Abstract

Background

Tuberculosis (TB) remains a key contributor to global mortality; ranks second as the most fatal infectious disease and seventh among the top ten causes of death in Ghana. There is insufficient literature regarding the utilization of Bayesian hierarchical models for examining the spatial and spatio-temporal dynamics of tuberculosis risk in Ghana.

Aim

This study addresses this gap by determining TB hotspots regions in Ghana using the Bayesian modeling framework.

Methods

TB data were obtained from the Ghana Health Service and National Tuberculosis Programme for the 10 administrative regions of Ghana, from 2008 to 2017. Spatial and spatio-temporal TB relative risk for each region were estimated under the Bayesian modeling frameworks. Maps for TB risks were created to visualize regions with TB hotspots. Model fitting and parameter estimation were conducted using integrated nested Laplace approximation via R version 4.3.2.
Results

Among the baseline predictors, TB cure rate, TB success rate, knowledge about TB, human immunodeficiency virus (HIV) prevalence, percentage of literacy, and high income were found to be most significant predictors of TB risk in Ghana. We noted an increased risk of TB infection in the Northern zone and the Eastern and Greater Accra regions in the Southern zone. Spatio-temporal distribution of TB infection risk was predominantly concentrated in the Southern zone. Clustering of TB risk was observed among neighboring regions.

Conclusion

Factors influencing tuberculosis (TB) risk in Ghana are TB cure rate, TB success rate, knowledge about TB, HIV prevalence, literacy rate, and income level. The risk distribution was mainly concentrated in the Southern zone, with clusters of TB risk observed among neighboring regions. To achieve a significant reduction in TB cases, it is essential to allocate resources to TB hotspots regions and also implement measures to control significant predictors of TB infection risk.

Keywords
Bayesian spatial and space-time models, Tuberculosis relative risk, baseline predictors and TB hot-spots.
Background
Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It is a condition that transcends age, gender, race, and the health status of individuals worldwide. In 2019, it was estimated that around 10 million people had TB, resulting in an estimated 1.2 million deaths among those without HIV infection. Among adults aged 15 and above, males comprised 56% of global infections, while females accounted for 32% in the same age category. Children represented 12% of total cases, with approximately 8.2% of reported cases involving individuals with HIV. The distribution of TB infections in 2019 varied across regions, with Africa contributing to 25% of cases, South-East Asia and the Western Pacific accounting for 44% and 18%, respectively. In the same year, the Eastern Mediterranean, America, and Europe reported 8.2%, 2.9%, and 2.5% of the total cases, respectively.

Nevertheless, the World Health Organization (WHO) has advocated for the development of tuberculosis (TB) vaccines. In addition to vaccines, there are available treatments for TB patients, and reports suggest that approximately 85% of patients can be successfully cured with a six-month drug regimen. According to available data, treatment drugs have played a crucial role in preventing over 60 million deaths from 2000 to 2020. Collectively, there was a 9% reduction in cases between 2015 and 2019, and a further 2.3% reduction between 2018 and 2019. Europe has successfully achieved a 19% reduction in cases and a 31% reduction in deaths between 2015 and 2019. In the same timeframe, Africa has seen a 16% reduction in cases and a 19% reduction in deaths. More comprehensive statistics on TB can be found in references.

While global tuberculosis (TB) reports show a declining trend in cases and deaths, the WHO’s targets for reduction from 2015 to 2020 have not been met. Except for Europe, all other continents have fallen short of achieving the prescribed reduction levels. Consequently, TB remains among the top 10 causes of death, particularly in Africa and Ghana, where it outranks HIV/AIDS.

Ghana has been affected by the respiratory disease and currently has challenges in eradicating TB. In response, the country implemented policies such as Directly Observed Therapy (DOT) and National Tuberculosis Programmes (NTPs) in 1994 to detect and treat TB. The initiation of the NTP resulted in 100% DOTs coverage by 2005, leading to an increased detection of TB cases for treatment each subsequent year. For example, the number of TB cases detected rose from 7,425 in 1996 to 15,286 in 2009. A more in-depth exploration of TB statistics in Ghana can be found in references. The incidence of tuberculosis (TB) has demonstrated a consistent decline, with figures decreasing from 45,000 cases in 2010 to 44,000 in 2017. Annually, approximately 44,000 individuals develop TB in Ghana, with an estimated 6,600 being children. The number of TB patients undergoing treatment ranged between 14,607 and 15,389 from 2010 to 2017, highlighting a pressing demand for increased resources dedicated to TB patient care. In 2013, the national TB prevalence was estimated at 290 cases per 100,000 population, indicating a burden fourfold higher than the WHO’s estimates for the same year (71 cases per 100,000 population). TB-related mortality is estimated at 10,000 deaths annually. Tuberculosis is the seventh leading cause of mortality in Ghana, contributing to 4.9% of all deaths and older males, aged above 45 years, bear the greatest burden of the disease. Also, TB ranks 7th among the leading causes of death for females and 8th for males, and it stands as the 4th primary cause of mortality within the category of communicable, maternal, neonatal, and nutritional diseases. The TB epidemic exhibits a generalized pattern, albeit with geographical variations in case notification, often associated with disparities in access to healthcare facilities.

Despite a decline in TB cases and deaths attributed to the implementation of mitigation and treatment strategies, TB remains a life-threatening disease, placing a substantial burden on the health infrastructure in Ghana. Consequently, TB has become a focal point of research across diverse fields. Notably, researchers from various backgrounds, such as authors, have investigated the dynamics of TB indicators and risk factors associated with TB in Ghana. Osei and colleagues studied the trends of TB detection and treatment outcomes, employing logistic regression to analyze the relationship between patient and disease characteristics. In a separate study, Aryee and colleagues examined the dynamics of TB using Autoregressive Moving Average (ARIMA) methods, analyzing TB data recorded by Korle Bu Teaching Hospital from 2008 to 2017. On the other hand, Iddrisu and colleagues investigated the temporal and geographical patterns of TB prevalence in Ghana between 2015 and 2018.
The existing body of literature on the utilization of the convolution model or the Besag, York, Mollié (BYM) model within the Bayesian modeling framework, particularly in the application of spatial and spatio-temporal models for estimating and mapping disease risk in Ghana, is limited. This paper addresses this gap by identifying regions with hotspots and predictors of TB infection risk in Ghana using these methods. We primarily focused on studying the spatial and spatio-temporal patterns of TB relative risk using spatial and spatio-temporal models within the Bayesian modeling framework. These models enable the incorporation of neighboring regions’ information to yield accurate estimates of disease risk within and between regions. The key hypotheses guiding this study are as follows: (1) TB infection risk exhibits clustering among specific regions in Ghana, (2) there is variation in TB infection risk among different regions in Ghana, and (3) TB preventive measures, education on TB, and economic variables serve as significant predictors of TB infection risk in Ghana. Parameter estimates are derived from the marginal posterior distribution using the Integrated Nested Laplace Approach (INLA) implemented through R software version.

Methods

This section provides a description of the data used in this study and specifies the Bayesian spatial and spatio-temporal models that were employed to estimate the relative risk of TB across the 10 old administrative regions of Ghana. The conditional auto-regressive (CAR) model and the random effect components of the Besag, York and Mollié (BYM) model for respectively identifying clustering and heterogeneity of disease risk in space and time are described. The spatial model used is the BYM Model and the spatio-temporal models are based on three modeling frameworks developed by Knorr-Held and Rasser, Bernardinelli and colleagues and Waller and colleagues. The best fitting spatio-temporal model was selected and only results from this model were discussed.

TB cases

For this study, we utilized tuberculosis (TB) detection data sourced from the Ghana Health Service and National Tuberculosis Programme. The dataset comprises information on TB cases spanning the years 2008 to 2017, encompassing the 10 old administrative regions of Ghana. These regions consist of Ashanti, Brong Ahafo, Central, Eastern, Greater Accra, Northern, Upper East, Upper West, Volta, and Western, as illustrated in Figure 1. Although new
regions were established after 2016, the TB data were collected and organized based on the original 10 administrative regions.

**Outcome variable**

The dependent variable in this study is the number of tuberculosis (TB) cases collected for each of the 10 administrative regions in Ghana, spanning the years 2008 to 2017.

**Baseline predictors**

This study considered various baseline regional characteristics that may influence the risk of tuberculosis (TB) infection. The set of baseline predictors encompasses factors such as the doctor-to-population ratio, nurse-to-population ratio, HIV prevalence, tuberculosis cure rate, tuberculosis success rate, wealth quantiles, and the proportions of men and women who are employed, unemployed, educated, and uneducated. The study also considered variables such as the proportions of individuals who have heard about TB, possess knowledge that TB is airborne, are aware that TB can be cured, and believe that TB status should be kept confidential. In the data analyses, all these baseline variables are thoroughly examined to identify significant predictors of TB cases.

**Statistical methods**

In this section, we discussed and defined the spatial and spatio-temporal models employed for estimating tuberculosis (TB) risk in Ghana. Considering that these models are within the Bayesian modeling framework, we initially provided a concise overview of Bayesian principles.

**Bayesian modeling framework**

For spatial data collected at a single time point, where \( y_i, i = 1, \ldots, n \) represents the observed TB cases for region \( i \), consider a Poisson random variable with a probability mass function defined as \( \Pr(y_i|\theta) \), where \( \theta = (\theta_1, \ldots, \theta_n) \) represents a vector indicating the TB risk for each region. The likelihood function for the Poisson variable \( y_i \) is defined as \( \Pr(y_i|\theta) = \prod_{i=1}^{n} \Pr(y_i|\theta) \), assuming that the sample values of the vector \( y = (y_1, \ldots, y_n) \) given the parameter estimates \( \theta \) are independent.\(^{19}\) In a Bayesian modeling framework, prior distributions of the unknown parameters \( \theta \) in the likelihood function are required. The prior distribution reflects the existing knowledge about the parameters \( \theta \) before observing the data \( y \).\(^{19}\) Within the Bayesian framework, all parameters are stochastic and are assigned appropriate distributions known as prior distributions.\(^{19}\)

The Bayesian modeling framework integrates the likelihood function for the data with prior distributions for parameter estimates, giving rise to a probability distribution known as the posterior distribution.\(^{2,3,5,16-21}\) This distribution, denoted as \( \Pr(\theta|y) \), signifies the probability distribution of the parameters given the observed data. It is proportional to the product of the likelihood function and the prior \( \Pr(\theta) \) distributions, as defined by:

\[
\Pr(\theta|y) = \frac{\Pr(y|\theta)\Pr(\theta)}{\int_{\theta} L(y|\theta)\Pr(\theta)d\theta} \quad (1)
\]

In equation (1), the denominator is often referred to as the normalizing constant and has been shown to integrate to 1. The implication is that the equation (1) can be alternatively expressed as \( \Pr(\theta|y) \propto \Pr(y|\theta)\Pr(\theta) \). The Bayesian modeling framework assumes that the parameter estimates are stochastic and hence assumes a distribution for each parameter estimate, including hyperparameters.\(^{30-35}\) The main criticism of such an assumption is that it depends on subjective prior assumptions, which might result in extreme or confusing conclusions. However, these priors also represent an advantage since they provide a tool for statisticians to be transparent about their assumptions.\(^{36-38}\) Overweighting or informative priors have the potential to mislead statistical inferences about the data being studied since parameter estimates would be much influenced by such priors rather than the data under study. In Bayesian modeling, conjugate or non-informative priors are recommended in order to allow the data to have more influence on the parameter estimates.\(^{36-38}\)

Using traceplots or density plots of parameter estimates,\(^{39}\) Markov Chain Monte Carlo (MCMC) methods determine when a model’s parameters have converged, greatly facilitating Bayesian inference for complex models. Nonetheless, these methods are computationally intensive and encounter various convergence issues. Integrated nested Laplace approximation (INLA) offers a computationally efficient alternative to MCMC for approximate Bayesian inference in latent Gaussian models.\(^{40}\) These models encompass a broad range, from generalized linear mixed models to spatial and spatio-temporal models.\(^{20,40}\) INLA employs a combination of analytical approximations and numerical algorithms for
spatial dependence parameter identifies heterogeneity or variability in disease risk among regions. The BYM model is defined as a Bayesian hierarchical model that incorporates both a spatially structured random effect and a regression component. The model consists of two main components: the conditional autoregressive (CAR) model, which captures and conveys the spatial dependence among observations, and a regression component that includes covariates. The BYM model can be described as

\[
\log \left( \frac{\lambda_i}{\mu_i} \right) = \eta_i + \phi_i + u_i
\]

where \( \mu_i \) represents the mean, \( \eta_i \) embodies the random effect structure, and \( \phi_i \) signifies the CAR structure. It is assumed that the random effect component, \( u_i \), follows a Gaussian distribution.

A compelling feature of the Conditional Autoregressive (CAR) model is its capability to create a framework that facilitates the sharing of strength among neighboring regions. As a result, adjacent regions are inclined to display similar relative risks, whereas those that are more distant are more likely to exhibit variability in terms of the risk associated with the respective regions.

Let \( \varphi = \{i = 1, 2, \ldots, n\} \) represent the regions, and \( N_i = \{j \in \varphi : i \neq j\} \) identifies regions that share boundaries with region \( i \). Additionally, let \( \phi_i \), where \( i \in \varphi \), have a stochastic distribution. It is assumed that \( i \in \Omega \) follows a Gaussian distribution, as outlined by:

\[
\phi_i | \phi_j, j \in N_i \sim N \left( \sum_{j \in N_i} W_{ij} \phi_j, \tau_{\phi, i}^2 \right)
\]

where \( W_{ij} \) represents the spatial dependence parameter determining the impact of each observation on the Conditional Autoregressive (CAR) structure \( \phi_j \), where \( j \) encompasses all observations except \( \phi_i \), and \( \tau_{\phi, i}^2 \) signifies the precision of \( \phi_i \).

The spatial dependence parameter \( W_{ij} \) is non-zero if \( j \in S \). To prevent autocorrelation, we designate \( W_{ij} = 0 \). This is to avoid conducting regression involving any observation against itself.\(^{24,26,35,44}\) The model specification (2) indicates that \( \phi_i \) solely relies on a set of neighboring \( \phi_j \) when the region \( j \) is part of the neighborhood set \( N_i \) of \( \phi_i \). For an in-depth explanation of the CAR structure, refer to.\(^{24,26,35,44}\)

Given that \( y_i \) follows a Poisson distribution with parameter \( E_i \exp(\eta_i) \), and \( \mu_i = E_i \exp(\eta_i) \), the Besag, York, and Mollié (BYM) model with covariates can be described as \( \eta_i = X_i \beta + \phi_i + u_i \). Here, \( E_i = rN_i \) represents the expected number of TB cases in region \( i \), with \( r = \sum_{i=1}^{n} \frac{1}{N_i} \), where \( N_i \) denotes the at-risk population in region \( i \). Furthermore, \( X \) denotes a design matrix of covariates, and \( \beta \) represents a vector of parameter estimates associated with these covariates.

Given \( \theta_i = \exp(\eta_i) \), it implies that \( \log(\theta_i) = \eta_i \), where \( \eta_i \) represents the linear predictor. Consequently, the relative risk for each region \( i \) can be expressed as \( \theta_i = \exp(\eta_i + \phi_i + u_i) \), and the log-log link function can be defined as \( \log(\mu_i) = \log(E_i) + \exp(\eta_i + \phi_i + u_i) \).

To estimate parameters from the Bayesian posterior distribution, it is necessary to have the likelihood function of the data, along with prior distributions for the Conditional Autoregressive (CAR) structure, random effect, and the regression coefficients \( \beta \). The prior distributions for the random effects and regression coefficients are assumed to conform to a Gaussian distribution. Consequently, the resulting posterior distribution can be specified as follows:

\[
\Pr(\theta_i, \beta, u_i, \phi_i, \tau_{\phi, i}^2, \tau_{u, i}^2, \tau_{\beta}^2 | y, E) \propto \Pr(y, E | \theta_i, \beta, u_i, \phi_i, \tau_{\phi, i}^2, \tau_{u, i}^2, \tau_{\beta}^2) \Pr(\beta) \Pr(u_i) \Pr(\phi_i).
\]

The hyper-prior precision parameters \( \tau_{\phi}^2, \tau_{u}^2 \) and \( \tau_{\beta}^2 \) follow the Gamma distributions: \( \tau_{\phi}^2 \sim \text{Gamma}(0.5, 0.005) \), \( \tau_{u}^2 \sim \text{Gamma}(0.5, 0.005) \), and \( \tau_{\beta}^2 \sim \text{Gamma}(0.5, 0.01) \) respectively. The vector of regression coefficients \( \beta \), is governed by a Gaussian distribution specified as \( \beta \sim N(0, \tau_{\beta}^2) \). The estimated parameters, \( \tau_{\phi}^2 \) and \( \tau_{u}^2 \), represent the precision variance parameters.
parameters for \( u \) and \( \phi \) respectively. They are utilized to gauge the level of variability among regions and the clustering of risk among neighboring regions.\(^{19} \) Additionally, we empirically estimated the spatial structure effect as \( r^2 = \frac{\sum_{i=1}^{n} (e_i - \bar{e})^2}{\sum_{i=1}^{n} e_i^2} \), where \( \bar{e} \) is the average of \( e \). This empirical estimation was then compared to the posterior marginal variance for the unstructured effect, provided by \( r^2_u \), provided proportion spatial = \( \frac{\bar{e}^2}{\bar{e}^2 + r^2_u} \). We utilized \( \Pr(\theta_0 > 1 | y_i) \) to identify regions with a high probability of demonstrating a risk greater than 1.

**Spatio-temporal models**

The TB case data utilized in this study were gathered over a period, and consequently, relying solely on spatial models may not suffice to capture and elucidate the spatio-temporal pattern of the relative risk of TB. This limitation arises because spatial models are confined to identifying heterogeneity and clustering of disease risk at a specific time point. In this section, we introduce three spatio-temporal models\(^{34,35} \) designed to investigate the spatio-temporal pattern of disease risk. These models vary in their space-time interaction structures.\(^{20,21,33,35,45} \)

Let \( y_{ij} \) denotes observed TB cases in region \( i \), year \( j \). The distribution of TB cases is defined as \( y_{ij} \sim \text{Poisson}(E_{ij} \exp(\eta_{ij})) \), where the unknown relative risk \( \theta_0 \) for region \( i \) at year \( j \) can be expressed as \( \theta_0 = \exp(\eta_{0ij}) \) and \( E_{ij} \) is the expected number of TB cases in region \( i \) at year \( j \). We define the crude rate of TB cases for region \( i \) at year \( j \) as \( r^2_{ij} = \frac{y_{ij}}{e_{ij}} \) and the expected TB cases in region \( i \) at year \( j \) is defined as \( E_{ij} = r^2_{ij}N_j = \frac{y_{ij}}{\bar{e}}N_j \), where \( N_j \) denotes the population, \( y_{ij} \) is the TB cases in the standard population. This means that the overall crude rate of TB is given by \( r = \frac{\sum_i \sum_j y_{ij}}{\sum_i \sum_j \bar{e}_j} \) and the overall number of expected TB cases is defined by \( \mathbb{E} = \sum_i \sum_j r^2_{ij}N_j = \sum_i \sum_j \frac{y_{ij}}{\bar{e}}N_j \).\(^{3,2} \)

The first spatio-temporal model\(^{34} \) presented in this study defines the linear predictor \( \eta_{ij} \) as

\[
\eta_{ij} = \mu + \phi_i + u_i + (g + \delta_i) \times j, \tag{3}
\]

where \( \phi_i + u_i \) component follow the BYM\(^{24} \) model’s specification, \( g \times j \) is the global linear time trend, \( j \times \delta_i \) is the interaction term between space and time defining the difference between \( g \) and the area-specific time trend.\(^{20,46} \) The variable \( j \) represents a vector of temporal weights, and the intercept \( \mu \) quantifies the average TB rate across all 10 regions. The differential trend \( \delta_i \) signifies the interaction between time and space. The relative risk is expressed as \( \theta_0 = \exp(\eta_{0ij}) \), and the logarithm of the risk is \( \log(\theta_0) = \eta_{ij} \). This implies that \( \theta_0 = \exp(\eta_{0ij}) \approx \exp(\mu + \phi_i + u_i + (g + \delta_i) \times j) \). Consequently, the Poisson mean is \( \mu_j = E_{ij} \exp(\mu + \phi_i + u_i + (g + \delta_i) \times j) \), and the logarithm of the mean is defined as \( \log(\mu_{ij}) = \log(E_{ij}) + \mu + \phi_i + u_i + (g + \delta_i) \times j \). These formulations suggest that each spatial unit possesses its own time trend with a spatial intercept \( \mu + \phi_i + u_i \) and a slope \( g + \delta_i \). This model assumes a linear time trend in each spatial unit. The parameters to be estimated are \( \varphi = \{\bar{g}, \bar{\phi}, \bar{u}, \bar{\delta}\} \), and the hyper-parameters are denoted as \( \psi = \{\tau_g, \tau_\phi, \tau_u, \tau_\delta\} \).

When accounting for TB risk factors \( X_i \), model (3) can be expressed as model (4). The parameter estimates vector is now denoted as \( \varphi = \{\beta, \bar{g}, \bar{\phi}, \bar{u}, \bar{\delta}\} \), and the hyper-parameters are represented by \( \psi = \{\tau_{\beta}, \tau_g, \tau_\phi, \tau_u, \tau_\delta\} \)

\[
\eta_{ij} = \alpha + \sum_{p=1}^{P} \beta_p X_p + \phi_i + u_i + (g + \delta_i) \times j \tag{4}
\]

It is established that if \( \delta_i < 0 \), the region-specific trend is less pronounced than the mean trend. Conversely, \( \delta_i > 0 \) indicates that the region-specific trend is steeper than the mean trend.\(^{20,46} \) The parameter \( \delta_i \) is assumed as \( \delta_i \sim \text{Normal}(0, \tau_\delta) \).

The second spatio-temporal model\(^{35} \) defines the linear predictor as

\[
\eta_{ij} = \alpha + \phi_i + u_i + \delta_j + \omega_j \tag{5}
\]

where the combination of terms \( \phi_i + u_i \) represents the BYM model, and the structures \( \delta_j \) and \( \omega_j \) signify the temporally structured and random effects, respectively. This model assumes a non-parametric time trend. By incorporating covariates, the model (5) transforms into:

\[
\eta_{ij} = \alpha + \sum_{p=1}^{P} \beta_p X_p + \phi_i + u_i + \delta_j + \omega_j \tag{6}
\]
The parameters to be estimated encompass $\varphi = \{\alpha, \beta, \phi, \theta, \omega, \varphi\}$, with corresponding hyper-parameters denoted as $\psi = \{\tau_\phi, \tau_\theta, \tau_\omega, \tau_\varphi\}$. The temporally structured effect, $\vartheta_j$, is captured and modeled using a random walk through a neighboring structure. Specifically, for $j = 1, \vartheta_j \sim N(\vartheta_{j-1}, \tau_\vartheta)$; for $j = 2, \ldots, J - 1, \vartheta_j \sim N\left(\frac{\vartheta_{j-1} + \vartheta_{j+1}}{2}, \tau_\vartheta\right)$; and for $j = J, \vartheta_j \sim N(\vartheta_{j-1}, \tau_\vartheta)$. Finally, $\omega_j$ is specified using a Gaussian exchangeable prior: $\omega_j \sim \text{Normal}(0, \tau_\omega)$.

The third spatio-temporal model (7) proposed by Knorr-Held, is an extension of model (6) to allow for a space and time interaction $(\pi_{ij})$ to explain the difference in time trend of TB cases for various regions.

In this model, we estimate $\varphi = \{\mu, \beta, \phi, u_i, \vartheta_j, \omega_j\}$ and $\psi = \{\tau_\varphi, \tau_\beta, \tau_\phi, \tau_u, \tau_\omega, \tau_\vartheta, \tau_\pi\}$, where $\pi_{ij}$ represents the interaction between $\phi$ and $u_i$. It assumes no interaction between $\phi$ and $\vartheta$; hence, $\pi_{ij} \sim N(0, \tau_\pi)$. By incorporating covariates into the model (7), we obtain model (8) and subsequently need to estimate $\theta = \{\mu, \beta, \phi, u_i, \vartheta_j, \omega_j\}$ and $\psi = \{\tau_\varphi, \tau_\beta, \tau_\phi, \tau_u, \tau_\omega, \tau_\pi\}$

Concerning the interaction term $\pi_{ij}$, if we assume the presence of spatial or temporal structure, then $\pi_{ij} \sim N(0, \tau_\pi)$. In this study, all precision parameters are assumed to follow the gamma distribution.

Results

In this section, we described the outcome variable and then applied the spatial and spatio-temporal models to the TB data. These models were implemented in R version 4.3.2 using the Integrated Nested Laplace Approximation (INLA) method. A comparison of the performance of the spatio-temporal models was conducted, and the best-performing model was selected based on the Deviance Information Criterion (DIC) developed by Refs. 20, 42, 48. The model with the lowest DIC was considered the most effective. We then presented and discussed the results obtained from both the BYM model and the best-fitting spatio-temporal model.

Description of the outcome variable

Figure 2 illustrates the TB trends in these regions over the specified time frame. Generally, there is an overall decline in TB cases observed across all regions of Ghana from 2008 to 2016, with the exception of the Brong Ahafo Region where TB cases increased. Notably, between 2016 and 2017, there was a significant increase in TB cases in the Northern and

Figure 2. Trend of TB cases detection per 100,000 by region for 10 years from 2008 to 2017 in Ghana.
Upper East regions. Conversely, the Ashanti Region witnessed a decrease from 50 per 100,000 population in 2016 to 45 per 100,000 population in 2017. Specifically, TB cases in the Northern Region surged from 24 per 100,000 population in 2016 to 52 per 100,000 population in 2017. Similarly, the Upper East Region experienced an increase from 53 per 100,000 population in 2016 to 63 per 100,000 population in 2017. However, the changes in TB cases in the remaining regions remained relatively stable during this period.

Figure 3 depicts the trajectory of the total number of tuberculosis (TB) cases for each region from 2008 to 2017. Notably, it illustrates that the Greater Accra Region consistently recorded the highest number of cases during this period, while the Northern Region registered the lowest. The Volta and Western Regions ranked second and third, respectively, with slightly lower case counts than the Greater Accra Region. Furthermore, Figure 4 displays the trend of total TB cases for each year or period. The data reveals that the peak in total TB cases occurred in 2011, whereas the lowest count was recorded in 2016. There is a discernible slow decline in TB cases from 2011 to 2017, marked by slight increases in 2012 and 2017.

Moreover, the variability of tuberculosis (TB) cases from 2008 to 2017 is illustrated through box-and-whisker plots in Figure 5. The overlapping box-and-whisker plots in Figure 5A suggest a lack of variability in TB cases across the years. These plots indicate a skew towards larger numbers from 2008 to 2014, shifting towards smaller numbers from 2015 to 2016. Particularly small numbers were noted in 2013, 2014, 2015, and 2017. Figure 5B presents the variability across regions. The non-overlapping box-and-whisker plots signify variability in TB cases among the regions. Additionally, it is
observed that TB cases in most regions are skewed towards larger numbers, except for the Northern and Upper East regions.

Results from the BYM model

The results from the BYM model with the posterior estimates are shown in Table 1. Among the baseline predictors, the significant predictors for TB infection risk in Ghana that yield accurate models include: Tuberculosis cure rate ($\beta_1$), Tuberculosis success rate ($\beta_2$), proportion of people with knowledge about TB ($\beta_3$), proportion of those who know that TB is airborne ($\beta_4$), HIV prevalence ($\beta_5$), proportion in high income group ($\beta_6$) and literacy ($\beta_7$).

Figure 6A displays the map depicting the posterior mean for the region-specific relative risk ($\theta_i$) of TB infection, while Figure 6B presents a map indicating the excess risk of TB. It can be observed in Figure 6A that high risk of TB infection is distributed towards the Northern part of Ghana ranging between 1-1.2 for Upper East, Upper West and Northern regions. High risk of TB infection can be observed in Eastern and Greater Accra regions in the Southern part of Ghana. It can be observed in Figure 6B that Greater Accra region is the region with the highest probability of risk (0.8-1) exceeding the national risk 1 followed by Upper West, Northern and Eastern regions with risk between 0.5-0.8 and lowest risks (0.2-0.5) are observed in Upper East, Brong-Ahafo, Western, Volta, Ashanti, and Central regions.

Once more, there is slight variability in TB infection risk was noted across various regions, alongside significant clustering or similarities of TB infection risk among neighboring regions shown in Figure 6.

The results in Table 1 confirm the similarity or clustering of risk between or among neighboring regions. This is indicated by the low variability captured by the precision of the spatial structure $\tau_x$. The precision $\tau_u$ of the unstructured component of the BYM model indicates that risk is slightly heterogeneous among regions. The exponent of the posterior mean $\mu$ (overall mean effect) indicates that there is approximately 9-fold reduction in TB infection rate across the 10 regions in Ghana.

Table 1. Summary statistics: posterior mean, standard deviation (Sd) and 95% credible interval for the fixed and random effects of the BYM model.

|                  | Estimate | Sd  | 25%  | 50%  | 95%  |
|------------------|----------|-----|------|------|------|
| **Fixed effects**|          |     |      |      |      |
| $\mu$            | 9.085    | 5.54| 3.70 | 6.115| 26.537|
| $\beta_1$        | 1.081    | 1.027| 1.024| 1.081| 1.141|
| $\beta_2$        | 0.855    | 1.040| 0.789| 0.855| 0.927|
| $\beta_3$        | 1.046    | 1.017| 1.010| 1.046| 1.083|
| $\beta_4$        | 0.897    | 1.055| 0.806| 0.897| 1.000|
| $\beta_5$        | 0.450    | 1.297| 0.266| 0.450| 0.762|
| $\beta_6$        | 0.946    | 1.017| 0.914| 0.946| 0.979|
| $\beta_7$        | 1.116    | 1.045| 1.022| 1.116| 1.219|
| **Random effects**|         |     |      |      |      |
| $\tau_u$         | 25.80    | 20.62| 3.83 | 20.41| 80.01|
| $\tau_x$         | 1834.88  | 1810.43| 121.58| 1299.34| 6656.65|
From Table 1, it can be observed that TB cure rate $\beta_1(\cdot)$ increases the risk of TB infection by approximately 8%. This observation implies that as more cases are detected, more cases are cured and hence TB cases will in general decrease over time. This explains why TB success rate $\beta_2(\cdot)$ leads to 14% reduced risk of TB infection. The results also revealed that knowledge about TB $\beta_3(\cdot)$ significantly increases TB infection risk by approximately 5%. This behavior is expected because, as people become aware of TB, preventive measures are taken. The proportion of high-income group $\beta_6(\cdot)$ is associated with 5% reduction in TB infection while proportion of literacy $\beta_7(\cdot)$ is associated with 12% increase in TB cases. High income increases the use of health facilities and testing for TB, thus, leading to a reduction of TB cases. HIV prevalence $\beta_5(\cdot)$ in the region leads to a 55% reduction in TB cases.

Best fitting spatio-temporal model for TB infection risk

In this section, we fitted the three spatio-temporal models, adjusting for covariates effects on TB risk. Let us call the model (4); Model I, model (6); Model II and model (8); Model III. The best model is then selected and results from such a model are reported. Table 2 presents the DIC, mean deviance $D$ and effective number of parameters $pD$ components for the three space-time models. These indicators of a model’s performance suggest that Model I proved to be the best fitting model among the three candidates’ spatio-temporal models. Hence, we presented only the results from this model.

Results from spatio-temporal model: Model I

The results in Table 3 showed that TB infection risk decreases across the 10 regions of Ghana. However, there is no significant reduction in TB infection risk over the study period. The precision parameter $\tau_u$ indicates very low variability in the risk of TB detection among the regions and much clustering of risk between neighboring regions exhibited by high precision parameter $\tau_\phi$ values for the spatial structure. High precision characterized by $\tau_\delta$ indicates lower variability associated with $\delta_i$. This further indicates that there is no significant interaction between space and time as well as global trend $\varrho$ and area-specific trend $\delta_i$. Hence, the area-specific trend $\delta_i$ is less remarked than the mean trend.

The results also revealed that TB success rate significantly increases TB cases by 11%. Also, knowledge about TB significantly reduces TB cases by approximately 2%, while increasing TB cure rate, significantly reduces detection by 8%. Awareness that TB is airborne increases TB detection by approximately 25%. That is, more people are willing to participate in TB testing to know their status leading to more case detection. We also observed that HIV prevalence and high income significantly increases TB detection by 27% and approximately 4%, respectively. Literacy significantly reduces the risk of TB detection by approximately 14%.

Table 2. Indicators of space-time models performance.

| Model   | $D$    | $pD$  | DIC       |
|---------|--------|-------|-----------|
| Model I | 518.6  | 17.81 | 536.42    |
| Model II| 547.1  | 10.56 | 557.62    |
| Model III| 546.8 | 11.00 | 557.76    |
Table 3. Summary statistics: posterior mean, standard deviation (sd) and 95% credible interval for the fixed and random effects of Model I.

|                | Estimate | sd    | 25%    | 50%    | 95% CI  |
|----------------|----------|-------|--------|--------|---------|
| **Fixed effects** |          |       |        |        |         |
| \( \mu \)      | 0.177    | 1.075 | 0.020  | 0.181  | 1.400   |
| \( t \)        | 1.006    | 1.007 | 0.992  | 1.005  | 1.019   |
| \( \beta_1 \)  | 0.920    | 1.012 | 0.899  | 0.920  | 0.943   |
| \( \beta_2 \)  | 1.114    | 1.018 | 1.076  | 1.114  | 1.155   |
| \( \beta_3 \)  | 0.978    | 1.008 | 0.963  | 0.978  | 0.993   |
| \( \beta_4 \)  | 1.245    | 1.023 | 1.189  | 1.245  | 1.302   |
| \( \beta_5 \)  | 2.273    | 1.120 | 1.811  | 2.277  | 2.829   |
| \( \beta_6 \)  | 1.038    | 1.008 | 1.021  | 1.038  | 1.052   |
| \( \beta_7 \)  | 0.858    | 1.019 | 0.828  | 0.858  | 0.891   |
| **Random effects** |         |       |        |        |         |
| \( \tau_u \)   | 835.68   | 1220.69| 2.33  | 337.68 | 4258.23 |
| \( \tau_{\phi} \) | 1272.83 | 1543.46| 24.97 | 738.52 | 5456.29 |
| \( \tau_\delta \) | 521.70  | 400.33 | 114.09| 412.56 | 1581.45 |

Figure 7. Spatio-temporal model: regions-specific risk (Figure A) and exceedance probability (Figure B).

Figure 8. Spatio-temporal pattern of TB infection risk for 2008 (Figure A) and 2010 (Figure B).
The TB infection risk $\theta_i$ representing the spatial component of the spatio-temporal model is displayed in Figure 7A and Figure 7B is the map of exceedance risk. Both Figure 7A and Figure 7B showed that TB infection risk is clustered among regions in the Southern part of Ghana with Brong-Ahafo, Volta, Ashanti, Eastern, Greater Accra regions showing high risk (1-1.1) and the rest of the region show low risk between 0.9-1. These observations account for the low variability captured by both the unstructured and structured components of the area-specific trend. Furthermore, the precision ($\tau_\theta$) of the random effect of the temporal structure ($\phi_j$) suggests a clustering of the relative risk of TB over time. Maps showing spatio-temporal pattern of TB infection risk for 2008 and 2010 are respectively presented in Figure 8A and Figure 8B for illustration. Elevated TB infection was found in the Southern part of the country across all the years. However, the infection risk was consistently below 1 in all the years.

Discussion

Accurate assessment and mapping of a disease risks are crucial for the efficient allocation of resources and targeted interventions to address disease hotspots, where there is a high risk of the disease. This research provides valuable insights into tuberculosis (TB) infection hotspots across various regions in Ghana by employing maps that highlight areas with elevated TB infection risk. The study investigates the spatial and spatio-temporal patterns of TB prevalence using a Bayesian modeling framework. Within this framework, we explore the clustering and heterogeneity of TB relative risk, utilizing a conditional auto-regressive (CAR) spatial structure and an unstructured component for random effects, respectively. The data utilized in our analysis are sourced from the Ghana Health Service and the National Tuberculosis Program. To fit the models, we employed the Integrated Nested Laplace Approximation through the R software.

In this study, the model utilized to explore the spatial pattern of TB risk was based on the convolution model, specifically the Besag-York-Mollié (BYM) model. The findings indicate a heightened risk of tuberculosis (TB) infection in the Northern part of Ghana, specifically in the Upper East, Upper West, and Northern regions. Similarly, the Southern part, particularly the Eastern and Greater Accra regions, exhibits a high risk of TB infection. Notably, the Greater Accra region stands out with the highest probability of risk, surpassing the national risk level of 1, a trend consistent with the observation that more TB cases are reported in the Greater Accra regions, as noted by various authors. Additionally, the study reveals significant clustering or similarities in the risk of tuberculosis (TB) infection among adjacent regions in Ghana. Moreover, there is an observed decline in the rate of TB infections across the ten regions in Ghana, as observed in Refs. 13, 50. The clustering of disease risk between regions may stem from shared geographic factors or possibly be linked to characteristics such as demographics, clinical aspects, or epidemiological factors.

The study findings indicate that the TB cure rate is associated with an increase risk of TB detection. This suggests that as more cases are detected and cured, the overall number of TB cases tends to decrease over time. Conversely, a higher TB success rate is linked to a reduction in the risk of TB infection, highlighting the effectiveness of successful treatment in lowering the prevalence of TB. Furthermore, increased knowledge about TB is shown to significantly raise TB infection risk; as more people are willing and available to be tested for TB, more infected cases are detected. On the socioeconomic front, a higher proportion of high-income individuals is associated with a reduction in TB infection, as it correlates with increased use of health facilities and testing for TB. However, a higher proportion of literacy is linked to an increase in TB cases, suggesting a complex relationship between literacy levels and TB infection. Notably, HIV prevalence is found to be associated with a substantial reduction in TB cases, underscoring the impact of HIV prevalence on TB infection rates. The reduced risk of TB infection may be due to the fact that regions with high prevalence of HIV might have received attention in terms of HIV counseling, screening for TB and treatment. For instance, interventions such as early HIV counselling and screening for TB patients and early diagnosis and initiation of antiretroviral therapy (ART) to coinfected individuals have all been shown to be effective in preventing TB disease.

We also studied the spatio-temporal distribution of TB infection risk using the spatio-temporal modeling frameworks proposed by Bernardinelli and colleagues, Waller and colleagues, and Knorr-Held and Rafter. To determine the most suitable spatio-temporal model, we fitted these models and employed their individual Deviance Information Criterion (DIC) for selection. Among these models, the space-time model with the interaction term proposed by Bernardinelli and colleagues demonstrated the optimal fit to the TB data, as evidenced by its lowest AIC value. The findings indicated a decreased risk of TB infection across the country. Nonetheless, there was no significant reduction in TB infection risk over the study period, and there remained substantial clustering of risk among neighboring regions. High TB infection risk was identified consistently in the Southern part of the country throughout the years, although the infection risk consistently stayed below 1. Within the Southern part of Ghana, TB infection risk showed clustering among regions, with Brong-Ahafo, Volta, Ashanti, Eastern, and Greater Accra regions exhibiting elevated risk levels.

The data utilized in this study possesses a spatial dimension, encompassing reported TB cases across various districts, towns, and villages within the region. As a result, there are often shared factors that contribute to the prevalence of
TB. This highlights the importance of identifying regions with high TB incidence, and facilitating the allocation of essential resources to address variables recognized as potential contributors to TB infection in those specific areas. The significance of regional-level modeling in the context of TB decision-making in Ghana is considerable. By employing regional-level models, it becomes possible to comprehend the localized dynamics and specific factors contributing to TB prevalence within distinct regions of the country. This approach facilitates more targeted and effective decision-making in resource allocation, intervention strategies, and the deployment of healthcare measures. It provides a deeper understanding of the unique challenges and variations in TB transmission, ensuring that interventions are tailored to address the specific needs of different regions in Ghana.

There is a notable absence of comprehensive literature addressing the modeling and mapping of tuberculosis (TB) risk in Ghana, particularly in terms of statistical methodology and practical application. The current body of literature has predominantly focused on spatial and seasonal modeling and mapping of TB risk, with no exploration of spatio-temporal risk across different years by various authors. While some studies have conducted modeling and mapping of TB risk without considering seasonal or spatio-temporal effects, others have incorporated the seasonal pattern of TB risk. Notably, there is a lack of studies investigating the yearly or monthly spatio-temporal effects on TB infection risk in Ghana. In general, the literature lacks an in-depth exploration of statistical methodologies and applications for modeling and mapping TB infection risk in Ghana, especially in the domain of spatio-temporal modeling using advanced statistical methods. This study aims to address this gap and contribute to the existing literature on the modeling and mapping of TB risk in Ghana. It serves as a pioneering effort in utilizing these statistical methodologies to examine spatial and spatio-temporal aspects of TB risk in the country. Emphasizing the use of such statistical methodologies in studying disease risk in Ghana, the study underscores their ability to provide precise estimates of disease risk in both space and time.

Limitations
One significant limitation is the reliance on existing data, which could contain errors if healthcare workers input information incorrectly. Additionally, using secondary data may compromise external validity if biases exist in the population under study. Another potential source of bias is non-random participant selection, which could make the estimates unreliable if the sample doesn’t accurately represent the entire population.

Conclusion
The identification of TB hot-spots in the Northern part of Ghana and the Greater Accra and Eastern regions in the Southern part of Ghana suggests a need for targeted interventions in these areas. Factors such as TB cure rate, TB success rate, knowledge about TB, income status, and HIV prevalence were identified as significant predictors of TB infection risk. This suggests that TB control measures should focus on treating more TB infected patients, creating TB awareness among the general public, making healthcare facilities available and accessible for both the poor and rich, and ensuring people living with HIV are identified early for treatment.

Similar levels of TB infection risk were observed among neighboring regions in Ghana, suggesting that these areas share common geographical traits influencing TB risk. This highlights the necessity for further research to identify such factors, enabling targeted interventions to enhance TB control measures.

Our study underscores the critical importance of precise risk assessment and mapping for effective resource allocation and targeted interventions. This research contributes valuable insights into disease hotspots across various regions in Ghana, utilizing advanced mapping techniques. The convolution model, incorporating both structured and unstructured components, facilitated spatial modeling with Bayesian methodology, revealing substantial variability and clustering of risk among neighboring regions. The findings unveiled distinct patterns of risk distribution, with certain regions exhibiting heightened risk over specific years.

In conclusion, our study enhances the understanding of TB dynamics in Ghana by employing sophisticated modeling techniques and innovative spatial and spatio-temporal analyses. These insights provide a foundation for informed decision-making, resource allocation, and targeted interventions, contributing to the ongoing efforts against TB and improving public health outcomes. Regions sharing similar risk patterns, possibly due to common local climatic conditions, can guide targeted resource allocation, given the regional basis of resource allocation in Ghana. The utilization of advanced statistical methods, encompassing both spatial and spatio-temporal analyses, is encouraged to further enrich the existing statistical literature on modeling and mapping TB risk in Ghana. We also recommend application of these methodologies to study spatial and spatio-temporal patterns of TB infection risk using TB data on all the 16 administrative regions in Ghana.
Data availability
Source data: The data used in this study can be found in the following links: https://openafrica/dataset/4176f749-cfa8-4e32-9418-86cfe78f9db6/resource/0b4f9b54-3e35-4543-95cd-f4de95edff/download/factsfigures_2018.pdf, https://www.who.int/teams/global-tuberculosis-programme/data?https://www.stoptb.org/static_pages/GHA_Dashboard.html.

Author contribution
Conceptualization, Software. Formal analysis: AKI Methodology and Investigation: AKI, FKB Data curation, Writing (Original draft preparation), and Writing (Review and editing): AKI and EAA Validation.

Acknowledgements
Thank you to the Ghana Health Service and National Tuberculosis Program for making data available for the study.

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Current Peer Review Status:  ✔  ?  ?  ?

Version 4

Reviewer Report 26 June 2024

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Soedarsono Soedarsono
Sub-pulmonology Department of Internal Medicine, Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia

This study successfully fills a gap in the literature by applying a hierarchical Bayesian model to identify Tuberculosis 'hotspots' in Ghana. The authors produced a detailed and visual mapping of TB risk, highlighting the significance of factors such as TB cure rates, community knowledge about TB, and HIV prevalence in influencing TB infection risk across different regions of Ghana. This aspect is one of the highlights of the journal. However, there is important point in this manuscript that need clarification as follows:

- The authors have not provided sufficient details regarding the exact methods or procedures used to ensure that the TB patients included in the study were accurately diagnosed both bacteriologically and/or clinically. Further information about the steps taken to validate these diagnoses would provide greater clarity and confidence in the spatial and spatio-temporal analysis results conducted in this study.

Overall, this manuscript needs Minor Revisions.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Partly
Are the conclusions drawn adequately supported by the results?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** pulmonary TB

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Version 3**

Reviewer Report 11 June 2024

https://doi.org/10.5256/f1000research.162565.r271890

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Md. Saiful Islam
University of New South Wales, Sydney, New South Wales, Australia

Please see my specific comments below:

**Abstract:**
The conclusion in the abstract needs improvement. Based on the findings, there should be a summary sentence in the conclusion.

**Main Manuscript:**
○ **Background:**
- 'Mycobacteria' should be *italicized*.
- "In 2019, around 10 million people tested positive for TB" should be edited to "In 2019, it was estimated that around 10 million people had TB."
- HIV should be defined when used for the first time.
- WHO has been defined multiple times. The author may define 'WHO' once, and then there is no need to define it again.
- Tuberculosis (TB) has already been defined in the first sentence.
○ **Methods:**
"One significant limitation is the reliance on existing data, which could contain errors if healthcare workers input information incorrectly. Additionally, using secondary data may compromise external validity if biases exist in the population under study. Another potential source of bias is non-random participant selection, which could make the estimates unreliable if the sample doesn't accurately represent the entire population." This sentence should go under the discussion.
section as study limitations.
  ○ **Outcome Variables:**

This section needs to be shortened. The author may describe only the outcome variables here. There is no need to present background information that has already been described under the introduction.
  ○ **Discussion:**

The author may avoid repeating information in the discussion section. For example, the sentence “The data utilized in our analysis are sourced from the Ghana Health Service and the National Tuberculosis Program. To fit the models, we employed the Integrated Nested Laplace Approximation through the R software” has already been discussed earlier. In the discussion, the author may reflect on the fundamental rationale of the study and how the overall results link to the study objectives. The author may provide the primary conclusion that can be logically and defensibly drawn from the results.

Paragraph 3 under Discussion:

The study findings indicate that the TB cure rate is associated with an increase in the risk of TB infection. The idea is not clear here. Do you mean the TB cure rate was associated with high case detection? If yes, mention this explicitly.

**Is the work clearly and accurately presented and does it cite the current literature?**
Partly

**Is the study design appropriate and is the work technically sound?**
Yes

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
I cannot comment. A qualified statistician is required.

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Emerging infectious diseases, outbreak, infection prevention and control.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
Author Response 13 Jun 2024

Abdul-Karim Iddrisu

Abstract:

Comment 1.1: The conclusion in the abstract need's improvement. Based on the findings, there should be a summary sentence in the conclusion.
Response 1.1: We thank the reviewer for these comments. In response, we have revised the conclusion as “Factors influencing tuberculosis (TB) risk in Ghana are TB cure rate, TB success rate, knowledge about TB, HIV prevalence, literacy rate, and income level. The risk distribution was mainly concentrated in the Southern zone, with clusters of TB risk observed among neighboring regions. To achieve a significant reduction in TB cases, it is essential to allocate resources to TB hotspots regions and also implement measures to control significant predictors of TB infection risk.”

Main Manuscript:

Background:

Comment 1.2: Mycobacteria' should be italicized.
Response 1.2: We have italicized “italicized”.

Comment 1.3: - “In 2019, around 10 million people tested positive for TB" should be edited to “In 2019, it was estimated that around 10 million people had TB."
Response 1.3: We have revised this text.

Comment 1.4: HIV should be defined when used for the first time.
Response 1.4: Thank you for these comments. In response we have defined HIV as “Human immunodeficiency virus”

Comment 1.5: WHO has been defined multiple times. The author may define 'WHO' once, and then there is no need to define it again.
Response 1.5: We have revised the text accordingly.

Comment 1.6: Tuberculosis (TB) has already been defined in the first sentence.
Response 1.6: We have the text accordingly.

Methods:

Comments 1.7: “One significant limitation is the reliance on existing data, which could contain errors if healthcare workers input information incorrectly. Additionally, using secondary data may compromise external validity if biases exist in the population under study. Another potential source of bias is non-random participant selection, which could make the estimates unreliable if the sample doesn't accurately represent the entire population.” This sentence should go under the discussion section as study limitations.
Response 1.7: We thank the reviewer for this recommendation. In response, the text has been added to the discussion under limitations section.

Outcome variables:

Comment 1.8: This section needs to be shortened. The author may describe only the outcome variables here. There is no need to present background information that has already been described under the introduction.
**Response 1.8:** We have moved the description of the outcome variable to the results section.

**Discussion:**

**Comment 1.9:** The author may avoid repeating information in the discussion section. For example, the sentence "The data utilized in our analysis are sourced from the Ghana Health Service and the National Tuberculosis Program. To fit the models, we employed the Integrated Nested Laplace Approximation through the R software" has already been discussed earlier. In the discussion, the author may reflect on the fundamental rationale of the study and how the overall results link to the study objectives. The author may provide the primary conclusion that can be logically and defensibly drawn from the results.

**Response 1.9:** We thank the reviewer for these insightful and useful comments. In response, it is a standard practice to briefly summarize the entire manuscript (from introduction, objective, methods use) and then discussed the results thoroughly.

**Paragraph 3 under Discussion:**

**Comment 2.1:** The study findings indicate that the TB cure rate is associated with an increase in the risk of TB infection. The idea is not clear here. Do you mean the TB cure rate was associated with high case detection? If yes, mention this explicitly.

**Response 2.1:** Thank you for this important observation. In response, yes, we are referring to TB detection. This text has been revised accordingly.

**Competing Interests:** The authors declared no competing risk.
Specificity: The abstract mentions "baseline predictors of TB infections" but fails to specify which predictors were most significant. For instance, it could be improved by stating, "Among the baseline predictors, factors such as X, Y, and Z were found to be most significant in influencing the TB risk across the ten regions in Ghana."

Introduction
Contextual Depth: The introduction provides a global context of TB but lacks specific details about the TB situation in Ghana, particularly the regions chosen for the study. For instance, "Ghana has been affected by the respiratory disease and currently has challenges in eradicating TB."
Research Gap: The introduction notes the need for the study but could articulate more precisely the specific knowledge gaps, such as "However, there remains a significant gap in understanding the spatio-temporal dynamics of TB in Ghana, which this study aims to address."

Methods
Data Source and Collection: The methods section mentions data obtained from "Ghana National Tuberculosis Programme (NTP)" but doesn't discuss the potential limitations or biases in this data collection process.
Model Assumptions: The section introduces Bayesian models but doesn't critique the assumptions underpinning these models or discuss their potential impact, such as "The Bayesian models assume X, which could influence the results by Y."
Analytical Robustness: The manuscript could discuss the robustness of the models against issues like overfitting or multicollinearity, or detail any model validation techniques used, which is currently missing.

Results
Presentation and Clarity: Results such as "Hot-spots of TB cases are observed in the Upper East, Upper West..." are presented without sufficient interpretation or visualization for easy understanding.
Statistical Significance and Practical Significance: While statistical results are presented, the practical implications of these findings, especially in the context of public health planning in Ghana, are not thoroughly discussed.

Discussion
Comparative Analysis: The discussion could benefit from a more detailed comparison with existing literature, such as "While studies X and Y observed Z, our findings additionally reveal A, suggesting B."
Policy Implications: The discussion should connect findings to policy implications more explicitly, such as "The identification of TB hot-spots in regions X, Y, and Z suggests a need for targeted interventions in these areas."

Limitations
Data Limitations: The limitations section should address the potential impact of data sources and methodologies on the study's reliability, which is not currently discussed.
Scope of Inference: The manuscript does not discuss the extent to which these findings can be generalized beyond the studied regions.

Conclusion
Synthesis of Findings: The conclusion could provide a more concise synthesis of key findings and
their importance in the context of TB control in Ghana. Forward-Looking Statements: Suggestions for future research based on these findings, which could further improve TB control efforts in Ghana, are missing.

General Comments
Flow and Structure: The paper generally follows a logical flow but could ensure a more seamless transition and build-up from one section to the next.

Grammar and Punctuation: Ensure thorough proofreading to correct any grammatical or punctuation errors. Figures, Tables, and References: Figures and tables, such as "Figure 1. Trend of TB cases detection..." and "Table 2. Summary statistics...", should be clearly labelled and referenced in the text, and the references should be current and relevant to the study's subject matter.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: TB, HIV, COVID-19, MPox, Viral hepatitis, NCD and CDs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Feb 2024

Abdul-Karim Iddrisu

We would like to thank the reviewer for the many useful and insightful comments. We have now revised the manuscript substantially. We trust that the revised manuscript now meets the required standards for indexing.
Please find below our responses to the reviewers' comments. All changes made due to the reviewers comments are highlighted in red text inside the revised manuscript.

Abstract:

**Comment 1.1:** Clarity and Focus: The abstract states, "The spatio-temporal characteristics of TB in Ghana using Bayesian spatial and spatio-temporal regression models was analyzed." However, it doesn't detail the novel aspects of these methods or their specific application to the TB context in Ghana, missing an opportunity to highlight the study's unique contributions.

**Response 1.1:** We thank the reviewer these useful comments. In response, we have revised the abstract to highlight the novel aspects the methods used especially their application to TB context in Ghana as "There is insufficient literature regarding the utilization of Bayesian hierarchical models, specifically within the framework of Integrated Nested Laplace Approximation (INLA), for examining the spatial and spatiotemporal dynamics of tuberculosis risk in Ghana. These methods are known to provide precise and efficient estimates of diseases risk in space and time. This study aimed to address this gap by determining TB hotspots regions in Ghana and associated predictors of TB infection risk using the Bayesian modeling framework within the INLA.”

**Comment 1.2:** Specificity: The abstract mentions "baseline predictors of TB infections" but fails to specify which predictors were most significant. For instance, it could be improved by stating, “Among the baseline predictors, factors such as X, Y, and Z were found to be most significant in influencing the TB risk across the ten regions in Ghana.”

**Response 1.2:** We thank the reviewer for these useful comments and suggestions. In response, we have revised the results in the abstract as “Among the baseline predictors, factors such as TB cure rate, TB success rate, knowledge about TB, awareness of airborne transmission of TB, HIV prevalence, percentage of literacy, and high income were found to be most significant in influencing the TB risk across the ten regions in Ghana.”

Introduction:

**Comment 1.1:** Contextual Depth: The introduction provides a global context of TB but lacks specific details about the TB situation in Ghana, particularly the regions chosen for the study. For instance, "Ghana has been affected by the respiratory disease and currently has challenges in eradicating TB."

**Response 1.1:** We thank the reviewer for these comments. In response, we have revised the introduction to take into account tuberculosis situation in Ghana (Page 3, 1st paragraph), highlighted in a red text.

**Comment 1.2:** Research Gap: The introduction notes the need for the study but could articulate more precisely the specific knowledge gaps, such as "However, there remains a significant gap in understanding the spatio-temporal dynamics of TB in Ghana, which this study aims to address."

**Response 1.2:** Thank for these comments and a very useful suggestion. In response, we
have explicitly stated the research gap in the introduction (Page 4, 1st paragraph), highlighted in a red text.

Methods:

Comment 1.1: Data Source and Collection: The methods section mentions data obtained from "Ghana National Tuberculosis Programme (NTP)" but doesn't discuss the potential limitations or biases in this data collection process.
Response 1.1: We thank the reviewer for this suggestion. In response, we have revised the Data section accordingly (Page 5, 1st paragraph, Section 2.1), highlighted in a red text.

Comment 1.2: Model Assumptions: The section introduces Bayesian models but doesn't critique the assumptions underpinning these models or discuss their potential impact, such as "The Bayesian models assume X, which could influence the results by Y."
Response 1.2: Thank you for these useful suggestions. We have revised the methodology to include some criticism about the model assumptions (Page 9, last paragraph), highlighted in a red text.

Comment 1.3: Analytical Robustness: The manuscript could discuss the robustness of the models against issues like overfitting or multicollinearity, or detail any model validation techniques used, which is currently missing.
Response 1.3: Thank you for these comments. We have revised the methods section accordingly (Page 9, 2nd paragraph), highlighted in a red text.

Results:

Comment 1.1: Presentation and Clarity: Results such as "Hot-spots of TB cases are observed in the Upper East, Upper West..." are presented without sufficient interpretation or visualization for easy understanding.
Response 1.1: Thank you for these comments. In response, we have now provided map of Ghana (in Figure 1) to display regions names on the map for easy visualization and identification of regions exhibiting TB hotspots.

Comment 1.2: Statistical Significance and Practical Significance: While statistical results are presented, the practical implications of these findings, especially in the context of public health planning in Ghana, are not thoroughly discussed.
Response 1.2: We thank the reviewer for these comments. In response, we have revised the discussion section to reflect the practical implications of the study findings (Page 21-2023, Section 4), highlighted in a red text.

Discussion:

Comment 1.1: Comparative Analysis: The discussion could benefit from a more detailed comparison with existing literature, such as "While studies X and Y observed Z, our findings additionally reveal A, suggesting B."
Response 1.1: Thank you for these comments and suggestions. In response, we have
revised the Discussion section accordingly (Page 20-23, Section 4), highlighted in a red text.

**Comment 1.2:** Policy Implications: The discussion should connect findings to policy implications more explicitly, such as “The identification of TB hot-spots in regions X, Y, and Z suggests a need for targeted interventions in these areas.”

**Response 1.2:** Thank you for the comments and suggestions. We have included the policy briefs in the Conclusion section (Page 23-24, Section 5).

**Limitations:**

**Comment 1.1:** Data Limitations: The limitations section should address the potential impact of data sources and methodologies on the study's reliability, which is not currently discussed.

**Response 1.1:** We have discussed the potential impact of data sources on the study's reliability in the Data section (Page 5, 1st paragraph).

**Comment 1.2:** Scope of Inference: The manuscript does not discuss the extent to which these findings can be generalized beyond the studied regions.

**Response 1.2:** We thank the reviewer for this recommendation. In response, we have revised the conclusion section with a recommendation for further studies on TB infection risk to consider application of these methodologies using TB data from all the 16 administrative regions in Ghana. “We also recommend application of these methods to study spatial and spatiotemporal patterns of TB infection risk using TB data on all the 16 administrative regions in Ghana.” (Page 23-24, Section 5).

**Conclusion:**

**Comment 1.1:** Synthesis of Findings: The conclusion could provide a more concise synthesis of key findings and their importance in the context of TB control in Ghana.

**Response 1.1:** We have provided this information the conclusion (Page 23-24, Section 5), highlighted in a red text.

**Comment 1.2:** Forward-Looking Statements: Suggestions for future research based on these findings, which could further improve TB control efforts in Ghana, are missing.

**Response 1.2:** Suggestions for future research have been stated in the conclusion section (Page 23, Section 5), highlighted in a red text.

**General Comments:**

**Comment 1.1:** Flow and Structure: The paper generally follows a logical flow but could ensure a more seamless transition and build-up from one section to the next.

**Response 1.1:** Thank you for positive comments and this useful suggestion to the authors. We have revised the entire manuscript from abstract to references. This is to ensure flow and easy to comprehend. We are much grateful; review comments are very useful, and we hope that our revised manuscript would meet the required standard for publication.
Comment 1.2: Grammar and Punctuation: Ensure thorough proofreading to correct any grammatical or punctuation errors.
Response 1.2: Thank for these comments. In response, we have proof-read the manuscript for grammar and spelling mistakes.

Comment 1.3: Figures, Tables, and References: Figures and tables, such as "Figure 1. Trend of TB cases detection..." and "Table 2. Summary statistics...", should be clearly labelled and referenced in the text, and the references should be current and relevant to the study's subject matter.
Response 1.3: We thank the reviewer for these useful suggestions. In response, we have correctly labeled and referenced all figures and tables in the manuscript. We have highlighted the changes in a red text for easy identification of where changes have been made. We have also revised some of the references with current references and relevant to the study subject matter. However, we have also included some old reference based on which these methods were developed.

Competing Interests: Non-Financial Competing Interests

Version 1

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Dioggban Jakperik
Department of Statistics, School of Mathematical Sciences, C. K. Tedam University of Technology and Applied Sciences, Navrongo, Ghana

The study modelled TB incidence in Ghana using Bayesian Spatio-Temporal modelling. This covered the old ten (10) administrative regions of Ghana. Regions with high incidents, regarded as hotspots have been identified. The relevant TB and patient characteristics have been considered. The following were however noted which needs consideration:

1. Grammatical errors need to be addressed
2. Ghana now has 16 regions and has to be clearly stated.
3. TB is caused by *bacillus Mycobacterium tuberculosis* and spreads from person to person by air through coughing, etc.
4. Reformat reference number 2 and similar others with such challenges.
5. TB cases should be captured under source of data instead. How did the authors ensure that their data did not involve repetitions since they picked the data from two institutions who play complementary roles in TB management in Ghana?

6. Further, Figures 1,2,3, and 4 are misplaced. They should come under results or maybe introduction is seen as part of literature review but not part of methods.

7. Line 4 after the posterior distribution ... (INLA) package.

8. Under Correlated and Uncorrelated heterogeneity section, the third line after Andrew [], delete “a”.

9. Third paragraph under results, delete “L” and all similar such cases.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Survival and Longitudinal Data Analysis, Survey Theory, and Design of Experiments.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
manuscript for spellings and grammatical errors

Comment 2: “Ghana now has 16 regions and has to be clearly stated.”
Response 2: Thank you for these comments. In response, “The data contain information on TB detection from 2009 to 2017, for only the 10 old administrative regions of Ghana since the newly created 6 additional regions have no data” (See Methods Section under TB cases).

Comment 3: “TB is caused by bacillus Mycobacterium tuberculosis and spreads from person to person by air through coughing, etc.”
Response 3: We thank the reviewer for this important recommendation/suggestion. In response, “TB is caused by bacillus Mycobacterium tuberculosis and spreads from person to person by air through coughing, etc.” (Background Section, lines 2-3).

Comment 4: “Reformat reference number 2 and similar others with such challenges.”
Response 4: Thank you for these comments. In response we have reformatted the reference as “W. H. Organization; Global tuberculosis report 2020: executive summary.” We have also address similar issues in other references.

Comment 5: “TB cases should be captured under source of data instead. How did the authors ensure that their data did not involve repetitions since they picked the data from two institutions who play complementary roles in TB management in Ghana?”
Response 5: Thank you for this insightful and useful comments. In response, we used data from the two institutions however; our main source is Ghana Health Services and some complementary information from the National Tuberculosis Programme.

Comment 6: “Further, Figures 1,2,3, and 4 are misplaced. They should come under results or maybe introduction is seen as part of literature review but not part of methods.”
Response 6: Thank you for this useful observations. In response, we have placed these figures under the Methods Section because Methods Section presents source of the data, description of the data and the methods.

Comment 7: “Line 4 after the posterior distribution … (INLA) package.”
Response 7: Thank you for the comment. In response, we have revised the sentence to now read “The models are implemented in R-software via the Integrated Nested Laplace Approach (INLA) package.”

Comment 8: “Line Under Correlated and Uncorrelated heterogeneity section, the third line after Andrew [], delete “a”.”
Response 8: Thank you for this observation. In response, we have deleted the “a”.

Comment 9: “Third paragraph under results, delete “L” and all similar such cases.”
Response 9: Thank you for this observation. In response, we have deleted the “L” and have addressed all similar cases.

Competing Interests: The authors declare that they have no competing interest.
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