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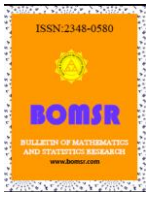
SPATIAL AREAL DATA ANALYSIS WITH APPLICATION TO VARIOUS TUBERCULOSIS OUTCOMES IN KENYA

Erick Okuto
School of Mathematics & Actuarial Science, Jaramogi Oginga Odinga University of Science & Technology, Bondo-Usenge Road, P.O Box 210-40601, Bondo, Kenya
*Erick Okuto (erickokuto@gmail.com)



ABSTRACT

Tuberculosis is second only to HIV as the greater killer worldwide due to a single infectious agent. Improving the treatment outcome of tuberculosis is part of the Millennium Development Goals. Given the infectious nature of tuberculosis, its distribution and treatment outcomes should consider spatial patterning. Information on the distribution of tuberculosis treatment outcomes in Kenya is scarce, yet treatment outcome is an important indicator of tuberculosis management. Spatial analysis tools can be used to characterize spatial patterns of these treatment outcomes, thereby identifying areas at risk of the given outcomes. This study presents a Bayesian model for analysing spatial distribution of tuberculosis treatment outcomes in Kenya. Data was obtained from the national tuberculosis registers from January 2014 to March 2014 with incorporation of data from the Kenya Demographic and Health Survey 2014 and Census 2009. Treatment outcomes were categorized as cured, dead, defaulted, failure and treatment complete. Exploratory data analysis was done to estimate the proportions of the various covariates, and tests for global and local spatial auto correlation done to assess the relationship of the various outcomes per county. Covariates were selected using purposeful selection of variables, and variables with a significant univariate test were selected as candidates for the multivariate analysis. Augmentation of the linear predictors with a set of spatially correlated random effects was done, using conditional autoregressive prior distributions, specified by a set univariate full conditional distributions. Inference was based on obtaining the posterior distribution, of the different TB treatment outcomes, using the Integrated Nested Laplace Approximation Methodology (INLA) as a way of

approximating the posterior marginal. There was significant global spatial autocorrelation seen for the patients who were cured, failed treatment, died and those who completed treatment. However, most of the covariates did not have a mean with significant spatial dependence. The fitted data also showed uniform distribution of the outcomes of tuberculosis treatment across the counties with occasional high risk spots. The spatial effect of the tuberculosis treatment outcomes appeared weak across the various counties. This may imply that appropriate risk factors be adjusted for in the model such that the spatial random effect became less important. Future related studies involving various TB outcomes should be traced at household level to minimize mismatch between risk factors and the TB outcomes.

Key Words: Bayesian Inference; Intrinsic Autoregressive Model; Tuberculosis Treatment outcome; Spatial Analysis; Gaussian Markov Random Field (GMRF); Latent Gaussian Model (LGM)

1 Introduction

The relationship between space and health dates back to Hippocrates who stated that "airs, waters, places" all played significant roles impacting human health and history (Schatz et al., 1944). Concentration of a disease or outcome in a given area implies unusual presence of factors that cause that disease and spatial localization can provide hints as to why the disease occurs in that particular geographical region. Spatial analysis tools are used to characterize spatial patterns of diseases, thereby facilitating cost effective targeting of intervention measures by visualization and exploration of disease patterns (Hoeven et al., 2008). Tuberculosis (TB) is an infectious disease caused by a bacillus belonging to a group of bacteria grouped in the Mycobacterium tuberculosis complex (Daniel, 2000). World Health Organization estimates one third of the humans on earth are infected with TB, but are asymptomatic and cannot transmit it to others, with a 10 percent chance that their infection will develop into TB (Alvarez-Hernandez et al., 2010). People infected with TB bacteria have a 10% lifetime risk of falling ill with TB, but in the presence of compromised immune systems (as with people living with HIV, malnutrition or diabetes, or people who use tobacco) the risk of TB is much higher (Kirenga et al., 2014; Oshi et al., 2014).

According to WHO, TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent (Clements et al., 2006). In 1993, the World Health Organization (WHO) declared tuberculosis a global emergency. Improving TB treatment outcomes was part of the Millennium Development Goals (Gelmanova et al., 2007). There has been continued occurrence of high TB mortality despite effective treatment. 95% of TB deaths occur in low and middle income countries (Bakker et al., 2006). In 2010, Africa alone contributed 26% of the global burden with nine out of the 22 high burden countries contributing 81% of the global burden coming from Africa. During this time, Kenya was ranked position 10 amongst the high burden countries (Getahun et al., 2013). TB is the leading killer of HIV patients accounting for 25% of deaths. TB has a great impact on quality of life, contributing to a high estimate of disability adjusted life years (DALY) at 706.9/100,000, age standardized (Bhatti et al., 1995). One disability adjusted life year (DALY) can be thought of as one lost year of healthy life. The sum of these DALYs across the population, which is also known as the burden of disease, is the measure of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability (Borgdorff and others, 2004). Because of the long duration and associated side effects of standard TB drug treatment, patients often do not complete the full course of therapy (Gelmanova

et al., 2007). This fosters emergence of single- and multi-drug resistant TB (MDR-TB) strains, which has made diagnosis difficult and costly (Vasankari et al., 2007).

Information on the spatial distribution of tuberculosis treatment outcomes in Kenya is scarce, yet treatment outcome is an important indicator of the tuberculosis control program (Kolifarhood et al., 2015). Spatial analysis tools can be used to characterize spatial patterns of the various outcomes of TB, thereby identifying areas at risk of unfavourable treatment outcome (failure, death and default), and areas with successful TB outcomes can have their success strategies emulated (Herrero et al., 2015; Liu et al., 2011). Objective of this study is to evaluate spatial distribution given risk factors estimates of various TB outcomes in Kenya following suggestion by (Vasankari et al., 2007). Most studies on TB outcome have used non-spatial methods to analyse and assess various factors associated with the disease (Kirenga et al., 2014; MacIntyre et al., 1997).

The region based TB outcomes are epidemiological disease outcomes which are characterised by spatial structure which needs to be taken into account when estimating risk factors and relative rates (Kolifarhood et al., 2015). Under such circumstances, the Bayesian approach is generally particularly more effective than the classical approach (Box and Tiao, 1973). For instance, if the TB outcome consists of counts of outcomes and covariates, typically disease mapping can be used (Lawson, 2009). The model can be adopted in a Bayesian framework hierarchically by extending the additive structure, allowing strength borrowing from neighbouring regions (Besag and Newell, 1991). However, the main challenge with the more traditional Bayesian method typically based on simulation scheme using Markov Chain Monte-Carlo (MCMC) approach is computation (Brooks et al., 2011; Robert and Casella, 2013). Though MCMC method is extremely flexible and nearly any data/model can be fit, but it is computationally more intensive with convergence problems sometimes resulting into inference from a false positive posterior distribution (Lunn et al., 2009). Unlike MCMC, Integrated Nested Laplace Approximations (INLA) recently introduced by Rue et al., 2009, is less constrained by model complexity and database dimension, particularly suitable for latent Gaussian models (LGMs) (Best et al., 2005). The technique is computationally more flexible, efficient, and produces comparable results to MCMC in seconds/minutes (Geirsson et al., 2014). LGM is a very wide class of models ranging from (generalized) linear mixed to spatial and spatiotemporal models (Blangiardo et al., 2013).

The paper is organized as follows: In section 2.1, the TB database used in the study is described; in sections 2.2.1-2.2.2, An overview of INLA conceptual framework, spatial model for areal outcome are provided, results and discussion of some of the issues are provided in sections 3 and 4 respectively while the study conclusions is presented in section 5.

2 Data, Processing and Methods

2.1 Data and Study Area

The study area was carried out in Kenya, a country in East Africa, with an area of 581,313.2 Km^2 and a population of 38,610,097. Kenya is divided into 47 counties, which are geographical units representing a devolved government.

Figure 1: Map of Kenya by the counties

This study was a retrospective study of the newly detected TB cases registered between January 2014 and March 2014. The observation unit considered in this study was the county. TB in Kenya is managed by the NTLD program, which oversees diagnosis, treatment and reporting of patients with TB. Suspects undergo sputum smear microscopy and culture at the time of diagnosis. Those who are culture-positive also undergo drug sensitivity testing to isoniazid, rifampicin, ethambutol, streptomycin and kanamycin. Susceptibility is determined using the absolute concentration method on Lowenstein-Jensen medium, based on the following drug concentrations: isoniazid 1 mg/ml, rifampicin 40 mg/ml, ethambutol 5 mg/ml and streptomycin 10 mg/ml. Those with multidrug resistant TB (MDR-TB) are switched to an individualized regimen based on the drug resistance profile. Patients undergoing TB treatment are assessed with repeat sputum smear, culture and drug-sensitivity testing in months 2, 3 and 5 as well as at the end of treatment and at six-month intervals thereafter. This information is kept in case registration books. For the current study, we used secondary data collected from an existing patient database from the national TB registers with permission from the NTLD-P. NTLD-P aims at accelerating the reduction of TB burden through provision of people-centred, universally accessible, acceptable and affordable quality services. The following information had been collected routinely, at county level, for all patients undergoing TB therapy under the NTLD-P: the demographic data (age, sex, county, sector, weight, height, BMI) and

clinical information (type of TB, type of patient, regimen given, HIV status and outcome of treatment).

To investigate determinants of treatment outcome of TB, we included data from the Kenya Demographic and Health Survey (KDHS) 2014 and the Kenya Population and Housing Census 2009. KDHS provides information to monitor and evaluate population and health status in Kenya. The Kenya National Bureau of Statistics conducts this survey every five years. This was the most recent survey conducted, and was the first to provide county information. Details on how KDHS 2014 sampling, data collection, data quality control and analysis was done is available in the KDHS 2014 report. Each TB outcome was matched with the demographic characteristics, county information and socioeconomic characteristics. The dataset comprised 23488 individuals who registered at the TB clinics across the country in the first quarter of 2014.

2.2 Method

2.2.1 Integrated Nested Laplace Approximation (INLA)

Usually, the goal of statistical modelling and analysis is to evaluate magnitude and direction of model parameters (fixed effects) and predicted outcomes given a set of covariates while accounting for spatial correlation in the data.

A very general way that follows the conceptual framework of generalized linear model is to specify the problem by modelling the mean for the $i-th$ unit by means of an additive linear predictor defined probabilistically.

$\eta_i = \alpha + \sum_{m=1}^{M} \beta_m x_{mi} + \sum_{m=1}^{M} f_l z_{li}$ (1)

Where α is an intercept; the coefficients $\beta = \{\beta_1, \cdots, \beta_m\}$ quantify the effects of some covariates $x = \{x_1, \cdots, x_m\}$ on the TB outcome of interest; and $f = \{f_1, \cdots, f_l\}$ is a collection of functions defined in terms of a set of covariates $z = \{z_1, \cdots, z_l\}$.

Given the specification provided in Equation (1), the vector of model parameters can be expressed by $\theta = \{\alpha, \beta, f\}$. Following a proposal by Rue et al., 2009, for a sub class of structured additive regression models, latent Gaussian models, controlled by a few hyper-parameters, approximate Bayesian inference can be adopted to obtain the necessary posterior marginal distributions. We can assume a Gaussian Markov random field (GMRF) prior on, with mean 0 and a precision matrix Q.

The fundamental goal for this is the computation of marginal distributions for each of the elements of the model parameters vector.

$\pi(\theta_i|y) = \int \pi(\varphi|y)\pi(\theta_i|\varphi, y)d\varphi$ (2)

And possibly,

$\pi(\varphi_k|y) = \int \pi(\varphi|y)d\varphi_{-k}$ (3)

Where $\boldsymbol{\varphi} = \{\boldsymbol{\varphi}_1, \cdots, \boldsymbol{\varphi}_k\}$are the k hyper-parameters introduced by the conditional independence relationships introduced by the GMRF (see Rue and Held, 2005 for more details).

Thus, we need to compute $\pi(\boldsymbol{\varphi}|\boldsymbol{y})$, from which other necessary posterior marginal distributions $\pi(\varphi_k|y)$can be obtained; and $\pi(\theta_i|\varphi, y)$, which is necessary to compute the marginal posterior distributions for the parameters.

The INLA approach exploits the flexibility of numerical approximations using series of Laplace approximations and numerical integration to obtain the marginal distributions of interest. (See, Rue et al., 2009 for further details)

2.2.2 Spatial Model for Areal Outcome

Disease outcome mapping is a very useful when data is taken at areal level to assess pattern of a particular disease and identify distribution of risk in different areas. For the i-th area, the number of cases of TB outcome of interest y_i is modelled as $y_i \sim$ Poisson (λ_i), where the mean λ_i is defined in terms of a rate ρ_i and the expected number of TB outcome as $\lambda_i = \rho_i E_i$. In this case, the linear predictor is defined on the logarithmic scale $\eta_i = \alpha + \sum_{m=1}^{M} \beta_m x_{mi} + \gamma_i$, Where α is the model intercept denoting the TB outcome rate in all the 47 counties; $\gamma_i = f(i)$ is the area specific effects; $i = \{1, \cdots, n\}$ is the indicator for each county (spatial area) and correspond to a unique identifier (ID) in the database.

We assume further that γ_i is spatially structured and modelled using intrinsic autoregressive structure (iCAR) such that

$$\gamma_i \mid \gamma_{j \neq i} \sim N(m_i, s^2{}_i), \quad (4)$$

Where $m_i = \frac{\sum_{j \in \aleph(i)} \gamma_j}{\#\aleph(i)}$ and $s^2{}_i = \frac{s^2{}_\gamma}{\#\aleph(i)}$, for $\#\aleph(i)$ is the number of counties that share boundaries with the i-th county (i.e. its neighbours).

We adopt INLA method with default priors. Parameter estimation is then represented by $\theta = \{\beta_m, \vartheta\}$ where β_m is the vector of estimated effects of the fixed effects including an intercept and ϑ the spatial effects. If exponentiated, the fixed effects can be interpreted as relative risk.

Spatial distribution of these effects and their estimated risk, posterior probabilities of exceeding 1 can be extracted and compared.

Variable selection

Despite the fact that most TB patients were aged between 15 and 45, counties like Lamu, Isiolo, Nyandarua and Marsabit had more children aged less than 15 years affected by TB at 100%, 90.9%, 91% and 80.7% respectively. In Turkana, only 37.8% of patients attended public facilities for TB treatment, while Garissa had 54%. The county with the highest number of TB patients with HIV were Siaya, Homabay and Kisumu at 69.18%, 66.19% and 63.7%. Garissa, Wajir, Mandera and Marsabit had the highest number of patients who were HIV negative at 94.9%, 96.9%, 96.7 and 90.8%. Since there was a generally low probability of occurrence of outcomes of interest (cured, dead, defaulted, failure and treatment completed), a Poisson probability distribution was used for the likelihood distribution. Assessment of risk factors importance was done separately for each of the TB treatment outcomes using leave-one-out cross-validated residual mean squared error (RMSE). Percentage increase in RMSE computed with *randomForest* package. The risk factors include: HIV status of the patient; employment sector; BMI index; gender; and TB type. Performance of various risk factors in explaining variabilities in various treatment outcomes is displayed in **Figure 2** below.

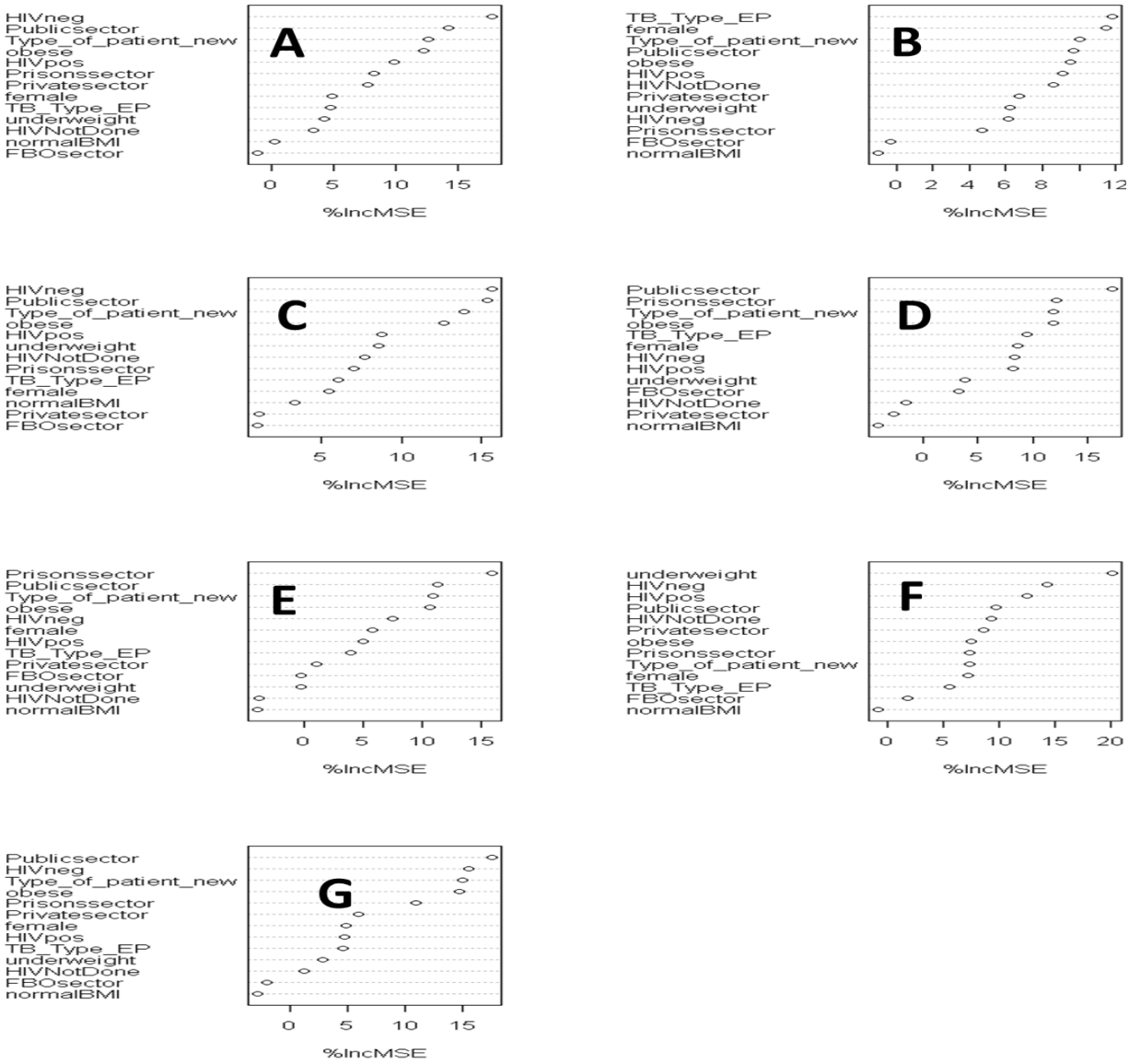


Figure2: Shows variable importance cross-validated percentage increase of mean squared error when individual risk factors are dropped from the model (A = outcome cured, B= on treatment, C=dead, D=transferred out, E=defaulted, F=failure and G=treatment completed).

Based on the degree of variable importance, a chance of being cured depends mostly on HIV status, employment sector, and BMI; chances of being on treatment depends on type of TB, gender, employment sector BMI etc. General trend indicate that for most TB outcomes considered in this study, most dominant important dependence variables explaining significant amount of variabilities include: HIV status, sector of employment, BMI, TB type and gender of the victim (see, **Figure 2** for more details). The Figure provides percentage increase in mean squared error based on leave-one-out cross-validation. The variables are then ordered in ascending order from top.

3 Results

Exploratory Data Analysis

Expected number of TB treatment outcomes, a product of county level population at risk and corresponding success probability. The success probability is the number of observed cases divided by the number sampled in a given county. Number at risk is provided by the county level

2009 population census. The expected number of various TB treatment outcomes was calculated and shown in **Figure 3.**

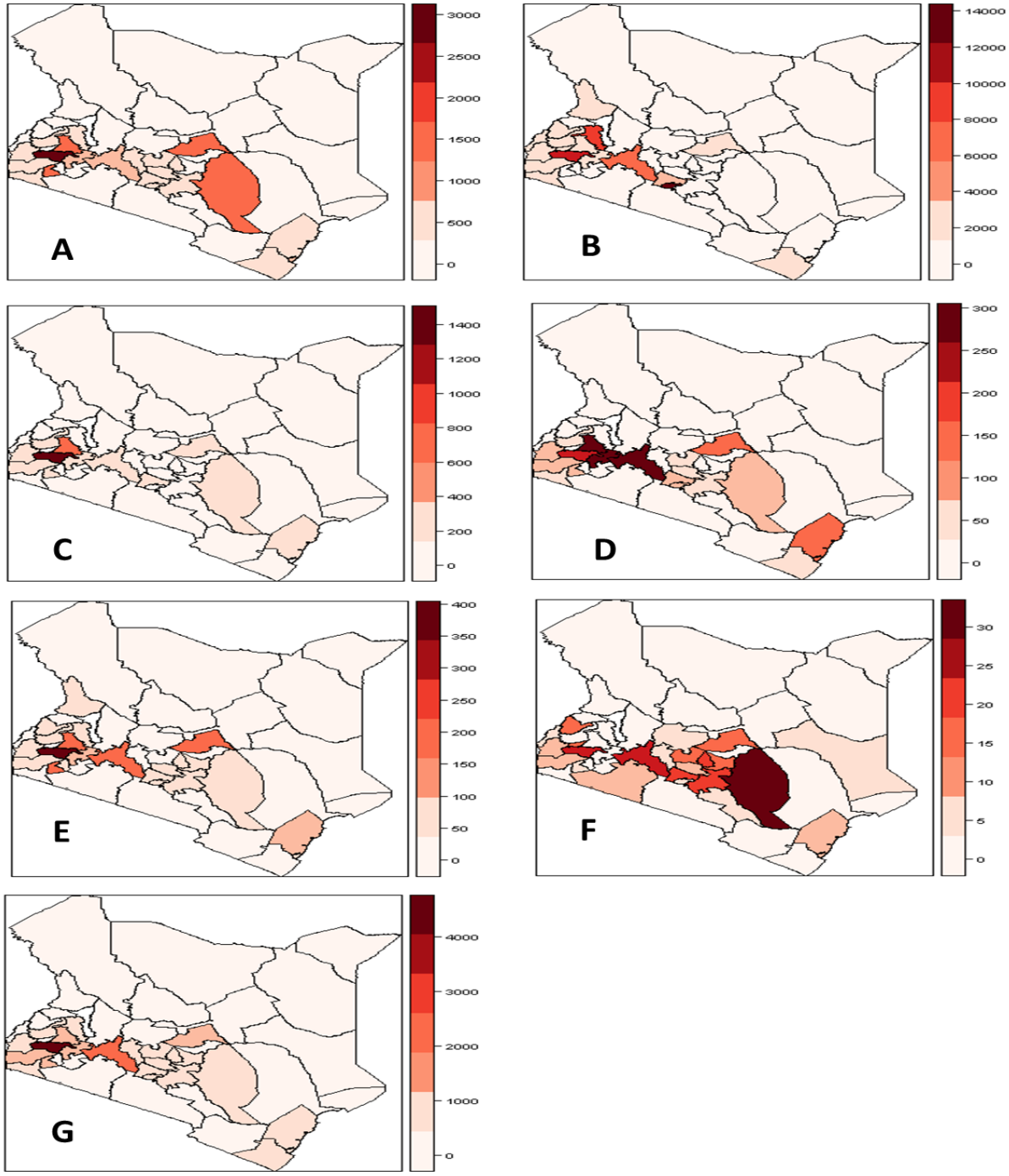


Figure 3: Shows expected number of various Tuberculosis outcomes in Kenya observed between March and May 2015 with A = outcome cured, B= on treatment, C=dead, D=transferred out, E=defaulted, F=failure and G=treatment completed.

Most of the counties recorded low expected number of the various treatment outcomes with some having high expected favourable (cured and treatment completed) outcomes, and others high expected unfavourable (defaulters, those who died and those who had treatment failure) outcomes. The relative risk of TB treatment outcomes was thereafter calculated as shown in **Figure 4.**

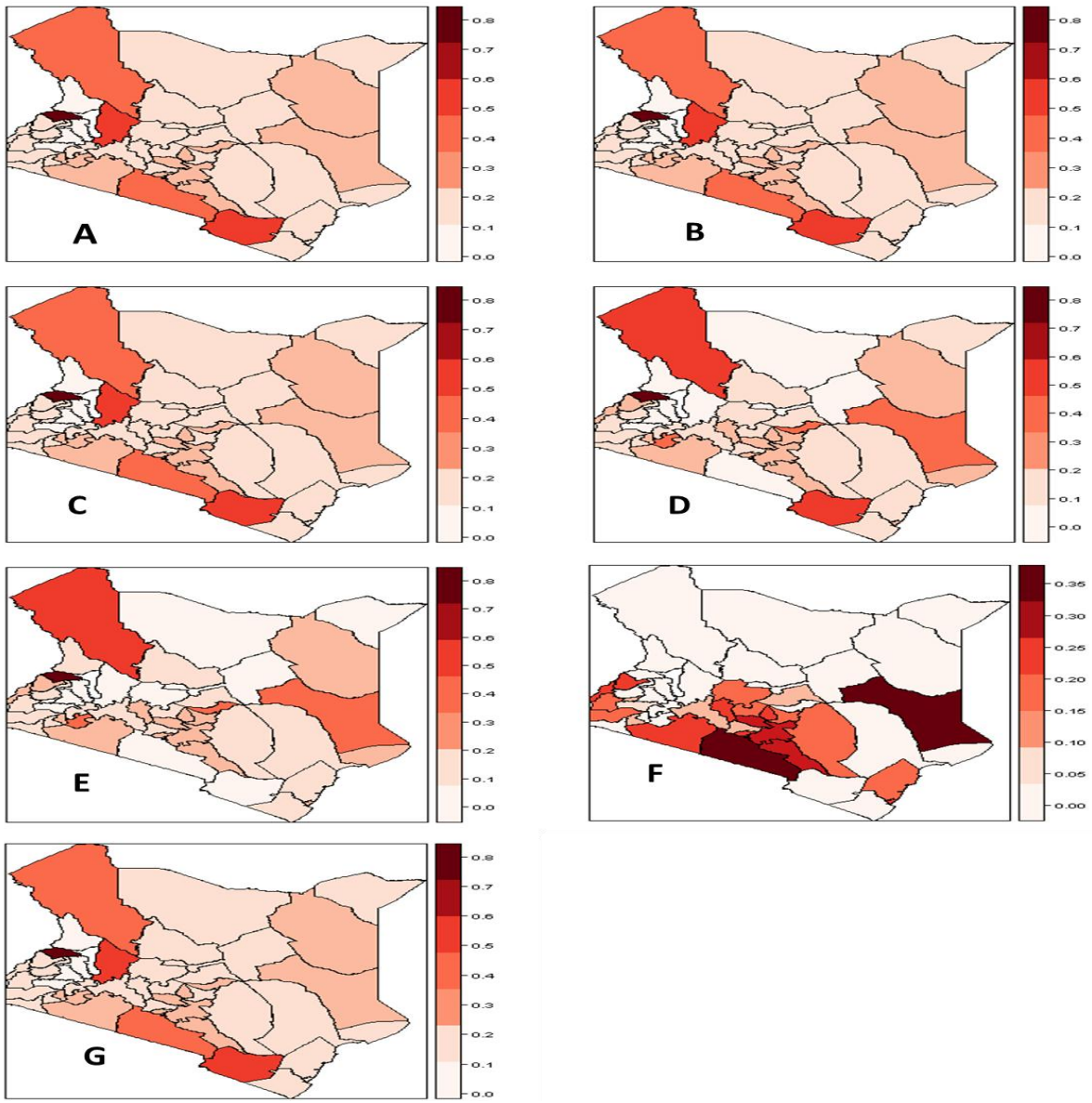


Figure 4: Estimated risk (relative risk) based on exponentiated linear predictors for various Tuberculosis outcomes in Kenya observed between March and May 2015 with A = outcome cured, B= on treatment, C=dead, D=transferred out, E=defaulted, F=failure and G=treatment completed.

The relative risk for various TB treatment outcomes was consistently high in the North Western counties (e.g. Turkana) and in a few counties to the South. Also, Eastern and North Eastern counties recorded relatively high rate of treatment outcomes**.** Nevertheless, Failure was most prevalent in Garissa and Kajiado counties. Interestingly, all the Trans-zoia county relative risk for various treatment outcomes was high except for the Failure outcome.

The estimated risk for the patients who were cured was high in Meru and its surrounding counties. Other areas were Murang'a, Machakos and Kisii. Estimated risk for the patients who died, defaulted, failed treatment and those who completed treatment were highest in Kisumu, Kisii, Kitui and Nakuru respectively. Neighbouring counties had a relatively high estimated risk. There was a significant spatial effect across the various TB outcomes, though most of the covariates did not explain the spatial autocorrelation seen in this analysis. This could mean that there observed spatial autocorrelation could be explained by other unobserved variables. and 80% posterior probability maps (not displayed) indicated that there was no statistically significant association of county-level spatial characteristics and the HIV test result. This suggests that there might be a strong relationship

between modelled covariates and localized spatial processes that would differently expose respondents to HIV infection.

4 Discussions

Test for spatial autocorrelation was done in the study using Moran's I test statistic given that it is most widely used for global test. The result showed significant spatial autocorrelation laming the constant risk hypothesis as expressed by P-values <0.05 especially for outcome cured, dead, transferred, defaulted and treatment completed. However, defaulting outcome did not exhibit high level of significance compared with others. It was our view that the non-significance could be attributed to the low number of expected cases of failure outcome. Also, given that the low probability of occurrence of outcome of interest (treatment cured, on treatment, dead, transferred, defaulted, faulting and treatment completed) on preliminary tests shared that poison probability distribution was a better likelihood compared to binomial distribution.

Spatial dependence structure can be modeled in different ways using available statistical models. It is convenient to assume that the observations are independent and identically distributed, which may not always be the case when working with data that exhibits some correlation between areas. An intrinsic conditional autoregressive [CAR] model was adopted to express spatial dependence structure among the regions/county level. The CAR model was used due to its flexibility for region based spatial analysis. The treatment outcome TB cured estimated risk appears to be uniformly distributed across the 47 counties with hot spots appearing towards the western regions. The spatial effects enable pixels to borrow and share strength from neighboring pixels. By including the covariates in our models the aim is asses and removes the effect of potential cofounders and risk factors. The assessment of the importance of a covariate indicated by the estimated value of its coefficient and its associated probability intervals. If; for example, the 95% credible intervals do not contain the value 0, we may assume that the coefficient is significant and, if greater than zero, it will indicate a positive relationship between the risk and the variable. Analysis revealed that most of the risk factors were not significant at 95% credibility level of confidence (explain different slope coefficients for various outcomes here). This may partly be attributed to the fact that in region based analysis, covariates may not directly be linked to the cases. Also, although the conditional distributions are proper, it is usually not the case for the joint contribution. Nevertheless, the CAR specification is used as a prier distribution of the spatial random effects and it ca lead to a proper posterior under the sum to zero constraint as suggested in (Sigrist …et al 2013) to allow better identification of the effect.

Generally, the spatial effect appear to be weak across the various TB outcomes as shown in Figure (cite). This may imply that appropriate risk factors were adjusted for in the model such that the spatial random effect became less important. However, following Besag et al 1995, valid inference could still be done for the relative risks but adequate care should be taken to avoid having an improper posterior distribution. This is part of the reason why non simulation based techniques that do not require convergence to obtain the necessary posterior distributions for Bayesian inferential e.g. INLA could be recommended. INLA uses numerical methods to approximate posterior marginal distributions for latent Gaussian models. It is faster though it requires limited number of hyper parameters though that is not a limitation to a large extent. It is robust and fast for large scale complex spatial and spatiotemporal analysis where MCMC would be nearly impossible, so we don't have to be exact especially when approximation is good enough.

Also, INLA covers many set of problems that are unique in many fields, which generally facilitates the practitioners work with most of the commands similar to those applied in standard R routines (e.g. lm or glm).

However, due to its recent inspection, INLA is less established than MCMC methods. Consequently, its development is still ongoing, particularly with respect to stochastic partial differential equation approach (SPDE) which is partially helpful in point level spatial and spatiotemporal Bayesian inference.

We recommend that future related studies involving various TB outcomes be traced at household level (point level data). This will enable minimize mismatch between risk factors and the TB outcomes. we could also take advantage of the SPDE (Lindgren et al 2011) and a wealth of for statistical techniques (see Cressie 1991, Diggle and Ribeiro 2007 etc.) to develop a more robust spatial models. This could also be done over time to further adjust for the temporal autocorrelation in the model.

However, other methods in the meaning of classical statistical analysis are also available. They Range from generalized mixed effect models, generalized additive models (GAM) see mgcv package for details among others. A specific difficulty with most such methods is their use of point support for spatial dependency pattern rather than polygon so that the relationship between observations is distance based. Due to the complexity in the matrix algebra (covariance matrices) involved, such methods tend to focus on interpolation than modeling. Though, improvements are ongoing to increase their flexibility and are being employed with increasing frequency within the statistical community. Nevertheless, Bayesian approach is natural when technical inference is involved with non-linear terms is involved.

5 Conclusions

There is increased availability of spatial data has fuelled a growth in modelling in this area. We recommend that future related studies involving various TB outcomes be traced at household level (point level data). This will enable minimal mismatch between risk factors and the TB outcomes.

Other statistical techniques could be used to develop more robust spatial models. This could also be done over time to further adjust for the temporal autocorrelation in the model.However, other methods for classical statistical analysis are also available like generalized mixed effect models and generalized additive models (GAM). A specific difficulty with most such methods is their use of point support for spatial dependency pattern rather than polygon so that the relationship between observations is distance based. Due to the complexity in the matrix algebra (covariance matrices) involved, such methods tend to focus on interpolation than modelling. Nevertheless, Bayesian approach is natural when technical inference with nonlinear terms is involved.

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