Spatial Analysis of Tuberculosis and Risk Factors at the Lowest Administrative Level in Nigeria

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Summary

BACKGROUND

Few studies have utilized modern techniques of spatial data analysis to understand the distribution of tuberculosis (TB) and its possible predictors. In 2013, an estimated 9 million new TB cases and 1.5 million deaths occurred worldwide, out of which 360,000 deaths were HIV related.

AIM

To assist in planning key interventions for the control of TB at a sub-national level, the studysought to explore the spatial distribution of TB and associated risk factors at the lowest administrative level in Nigeria.

METHODOLOGY

This was an ecological study carried out using number of notified TB cases for the 774 Local Government Areas (LGAs) in 2013. Bayesian spatial regression analysis was conducted to identify high-risk clusters of the disease and to assess associated factors .

RESULTS

Analysis revealed that TB was significantly clustered in 138 (17%) LGAs. Significant associations were found with household size, urban residence, access to transportation, population density, number of TB diagnostic services. Other predictors, including a composite index of socioeconomic status, living in a single room, number of TB treatment centres, and total health facilities in the LGA were not significantly associated with TB incidence.

CONCLUSION

The study identified LGAs with elevated risk as well as significant factors associated with TB. This information can assist policymakers in rationally planning targeted specific interventions with the potential to effectively control TB in the country.

Keywords: Tuberculosis, Socioeconomic Indices, Bayesian, Mapping

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Introduction

Tuberculosis (TB) remains an important public health problem in the 21st century. It is the second leading cause of death from a single infectious disease agent1. In 2013 alone, an estimated 9 million new TB cases and 1.5 million deaths occurred worldwide, while 360,000 of these deaths are as a result of HIV. 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 [1]

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[2,3,4]

Similar inverse relationships have been documented between TB rates and socioeconomic indices in middle-income countries [5,6[. 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 [7,8]. 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 [9,10,11]. Interestingly, some studies observed a positive relationship between high socioeconomic indices and TB in rural Malawi, Zambia, and Karonga district in Malawi respectively [12,13,14]. The conflicting conclusions from these studies in low and middle-income countries bring into question whether indicators used in assessing socioeconomic status in the global north are appropriate for the south

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. Tuberculosis, like many infectious diseases, is prone to spatial aggregation or clustering.

Studies of the spatial distribution of TB have utilized different methods and approaches, ranging from exploratory techniques to spatial modelling[15,-17]. Very few studies have used Bayesian approaches in the spatial analysis of TB [18-23]. The Bayesian analysis allows for the smoothing of relative risk estimates in each region towards the mean risk in the neighbouring areas, thereby producing a more reliable and precise estimate of the mean and variance [24]. It also has the advantage of identifying areas of higher or lower risk relative to other regions within the overall study area. This can help target scarce resources for the control of tuberculosis.

There is a paucity of studies that have utilized Bayesian analysis in the study of tuberculosis in Africa, including Nigeria. This study is the first to use Bayesian analysis to explore the spatial distribution of tuberculosis in Nigeria at the lowest administrative level in the country.

MATERIALS AND METHODS

Study Population

Nigeria a relatively large country (approx. 924,000 sq km) in West of Africa, bordered to the north by Niger, to the east by Chad and Cameroon, to the south by the Gulf of Guinea and to the west by Benin. The population is 174 million [25], with an annual population growth rate of 2.8 per cent. The average population density is 104 per square kilometre with 45 per cent residing in urban areas [26]. The country has 36 autonomous regions, as well as the Federal Capital Territory. The country is further divided into 774 Local Government Areas (LGAs) which is the lowest administrative level.

Study Design

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

Data Sources

The dependent (outcome) variable is the TB case notification rate per 100,000 population. The TB data were obtained from the National TB and Leprosy Control Programme in Nigeria (NTBLCP).

The explanatory variables (covariates) are listed in Table 1. The covariates were selected based on previous studies. The composite standardized socioeconomic index was constructed using the principal component analysis to select 10 variables which were ownership of house, phone, vehicle, computer, motorcycle, house built with concrete, safe water supply, and sanitation, access to water, access to electricity, and ownership of land

Table 1: *Definition and Summary Statistics 0f 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	Standardized 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	The Mean household size in each LGA.	4.88(1.11)	4.76(4.04-5.70)	2.58-10.98
Access to public 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 a 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 km2	1276.10 (4714.95)	277.69 (125.97-640.02)	11.58-67613.39
Health/Medical Factors				
Health facility	No 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	No of DOTS treatment facilities per 100,000	3.51(2.81)	2.84(1.92-4.26)	0.00-22.61
Microscopy per capita	No of AFB microscopic facilities per 100,000	0.94(0.63)	0.80(0.53-1.25)	0.00-4.14

Data Analysis

Descriptive analysis was initially conducted on the TB case notification rate and the nine covariates *(Table 1)*. The Bayesian hierarchical Conditional Autoregressive (CAR) model was used for the spatial analysis in this study. Initially, the observed TB count in each LGA is modelled as a function of area-level disease risk. The CAR model allows for the smoothing of the disease risk in each LGA towards the mean risk of the neighbouring LGA [27].

The equation is represented as:

$Y_i \sim \text{Poisson}(\lambda_i \varepsilon_i)$ …… (1)

Where Y_i is the observed TB count in LGAi in 2013, λi is the risk in LGAi and is the observed number of TB cases divided by the expected number of TB cases in each LGA and εi is the expected TB count based on the population size of the LGAi 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 = ($Y1,\ldots\ldots Y_n$) in eachLGA(i=1,2,……..n) are non-independent Poisson random variables with a mean of μi ($\mu_1\ldots,\mu_n$).

The mean (μi) can also be stated as the multiplication of the expected number of TB cases (εi) and the relative risk of TB (λi) in each LGAi. Therefore $\mu i = \varepsilon_i \times \lambda_i$.

We then model the risks as a function of the explanatory variables.

The log risk is modelled by the equation:

$$\lambda i = \exp(\beta_0 + \beta_{1i} X_{1i} + \beta_{2i} X_{2i} + \beta_{3i} X_{3i} + \ldots\ldots\ldots\ldots + \beta_{ki} X_{ki} + v^i + u_i) \ldots\ldots\ldots (1)$$

The uncorrelated or non-spatial heterogeneity or unstructured random effect is designated as νi while the correlated spatial heterogeneity or spatially structured random effect is labelled as u_i. The Bayesian analysis assumes a prior distribution for the spatial random effects which takes 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 x 10-5, while a uniform prior distribution was assigned for β_0 [28,29].

The non-spatially structured random effects between LGAs $\nu_i = (\nu 1 \ldots\ldots \nu n)$, are independent of one another and assumed to have an independent Gaussian distribution with a mean of zero and a variance σ2 νi.

This non-spatial extra-Poisson variation followed an inverse Gamma distribution of

$1/\sigma 2\, \nu i \sim \text{gamma}(0.5, 5 \times 10\text{-}4)$

and the variance term ($\sigma 2 \nu_i$) was included because of important covariates that could influence the relative risk of TB but not included in the model.

The spatially structured random effects, $u_i = (u1 \ldots\ldots un)$ account 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.

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 σ2ui is the spatial extra-Poisson variation which controls the strength of this local spatial dependence.

The Gaussian intrinsic conditional auto-regression (CAR) model proposed by [27] was used to specify the spatial correlation term *ui:*

$$\rho(ui \mid uj, j \neq i) \sim N((\Sigma j \neq i\ Wij\ ui)/(\Sigma j \neq i\ Wij), \sigma 2ui/(\Sigma j \neq i\ Wij)) \ldots\ldots (3)$$

The {wij} are the weights, defined as 1(one) if LGAs i and j share a common boundary and 0 otherwise. The spatial variance ratio is described as the ratio of

(spatial variance)/(spatial variance+non-spatial effect) … ……..(4)

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 is close to unity (1) then the spatial random effects dominate the total variation in the data while a value close to zero shows that the spatial variation in the data was insignificant [29].

The Bayesian analysis was carried out using the R-INLA package in R statistical software [30]. The full model consists of the addition of all covariates fitted with both spatially structured and unstructured random effects. The output of the models includes the Deviance Information Criterion (DIC), effective parameter (pD) which informs about the simplicity of the model 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 have been accounted for. The goodness of fit of the Bayesian models was determined by DIC values and the number of effective parameters (pD) with the lowest value.

Ethical Issues

Ethical approval was obtained from the ethics board of the Olabisi Onabanjo University Teaching Hospital Research Ethics Committee Ogun State, Nigeria.

Results

The output of the Bayesian conditional autoregression model is shown in *Table 2*. 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.

The composite socio-economic index and the number of DOTS TB treatment facilities per capita are inversely related to TB CNR though the associations were not statistically significant. Conversely, the percentage of households living in a single room and the total number of health facilities were positively related but not significantly associated with TB CNR.

In addition, *Table 2* presents the exponentiated fixed effects of regression coefficient estimates of the explanatory variables in the Bayesian conditional autoregression model in INLA and these were interpreted as the relative risk of TB for one standard deviation increase in each independent variable value. The full model (Model 5) is selected for subsequent analysis because it has the lowest number of effective parameters (746.21) compared to the other models.

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 1*.

The map reveals LGAs with higher or lower TB risk. About 13% (100) LGAs have a relative risk between 1-1.8. *Figure 2* represents the posterior probability associated with the smoothed relative risk of TB SNR without covariates.

The black-coloured areas display LGAs where there is more than an 80% probability of the relative risk being higher than the national average.

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 3.*

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.

Figure 4 shows the posterior probability of the SNR exceeding 1 after adjustment for covariates. *Figure 5* shows the percentage of the total LGAs in each state that has LGAs with SNR>1 in the 37 states in the country. Akwa Ibom State had the highest percentage of LGAs with SNR>1 in the country.

Table 2: *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
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			1.000	0.999	0.999	0.999	1.001
Socio-economic index			(0.996- 1.005)	(0.995-1.003)	(0.995-1.003)	(0.996-1.003)	(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 a 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 km²					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)
The 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 (PD) Maximum log-likelihood	6179.19 (756.52)-4460	6173.30 (751.79)-4262.08	6173.33 (751.83)-4271.64	6173.25 (750.28)-4262.44	6172.74 (746.74)-4208.08	6173.38 (746.21)-4220.80	6181.42 (751.79)-4416.87

Key: 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.

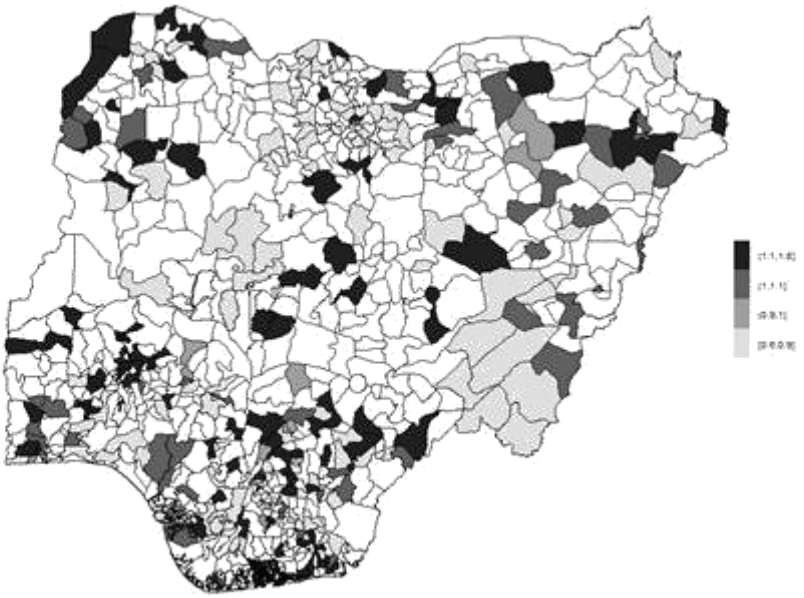

Figure 1: *Spatially structured estimates for TB SNR without covariates*

Figure 2: *Posterior probability associated with the smoothed relative risk of TB SNR based on the CAR regression model without covariates*

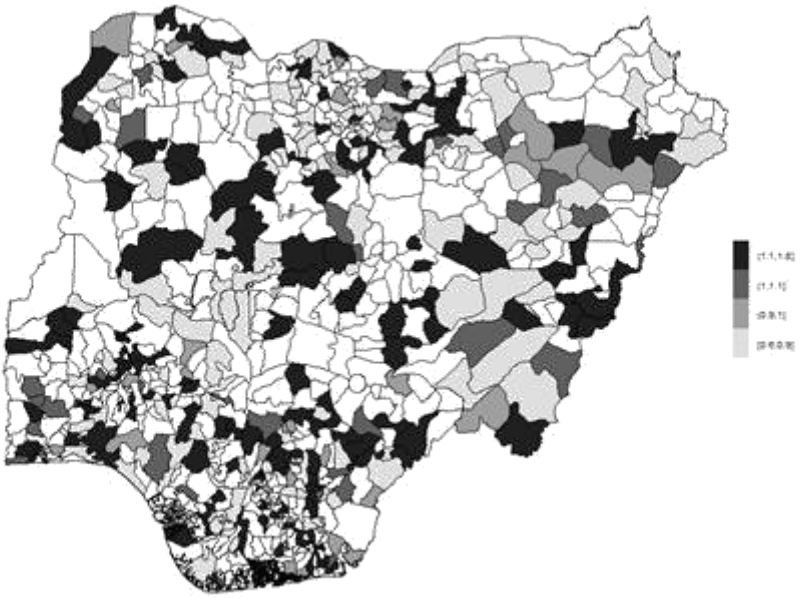

Figure 3: *Spatially structured estimates for TB SNR after adjustment for the covariates, in Nigeria.*

Figure 4: Posterior probability of the TB SNR exceeding or >1 after adjustment for covariates, in Nigeria.

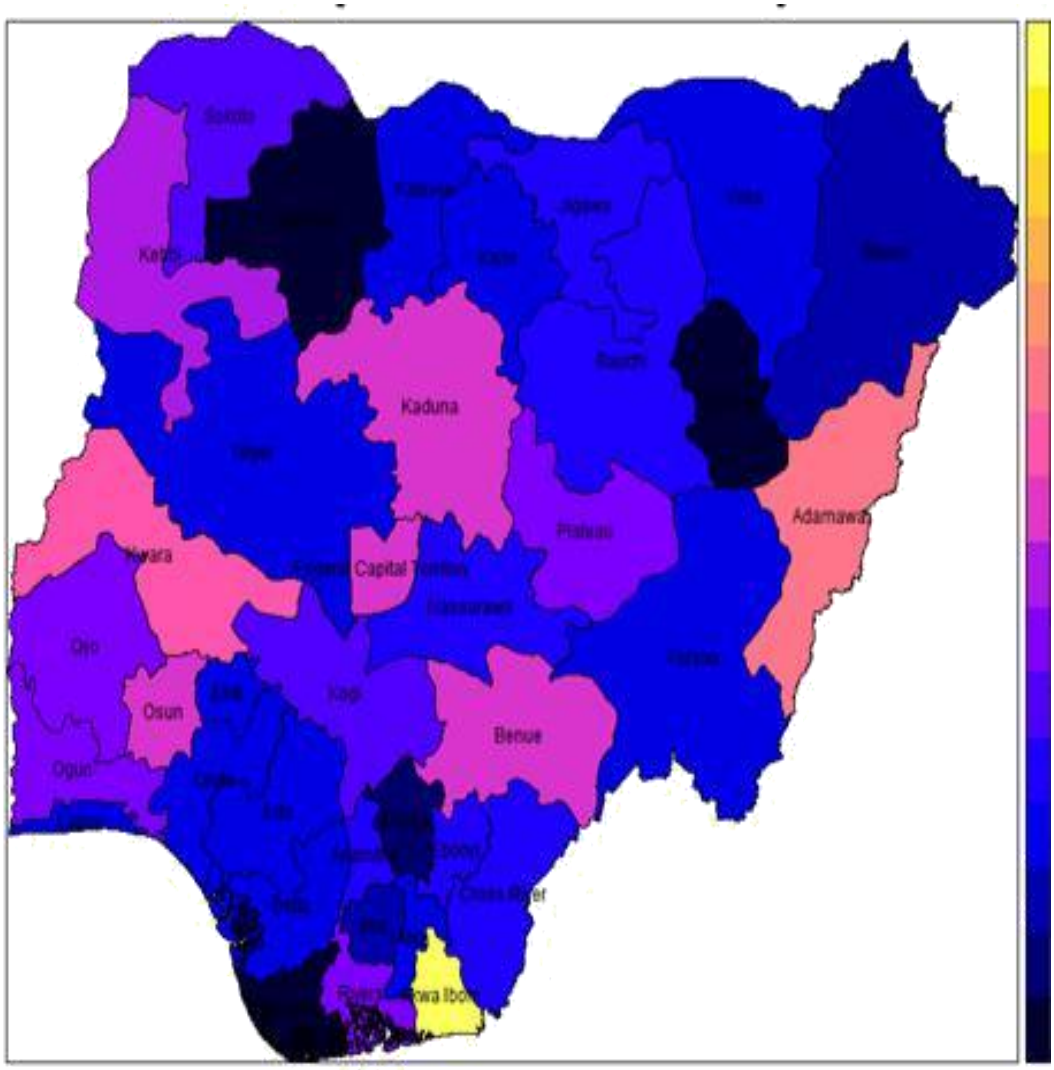

Figure 5: *Percentage of LGAs with TB SNR>1 in each State in Nigeria*

Discussion

To the best of our knowledge, this is the first study to use Bayesian analysis of TB at the lowest administrative level of governance in Nigeria. Our study has demonstrated spatial heterogeneity of TB in Nigeria, identified significant clusters of high TB risk in 138 (17%) of the local government areas (LGAs). The States with the high proportion of LGAs with SNR>1 such as Akwa Ibom, Adamawa, Benue, and FCT has high HIV prevalence rates while Kebbi and Osun states on the other hand have high poverty rates in the country31

Several studies have elucidated the relationship between the socioeconomic index and TB incidence, this study however did not find a significant association between TB and the composite asset-based socioeconomic index used in this study as a measure socioeconomic status of each LGA. A study in South Africa showed that the inverse relationship between TB and SES may not be that apparent in Africa because of the increasing income inequality and the interwoven nature of African society, which increases the likelihood of TB transmission as a result of contact between individuals with higher and lower SES.32. This study however showed that some proxy indicators of

socioeconomic status such as household overcrowding, urban residence, population density were significantly associated with TB incidence.
Household crowding has been identified as a risk factor for the development of TB both in some studies 32,33. However, some other studies did not find a significant association between household crowding and TB 34,35. Household crowding increases the shared space among household members and the possibility of contact between infected TB patients and susceptible persons thereby increasing the risk of exposure to TB infection and disease.

Living in an urban area was positively associated with TB. This finding was 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 36. Another study conducted in South Africa reported that urban residence was a strong predictor of TB irrespective of the effect of poverty and that the effect may be partially mediated by the higher HIV/AIDS rates in urban areas32. This current study however did not assess the effect of HIV/AIDS on TB for lack of HIV data at the LGA level. The residents of urban areas tend to adopt risky lifestyle practices such as smoking, alcohol abuse, and unhealthy diet which are independent risk factors for TB. Furthermore, the urban poor tend to live in areas of cramped conditions that increase the risk of TB.

The high population density was associated with TB incidence. This is consistent with other studies that observed that population density was a predictor of high tuberculosis rates regardless of poverty and urban residence 32,37,38. This was found also to be partially mediated also 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.

The study found that LGAs with better access to public transportation had a higher risk of TB. The increased access to public transportation especially in areas where crowded public transportation presents the potential for increased exposure and risk for TB transmission. This situation has been described in the literature especially in regions with a high TB burden 39 Also, the LGAs that had better access to public transport facilities were more likely to have better access to TB diagnostic services and therefore more likely that patients were diagnosed and notified compared with LGAs that had poor access to public transportation.

The LGAs with a higher density of TB diagnostic facilities notified more TB patients. The study observed that a unit increase in the number of microscopy centres per capita will increase the TB notification rate by 23%. The increased accessibility of TB diagnostic services in the country is crucial for the control of TB. The rapid deployment and expansion of new TB diagnostic technologies to replace the conventional AFB microscopy currently in use in many areas will further boost case-finding efforts especially in rural hard to reach areas of the country.

Study Limitations

This study has some potential limitations. Firstly, the dependent variable is the TB case notification rate rather than the true TB incidence in the LGAs. However, this study provides a lower bound estimate of the TB incidence in the country. Secondly, this study is an ecological one, based on administrative area units, and inferences about individuals cannot be made from the associations uncovered here. Thirdly, some States and LGAs in Nigeria are currently affected by the current terrorism insurgency in the North-East geo-political zone of the country and this may lead to underreporting in some of the LGAs in this region. Lastly, the absence of data on factors such as HIV infection rates, smoking, alcohol consumption, history of diabetes among others which are considered key determinants of TB at the LGA level precluded their addition to the regression model.

Conclusion

This study has demonstrated the usefulness of the Bayesian modelling approach in the disease mapping of LGAs with the elevated risk of TB in Nigeria. This analysis can complement routine surveillance and assist program managers and policymakers to make evidence-based informed decisions to rationally allocate resources and plan targeted local interventions to the identified

138 high-risk LGAs in this study. However, some of the unexplained variances 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 a 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 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 in small geographical areas. 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 to reduce the overall burden of TB in Nigeria.

Authors' Contributions:

Conceptualization and study design: OJD, OAA

Data collection: OJD, ADA, KSO

Data analysis: OJD, OK,

Study supervision: OJD, OAA

Manuscript writing: OJD, OAA, JOB

Revision of manuscript: OJD, OAA, ADA, JOB, KSO

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The data underlying this article were provided by the National Tuberculosis and Leprosy Control Program with permission. Data will be shared upon request to the corresponding author with permission from the National Tuberculosis and Leprosy Control Program

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