiguous LGAs. The patients in this study are not geo-referenced to their place of residence as this information was not available. This situation may not however contribute a large bias to the study because the TB policy guideline of the NTBLCP stipulates that patients should be treated at the DOTS treatment centres closest to their place of residence irrespective of where diagnosis was made. The TB cases notified were collected and collated from the TB treatment registers at the TB treatment facilities. There may be some instances where sick TB patients in the urban areas were relocated to access treatment and care at the countryside or hometown of origin usually in rural areas as a result of stigma. The patients return to their original location when they get better or are cured of the disease. This kind of situation may increase TB rates in some rural LGAs and reduce in others. Furthermore, LGAs that have tertiary facilities located within them may have a pooling effect of patients from the neighbouring LGAs because of the perception of better quality of care because of the specialised services they offer. These LGAs with tertiary facilities located within them may report a high TB risk compared to others. This situation may not have a significant effect in this

study because even when they are diagnosed by these tertiary facilities the patients are referred to continue treatment at the treatment facility closest to their place of residence.

Sixthly, some States and LGAs in Nigeria are currently affected by the current terrorism insurgency in the North-East geo-political zone of the country where families and communities have been displaced. The TB burden may be lower in the affected LGAs where people have been displaced and increase in LGAs that harboured the internally displaced persons (IDP) camps. These IDP camps provide a good environment for TB germ to thrive due to the many TB predisposing factors such as crowding, poor nutrition and sanitation among others which are prevalent in these IDP camps.

Lastly, the absence of data on some known key determinants of TB at the LGA level precluded the addition of data on factors such as HIV infection rates, smoking, alcohol consumption, history of diabetes among others to the regression model. Therefore, the effect of these factors on TB was not accounted for in the analysis of this study.

In spite of the above limitations, this is the first study in Africa on a national scale and at the lowest administrative level of the country to explore the spatial distribution of TB and its associated socioeconomic, demographic and health related determinants using a contemporary, advanced spatial analysis and modelling approach. This study has demonstrated the usefulness of the Bayesian approach in the mapping of LGAs with elevated risk of TB in Nigeria. This analysis can complement routine surveillance and assist programme managers and policy makers to make evidence based informed decision to rationally allocate resources and plan targeted local interventions to the identified priority LGAs.

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Chapter 8: Conclusion and Recommendations

This study described for the first time the application of spatial analysis techniques to determine the spatial pattern of TB and its relationship with socioeconomic indices at the lowest administrative level in Nigeria. Initial non-spatial analysis showed significant associations between TB and household size, access to public transportation, living in a single room, living in urban residence, population density, and the number of AFB microscopy diagnostic centres. The asset-based socioeconomic index, number of DOTS treatment centres and total health facilities per 100,000 populations were not significantly associated with TB. Significant spatial autocorrelation and significant clusters of TB was observed in 19 LGAs located within eight states. These states were Lagos (Lagos Mainland), Oyo (Oluyole, Ibadan North, Ibadan North East, Ibadan North West, Ibadan South West, and Ibadan South East), Cross river (Calabar South), Benue (Ukum and Katsina Ala) Taraba (Ardo kola and Jalingo), Nasarawa (Nasarawa egon and Nasarawa) Federal Capital Territorry (Abaji, Kwali and Kuje) and Sokoto (Wamakko and Sokoto South). These LGAs were primarily in states that were largely urban, densely populated areas and those with a high HIV prevalence rates.

The study produced maps that allowed visualization of the distribution of TB in Nigeria on national scale with the identification of 138 (17%) LGAs that have elevated risk pattern above the national average after adjustments were made for spatial dependence and nine explanatory variables. The high risk LGAs were distributed in all the six geopolitical zones and in 34 of the 37 states in the country and represented a more widespread pattern not localised to any particular state or geopolitical zone. In addition, this study allowed for the quantification of the magnitude of the risk TB for each of the 774 LGAs.

The study further explored and quantified the contribution of some social determinants (socioeconomic, demographic and health related risk factors) of TB. TB was significantly associated with larger household size, access to public transportation, urban residence, population density and the number of AFB microscopy diagnostic centres per capita. In addition, the levels of uncertainty associated with each of the explanatory variables were also quantified. This information will be of interest to spatial epidemiologist and public health practitioners in the realistic prediction of future risk of TB in each of the LGAs.

This study highlighted the use of Bayesian modelling methodology in disease mapping and spatial analysis as a complimentary tool for National TB programme managers in understanding the TB epidemic and factors responsible for the spatial distribution of TB in the country. This information is of interest to policy makers to rationally plan targeted specific interventions and guide resource allocation to LGAs that are worst affected by TB. The study has also provided a benchmark for which future strategic inputs for TB control can be evaluated.

Some of the unexplained variance in this study may be attributed to important risk factors that were related to TB but not captured by our model. This study addressed the effect of socioeconomic position mediated by factors related to material living standards and the health system. The addition of other variables mediated through behavioural or lifestyle choices (such as smoking, alcohol abuse, poor diet), biological (such as HIV, diabetes) and psychosocial risk factors may improve the model and provide further understanding of the effect of the complex interaction between social, economic and health related processes on TB risk. It is therefore important to develop a district health information management system at the LGA level that can provide accurate and timely information on TB and its risk factors

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which can be monitored over time. The information obtained from this surveillance system can assist in the timely prediction of disease occurrence and for the planning of timely interventions that can mitigate the spread of TB at the LGAs.

Policy implications

The findings from this study have several policy implications. Firstly, the study confirmed that there is a true spatial heterogeneity in the distribution of TB in the country with the identification of LGAs with excess TB risk compared to the national average. This finding provided useful information that can assist policy makers and other stakeholders to target the scarce resources to the identified 138 priority LGAs with high TB risk above the national average. The deployment of targeted specific interventions such as active case search and contact tracing may be helpful in rapidly finding more TB cases in these priority LGAs and initiating them on prompt treatment in order to reduce the overall burden of infectious TB cases and consequently reduce the continued transmission of TB in the community. In addition, the implementation of preventive strategies such as increasing BCG vaccination coverage for children at birth, administration of isoniazid preventive therapy (IPT) to household child contacts of patients with active smear positive TB and people living with HIV (without active TB) to reduce the risk of acquisition of infection after exposure to an infectious TB case. Improving the uptake of antiretroviral drugs among TB/HIV co-infected patients will also decrease the reactivation of TB and therefore reduce overall TB incidence in the country. This information is essential in understanding the epidemiology of TB in Nigeria and enables policy makers to visualise LGAs with high TB risk that may require special attention. Furthermore, attention must be placed on low risk LGAs contiguous with high risk LGAs to forestall diffusion of infection from one LGA to another.

Secondly, TB is still a disease of poverty. There is the need to move beyond the biomedical strategies in TB control and address some of the fundamental social determinants of TB by closing the "tap" which creates avoidable social inequality that generate and maintains diseases in society. The provision of affordable well-ventilated social housing schemes especially in socially deprived LGAs, providing, urban renewal and upgrade of slums, providing access to family planning and population control measures especially in rural areas will further reduce the risk of TB in the country. The relationship between TB and public transportation however has a very important policy implication depending on what the mechanism of the relationship is: if public transportation is regarded a risk factor for TB transmission, then measures to improve the conditions within the vehicles, such as health education of bus users on cough etiquette, prevention of overcrowding and ensuring good ventilation in vehicles need to be implemented. On the other hand if availability of public transportation improves access to diagnosis and treatment, then the policy response will be to improve the availability and accessibility of public transportation and ensure the construction and maintenance of roads that will improve access of communities to TB diagnostic and treatment services. The provision of social support to TB patients to cushion the economic burden on TB patients and their households is also desirable. In general, economic growth and the improvement in the socioeconomic and general living condition of the populace will reduce the burden of TB similar to the experience of developed countries before the advent of anti-TB chemotherapy (Marmot, 2005).

Thirdly, TB case finding can be improved in the country by the expansion of quality assured TB microscopy services to all LGAs taking into consideration the terrain and distribution of these services to ensure equitable access to TB diagnostic

services. The country needs to provide considerable investment of resources into the maintenance of existing TB microscopy centres, by training and re-training laboratory personnel and embark of infrastructural upgrade and expansion of TB diagnostic network to all LGAs and political wards. The current initiative by the Federal Government of Nigeria to provide one modern facility per political ward is laudable and this is expected to improve access to modern health facilities by remote communities (FMoH Nigeria, 2016). The rapid deployment and expansion of new more sensitive TB diagnostic technologies such as Gene Xpert MTB/RIF to replace the conventional Ziehl Neelson (ZN) test currently in use will further boost case finding efforts in the country. Furthermore, there is the need to strengthen the overall health systems in the country by considerable financial investment by governments at all levels especially into primary health care which is the entry point to the national health service, in order to ensure the provision of accessible, affordable, and equitable health care service to all irrespective of where people live, work or their ability to pay for such services. The elimination of all forms of user fees as it relates to TB diagnosis and treatment and the engagement of all care providers (public and private) including communities in TB control will lead to early diagnosis and improved TB case notification (Mcpake, Brikci, Cometto, Schmidt, & Araujo, 2011; Watson et al., 2016). In addition, the government needs to ensure that all care providers mandatorily report all cases of diagnosed TB to the NTBLCP to accurately determine the burden of the disease in each LGA in the country.

Fourthly, the current resource allocation policy of the National TB and Leprosy Control programme is to provide equal funding for TB control activities to all LGAs regardless of their need based on political exigencies. This current practice of inequitable allocation of resources needs to be substituted with a more equitable

distribution of resources according to the disease burden in each LGA. The 138 LGAs with a higher TB risk identified in this study needs to be prioritised in the allocation of resources for the control of TB.

Finally, spatial analysis techniques can be integrated into routine epidemiological surveillance of socioeconomic risk factors associated with TB. The identification of LGAs most at risk of developing TB can assist policy makers to rationally plan public health interventions such as affordable social housing, urban regeneration projects among others in an attempt to address the health inequities and reduce risk that predisposes individuals to TB. The study has demonstrated that the Bayesian approach can complement routine TB notification data in identifying the true variation in TB across the country that cannot be evident from crude rates or unsmoothed standardized notification rates currently in use. This will assist programme managers to identify priority LGAs and rationally plan targeted specific interventions to effectively control TB while addressing the underlying social determinants of TB in the country.

Implications for future research

Future research should consider the use of alternative measures to determine an appropriate socioeconomic status such as income and expenditure data and explore its relationship with TB. In addition the use of true TB prevalence data (which can be obtained in future from a national TB prevalence survey involving all the 774 LGAs) can provide better insight into the TB situation in the country rather than the case notification data utilised in this study. This study employed an ecological approach without the use of individual level characteristics. Future studies can utilise multilevel analysis to determine the interaction between individual and community level characteristics on the risk of tuberculosis in the country. The addition of genotype

studies to disease mapping techniques will be helpful in future to distinguish between recent on-going infection and that due to reactivation of old disease in order to provide appropriate intervention. Future research can also explore some risk factors not included in our model such as behavioural or lifestyle choices (such as smoking, alcohol abuse, poor diet), biological (such as HIV, diabetes), psychosocial and factors associated with quality of TB care (such as treatment success and loss to follow-up rates). The exploration of these factors will provide a better understanding of the effect of social determinants on the epidemiology of TB in Nigeria.

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