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Spatio-temporal patterns of pneumonia in Bhutan: A Bayesian analysis

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Abstract

Pneumonia is one of the top 10 diseases by morbity in Bhutan. This study aimed to investigate the spatial and temporal trends and risk factors of pneumonia in Bhutan. A multivariable Zero-inflated Poisson regression using a Bayesian Markov chain Monte Carlo simulation was undertaken to quantify associations of age, sex, rainfall, maximum temperature and relative humidity with monthly pneumonia incidence and identify underlying spatial structure of the data. Overall pneumonia incidence was 96.5 and 4.57 per 1,000 populations over nine years in people aged <5 years and ≥5 years, respectively. Children <5 years or being a female are more like to get pneumonia than ≥5 years and males. A 10mm increase in rainfall and 1°C increase in maximum temperature was associated with a 7.2% (95% (credible interval [CrI] 0.7%, 14.0%) and 28.6% (95% CrI 27.2%, 30.1%) increase in pneumonia cases. A 1% increase in relative humidity was associated with a decrease in the incidence of pneumonia by 8.6% (95% CrI 7.5%, 9.7%). There was no evidence of spatial clustering after accounting for the covariates. Seasonality and spatial heterogeneity can partly be explained by the association of pneumonia risk to climatic factors including rainfall, maximum temperature and relative humidity.

Keywords: Bhutan, pneumonia, Bayesian, spatial, temporal, risk factors, modelling

Introduction

Pneumonia is a major cause of morbidity and mortality worldwide[1]. Each year, pneumonia accounts for over 12 million hospital admissions and 1.3 million deaths in children aged less than 5 years worldwide[2,3]. In 2017, pneumonia was the fourth-leading cause of death and it is estimated that it will be the third-leading cause of death by 2040[4]. The World Health Organization (WHO) estimates that respiratory infections account for 6% of the total global burden of disease. This accounts for a higher percentage compared to the burden of diarrheal disease, cancer, human immunodeficiency virus (HIV) infection, ischemic heart disease or malaria[5].

Pneumonia is a potentially life-threatening illness with a particularly high burden in South Asia and sub-Saharan Africa[3,6,7]. It is not only a major cause of morbidity and mortality but is also associated with a substantial economic burden on healthcare systems[8,9] and household income[10]. Pneumonia often has a complex aetiology involving multiple pathogens, including many that are transmitted person-to-person. Past time-series analyses have identified various pneumonia and influenza outcomes to be temporally seasonal, demonstrating highly consistent peaks in winter months and troughs in summer months[11,12]. Other studies have found that pneumonia admissions were highly spatially clustered[13], driven by contact with infected people during indoor activities[14].

Pneumonia continues to be an important communicable disease in Bhutan- locate in the Eastern Himalayas[15-17] (**Fig. 1**). In 2019, pneumonia was one of the top-ten ranked diseases in terms of morbidity and accounted for 19% of the overall disease burden[18]. Every year the Bhutanese government spends a huge amount on the treatment and management of pneumonia. In the financial year 2017–2018, 7.1% of current health expenditure was spent on treating infectious respiratory diseases[19,20]. Despite the importance of pneumonia, and the infectious nature of the disease, there have been no previous studies to understand the underlying ecological drivers of pneumonia in the country[21,22]. Understanding the spatial and temporal patterns of pneumonia will be important for prevention and preparedness through more efficient targeting of scarce health care resources. This study aims to investigate the trends of pneumonia, identify potential high-risk geographical areas and quantify associations between disease risk and climatic risk factors.

Results

Descriptive analysis

A total of 100,015 pneumonia cases were reported in the country during the study period (2010-2018). This corresponded to 71,807 and 28,208 cases in people aged <5 years and ≥5 years, with an incidence of 96.5 and 4.57 cases, respectively, per 1,000 people during the nine years (**Table 1**). In both the age groups incidence decreased: from 119.28 and 47.73 cases per 1,000 population in 2010 to 54.73 and 3.19 cases per 1,000 in 2018 for the <5 years and ≥5 years age groups, respectively (**Table 1**). The seasonal-trend decomposition of monthly pneumonia cases based on locally (STL) is illustrated in Figure 2. The highest cases were reported in 2014 and pneumonia displayed a strong seasonal pattern. There were two peaks in May and September of each year. The standard morbidity ratio (SMR) of pneumonia at sub-district level varied from 0 to 13.02, with a Standard Deviation=1.45 (**Fig. 3**).

Spatio-temporal model

Model I, containing the unstructured random effects was better fitting than Model II and Model III containing the spatially structured random effects with lower deviation information criterion (DIC) (206,093). The incidence of pneumonia was 21.3% (95% credible interval [CrI] 21.0%, 21.6%) times higher in people aged <5 years as compared to ≥5 years. Females were 8% (95% CrI 7.0%, 9.0%) more like to get pneumonia compared to males. Pneumonia decreased by 11% (95% CrI 10%, 13%) during the study period. A 10mm increase in rainfall was associated with a 7.2 % (95% CrI 0.7%, 14.0%) increase in incidence of pneumonia. Similarly, a maximum temperature increase of a 1°C was associated with a 28.6% (95% CrI 27.2%, 30.1%) increase in pneumonia cases. However, a 1% increase in relative humidity was associated with a decrease in the incidence of pneumonia by 8.6% (95% CrI 7.5%, 9.7%) (**Table 2**).

There was no evidence of spatial clustering after accounting for the covariates (**Table 2** and **Fig. 4**). There was >95% probability of a higher than the national average trend of pneumonia in 56/205 sub-districts, whereas 67/205 sub-districts had >95% probability of a trend less than the national average. There was no clear spatial pattern, with sub-districts showing higher and lower average trends across all the 20 districts (**Fig. 5**).

Discussion

Pneumonia was spatially and temporally heterogeneous across sub-districts of Bhutan during the study period. There was a decreasing trend, in addition to a strong seasonal pattern during the study period. Pneumonia mainly affected children aged <5 years and females. Rainfall and maximum temperature were associated with an increased incidence of pneumonia while relative humidity was associated with a decrease incidence.

In addition to climatic factors, spatial heterogeneity could be due to differences in the socio-demographic characteristics of sub-districts. The risk factors responsible for exacerbation and spread of pneumonia in Bhutan were low birth weights, malnutrition, smoky and overcrowding households, bottle-feeding of infants and poor personal and environmental hygiene[23,24]. This was evident from the two districts of Haa and Paro which has the lowest poverty[25], and also reported lowest SMR of pneumonia. Similar to the decreasing trend in the incidence of global childhood pneumonia[26], the national pneumonia trend decreased during the study period. This could be attributed to a decrease in exposure to key risk factors including poor housing conditions and overcrowding, incomplete immunisation and malnutrition[26].

Pneumonia is the single largest infectious cause of death in children worldwide. It accounts for 15% of all deaths of children <5 years[27]. In this study, children <5 years were at a much higher risk of pneumonia compared to those ≥5 years. Infants (aged between 0-11 months) was reported to contribute up to 24.2% of cases in another study[28]. The WHO and United Nations Children's Fund (UNICEF) initiated a Global action plan for pneumonia and diarrhoea (GAPPD) to accelerate pneumonia control in children[29]. The GAPPD strategies include promoting exclusive breastfeeding and adequate complementary feeding to protect children from pneumonia; prevent pneumonia through vaccinations, hand washing with soap, reducing household air pollution, HIV prevention and cotrimoxazole prophylaxis for HIV infected and exposed children; and treating children with pneumonia with antibiotics and oxygen. Strengthening GAPPD strategies should be considered in Bhutan, as is the case in other countries in the South Asia region (Bangladesh and India). The introduction of pneumococcal conjugate vaccines in Bhutan in 2019 is timely in prevention of pnuemonia[19,30]. Exclusive breastfeeding rates from birth until six months in Bhutan varies from 35.9–51.0%[31,32]. Increasing exclusive breastfeeding rates are likely to reduce pneumonia associated morbidity[33].

Pneumonia was highly seasonal and was associated with climatic factors including temperature, rainfall and relative humidity. The association of temperature with pneumonia has been reported in other studies[34,35]. A plausible explanation is the association of higher temperature with air pollution[36] which in itself is known risk factor and cause of pneumonia[37-40]. Most industries are located in the southern parts of Bhutan where air pollution is expected to be higher as compared to other districts. This was reflected by these sub-districts having higher SMR for pneumonia. Additionally, traditional methods of cooking in rural Bhutan using fire wood could also contribute to respiratory illness such as pneumonia[41,42].

The incidence of Pneumonia tends to be higher during the rainy season[43-45]. Rainfall may trigger socio-ecological behavioural changes such as increased contact between people and the distribution of pathogens. Further, heavy rainfall during the monsoon is likely to pollute drinking water, particularly the surface water from streams, which is the main drinking water source for rural populations[46]. Unsafe drinking water and sanitation are important drivers of pneumonia[47]. Relative humidity was associated with a decrease in pneumonia incidence in this study which is in concordance with other studies[35,48]. Higher relative humidity decreases the survival of lipid-enveloped viruses such as influenza A, influenza b and Respiratory Syncytial Virus[49,50].

There are a number of limitations that need to be considered when interpreting the results of this study. First, the study used routine case reports to measure incidence of pnuemonia. Known issues exist surrounding completeness and representativeness of such data. Secondly, the causal organisms of pneumonia were not available and the association could be different based on the organisms. Thirdly, there was no reconciliation to accommodate different levels of aggregation of the climate variables (district) and the disease data (sub-district), and the climate conditions were assumed to be homogeneous within a district. Lastly, unaccounted risk modifiers were not included in the modelling due to a lack of available data. These important unmeasured factors, such as immunization coverage, air pollution level, living standards and socio-economic status, crowding, smoking, access to safe drinking water and latrine usage might have resulted in confounding, which was not able to be quantified[39,51,52].

Despite these limitations, the strengths of this study are the capacity to implement the spatial analysis at a relatively fine resolution, being the sub-district level, and over a long time series (108 months). Traditionally, spatial patterns of infectious disease risk have been displayed at larger geographical units, such as a district, province**,** national, regional, and global scales[46,53,54]. Such low resolution can mask localized disease patterns due to averaging[55].

Conclusion

Pneumonia is an important childhood disease and the introduction of pneumococcal conjugate vaccines to reduce the burden of this disease is timely. Pneumonia was highly seasonal and spatially heterogeneous across sub-districts. Seasonality can be explained by climatic factors including temperature, rainfall and relative humidity. The spatial and temporal variability of pneumonia should inform in better targeting of its prevention and control in the country through rational decision making and proper resources allocation.

Materials and methods

Study area

Bhutan located in the Eastern Himalayas, borders China in the north and India in the east, south and west. The country is divided administratively into 20 districts and 205 sub-districts, with a total projected population of 741,672 in 2019 [56]. Around 62.2% (452,178) of the population live in rural areas and practice subsistence farming. The altitude ranges from 75m above sea level in the south to more than 7000m in the Himalayas (**Fig. 1**).

Study design and data source

This is a retrospective study using secondary data on pneumonia from January 2010 to December 2018, stratified by sex and age (> 5 years and ≥5 years) at the sub-district level. The data were obtained from the National Acute Respiratory Infections surveillance system, hosted by the Bhutan Health Information and Management Systems (HIMS) under the Bhutan Ministry of Health. These data contain all pneumonia cases treated by health centres including hospitals and primary health care facilities and reported to the HIMS every month. Pnuemonia is defined as " a patient with history of cough or reported breathing difficulty, and increased respiratory rate (RR) or chest indrawing (RR ≥ 50 breaths per minute in children aged two months or more and less than 12 months or RR ≥ 40 breaths per minute in children aged 12 months or more and less than 60 months”[57]. Daily climatic variables (rainfall, relative humidity, minimum and maximum temperature) were obtained from the National Centre for Hydrology and Meteorology under the Ministry of Economic Affairs of Bhutan. Monthly average climatic variables were calcuted for this study. Population estimates used in the study were obtained from the National Statistical Bureau, Bhutan[58]. Administrative boundary maps were downloaded from the DIVA-GIS website[59].

Crude standardized morbidity ratios

An initial descriptive analysis of pneumonia incidence across the country was conducted. Crude SMR for each sub-district were calculated using the following formula:

$$Y_i = \frac{O_i}{E_i}$$

Where *Y* is the overall SMR in sub-district *i, O* is the total number of observed pneumonia cases over the entire study period in the sub-district and *E* is the expected number of pneumonia cases in the sub-district across the study period. The expected number was calculated by multiplying the national incidence by the average population for each sub-district over the study period.

Exploration of seasonal patterns and inter-annual patterns

The time series of pneumonia incidence was decomposed using STL weighted regression to show: the seasonal pattern, inter-annual patterns and the residual variability. The STL model was structured as follows:

$$Y_t = S_t + T_t + R_t$$

where Y_t represents numbers of local pneumonia cases with logarithmic transformation, S_t is the additive seasonal component, T_t is the trend, and R_t is the “remainder component”; t is time in months[60,61].

Spatio-temporal model

A Bayesian statistical framework was deployed for spatial analysis. It provides a convenient framework for the simultaneous inclusion of covariates and spatial autocorrelation in a single model, while providing robust evaluation of and expression of uncertainty. The posterior distributions can be used to quantify uncertainties in parameters of interest (e.g., covariate effects and spatial patterns of disease risk)[62].

Initially, a preliminary bivariate Poisson regression of pneumonia cases was undertaken to select the covariates. The covariates with a p-value of <0.05 and the lowest Akaike's information criterion (AIC) were selected. The co-linearity of the selected climatic and environmental variables was tested using variance inflation factors (VIF). In the final model, rainfall, maximum temperature and relative humidity were included.

Of the 88,560 observations stratified by sub-districts, <5 and ≥5 years and sex over 108 months, there were 55,975 (63.2%) zero counts of pneumonia. Therefore, Zero-inflated Poisson (ZIP) regression was constructed in a Bayesian framework. The first model (Model I), assumed that spatial autocorrelation was not present in the relative risk of pneumonia. This model was developed with selected climatic factors (rainfall, maximum temperature and relative humidity), age (<5 and ≥5 years) and gender as explanatory variables, and an unstructured random effect for sub-districts; the second model (Model II) contained a spatially structured random effect in addition to the covariates; and the final model (Model III), a convolution model, contained all of the components of the preceding two models. The best model with the lowest DIC was selected as the final explanatory model.

Model III assumed that the observed counts of pneumonia, Y, for i^{th} sub-district (i=1..205) in the j^{th} month (January 2010-December 2018) followed a Poisson distribution with mean (μ_{ij}), that is,

$$P(Y_{ij} = y_{ij}) = \begin{cases} \omega + 1\,(1-\omega)e^{-\mu}, & y_{ij} = 0 \\ (1-\omega)e^{-\mu}\,\mu_{ij}^{y_{ij}}/y_{ij}, & y_{ij} > 0; \end{cases}$$

$$Y_{ij} \sim \text{Poisson}(\mu_{ij})$$

$$\log(\mu_{ij}) = \log(E_{ij}) + \theta_{ij}$$

$$\theta_{ij} = \alpha + \beta_1 \times \text{Age} + \beta_2 \times \text{Sex} + \beta_3 \times \text{trend}_j + \beta_4 \times \text{Rainfall}_{ij} + \beta_5 \times \text{Humidity}_{ij} + \beta_6 \times \text{Tempmax}_{ij} + u_i + s_i + w_i$$

where expected number of cases in sub-district i, month j (acting as an offset to control for population size) was represented by E_{ij} and θ_{ij} is the mean log relative risk (RR). The intercept (α), and coefficients for age (≥5 as reference), sex (male as reference), monthly trend, rainfall, relative humidity and maximum temperature are *β1, β2, β3, β4, β5* and *β6.* The spatially unstructured and structured random effects are represented as u_i and s_i, respectively, with u_i excluded from Model II and s_i excluded from Model I. Spatiotemporal random effect with a mean of zero and variance of σ_w^2 was denoted by w_i as in other studies [63,64].

A conditional autoregressive (CAR) prior structure was used to model the spatially structured random effect. Spatial relationships between the sub-districts were based on a 'queen' contiguity matrix. A weight of 1 was assigned to sub-districts sharing a border and 0 otherwise. A flat prior distribution was specified for the intercept, whereas a non-informative normal prior distribution was used for the coefficients. The priors for the precision of unstructured and spatially structured random effects were specified using non-informative gamma distributions with shape and scale parameters equal to 0.01.

The model was run for an initial 10,000 iterations, which were then discarded. Subsequently, visual inspection of posterior density and history plots were used to note convergence at intervals of 20,000 iterations. Convergence occurred at approximately 100,000 iterations for all models. Following convergence, posterior distributions from model parameters were stored for inference. Markov Chain Monte Carlo simulation was used to estimate model parameters [65]. Summaries of parameters were calculated, including posterior mean and 95% credible CrI. In all analyses, an α-level of 0.05 was adopted to indicate statistical significance (as indicated by 95% CrI for relative risks (RR) that excluded 1).

Seasonality decomposition was carried out using the R statistical package, release 3.3.1. The ZIP regression model was constructed using WinBUGS software, version 1.4.3 (MRC Biostatistics Unit 2008)[66]. ArcMap 10.5 software (ESRI, Redlands, CA) was used to generate maps of the posterior means of the unstructured and structured random effects and the spatiotemporal random effects.

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Authors contribution

KW and KP were involved in the conception of the study. KW and TT undertook the analysis. KP and CT obtained the data. KW and KP drafted the manuscript. ACAC, PG and DJG critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

Competing interest

Authors declare there is no competing interest.

Ethical approval and patient confidentiality

Adminstrative approval to use these datasets was provided by the Ministry of Health, Bhutan. This study was a low-risk study since the surveillance data did not contain identifying information on individual participants.

Data availability

The datasets of thie current study will be made available from the corresponding author on reasonable request.

Figures

Figure 1 Map of Bhutan with districts and sub-districts with altitude.

Figure 2 Decomposed monthly cases of pneumonia: (a) under 5 years and (b) 5 years and older during the study period, 2010-2018.

Figure 3 Crude standardized morbidity ratios (SMR) of pneumonia by sub-districts the study period, 2010-2018.

Figure 4 (a) Spatial distribution (b) significance map of the posterior means of unstructured random effects of pneumonia in Bhutan, 2010-2018.

Figure 5 Trend of pneumonia by sub-districts of Bhutan during the study period, 2010-2018.

Tables

Table 1 Yearly incidence of pneumonia stratified by age.

Year	Under 5 years			5 years and older		
	Cases	Population	Incidence*	Cases	Population	Incidence*
2010	9,204	77,161	119.28	3,369	70,582	47.73
2011	7,975	78,618	101.44	3,210	718,702	4.47
2012	9,939	80,985	122.73	3,683	741,572	4.97
2013	8,956	81,899	109.35	3,064	749,937	4.09
2014	9,434	82,947	113.74	3,669	759,536	4.83
2015	7,489	84,009	89.15	3,037	769,258	3.95
2016	8,150	85,084	95.79	3,023	779,105	3.88
2017	5,883	86,173	68.27	2,606	789,077	3.30
2018	4,777	87,276	54.73	2,547	799,177	3.19

*incidence per 1,000 population

Table 2 Regression coefficients, relative risk and 95% credible interval from Bayesian spatial and non-spatial models of pneumonia cases in Bhutan, January 2010-December 2018.

Model/Variable	Coeff, posterior mean (95% CrI)	RR, posterior mean (95% CrI)
Model I (Unstructured)		
α (Intercept)†	-4.18 (-4.32, -4.13)	
Age (base over 5 years)	3.06 (3.04, 3.07)	21.26 (20.95, 21.59)
Sex (base male)	0.08 (0.06, 0.09)	1.08 (1.066, 1.094)
Mean monthly trend	-0.12 (-0.14, -0.10)	0.886 (0.870, 0.902)
Rainfall (10mm)	0.07 (0.01, 0.13)	1.072 (1.007, 1.140)
Relative humidity**	-0.09 (-0.10, -0.08)	0.914 (0.903, 0.925)
Maximum temperature (°C)	0.25 (0.24, 0.26)	1.286 (1.272, 1.301)
Probability of extra zero	0.26 (0.21, 0.30)	
Heterogeneity		
Unstructured	0.43 (0.35 0.53)	
Structured (trend)	1.82 (1.43 2.29)	
DIC*	206,040	
Model II (Structured)		
α (Intercept)†	-4.18 (-4.32, -4.13)	
Age (base over 5 years)	3.06 (3.02, 3.09)	21.26 (20.55, 22.02)
Sex (base male)	0.08 (0.05, 0.10)	1.08 (1.052, 1.108)
Mean monthly trend	-0.12 (-0.14, -0.10)	0.886 (0.869, 0.903)
Rainfall (10mm)	0.07 (-0.01, 0.14)	1.070 (0.999, 1.014)
Relative humidity**	-0.09 (-0.10, -0.08)	0.914 (0.902, 0.927)
Maximum temperature (°C)	0.25 (0.24, 0.27)	1.287 (1.270, 1.304)
Probability of extra zero	0.18 (0.17, 0.19)	
Heterogeneity		
Structured (spatial)	0.09 (0.07, 0.11)	

Structured (trend)	1.82 (1.42, 2.28)	
DIC	206,093	
Model III (Mixed)		
α (Intercept)†	-4.15 (-4.36 -3.91)	
Age (base over 5 years)	3.06 (3.04, 3.07)	21.26 (20.72, 21.82)
Sex (base male)	0.08 (0.06, 0.09)	1.080 (1.059, 1.101)
Mean monthly trend	-0.12 (-0.14, -0.10)	0.886 (0.870, 0.902)
Rainfall (10mm)	0.07 (0.01, 0.13)	1.071 (1.000, 1.014)
Relative humidity**	-0.09 (-0.10, -0.08)	0.914 (0.903, 0.926)
Maximum temperature (°C)	0.25 (0.24, 0.26)	1.287 (1.271, 1.303)
Probability of extra zero	1.201 (1.191, 1.211)	
Heterogeneity	0.60 (0.42, 1.02)	
Unstructured	1.68 (0.13, 8.04)	
Structured (spatial)	1.68 (0.13, 8.04)	
Structured (trend)	1.82 (1.42, 2.28)	
DIC	206,058	

* best-fit model; ** Lagged three months, †coefficient

Abbreviations: coeff-coefficients; CrI- credible interval; RR-relative risk; DIC- deviation information criterion

Figures

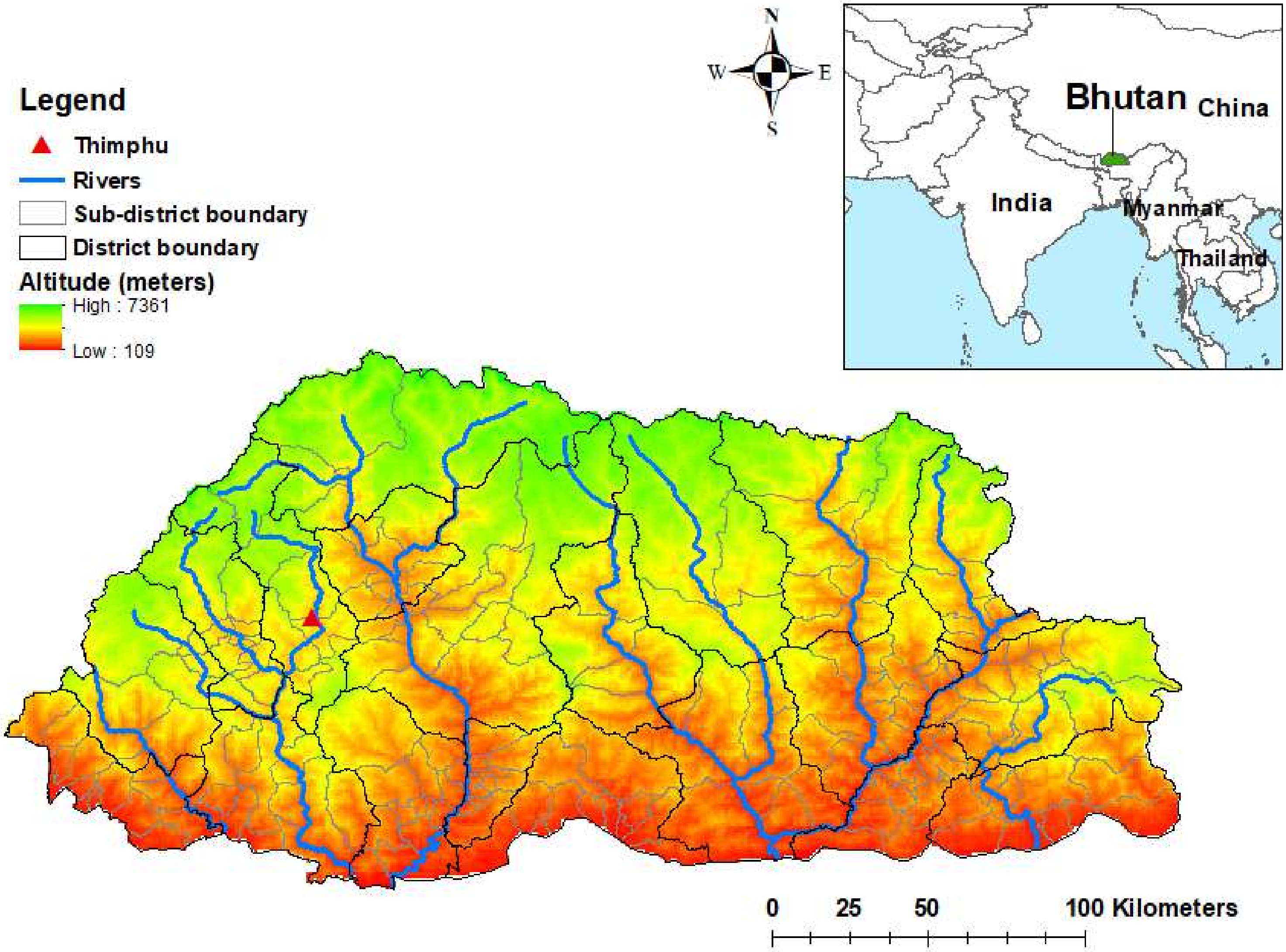

Figure 1

Map of Bhutan with districts and sub-districts with altitude. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

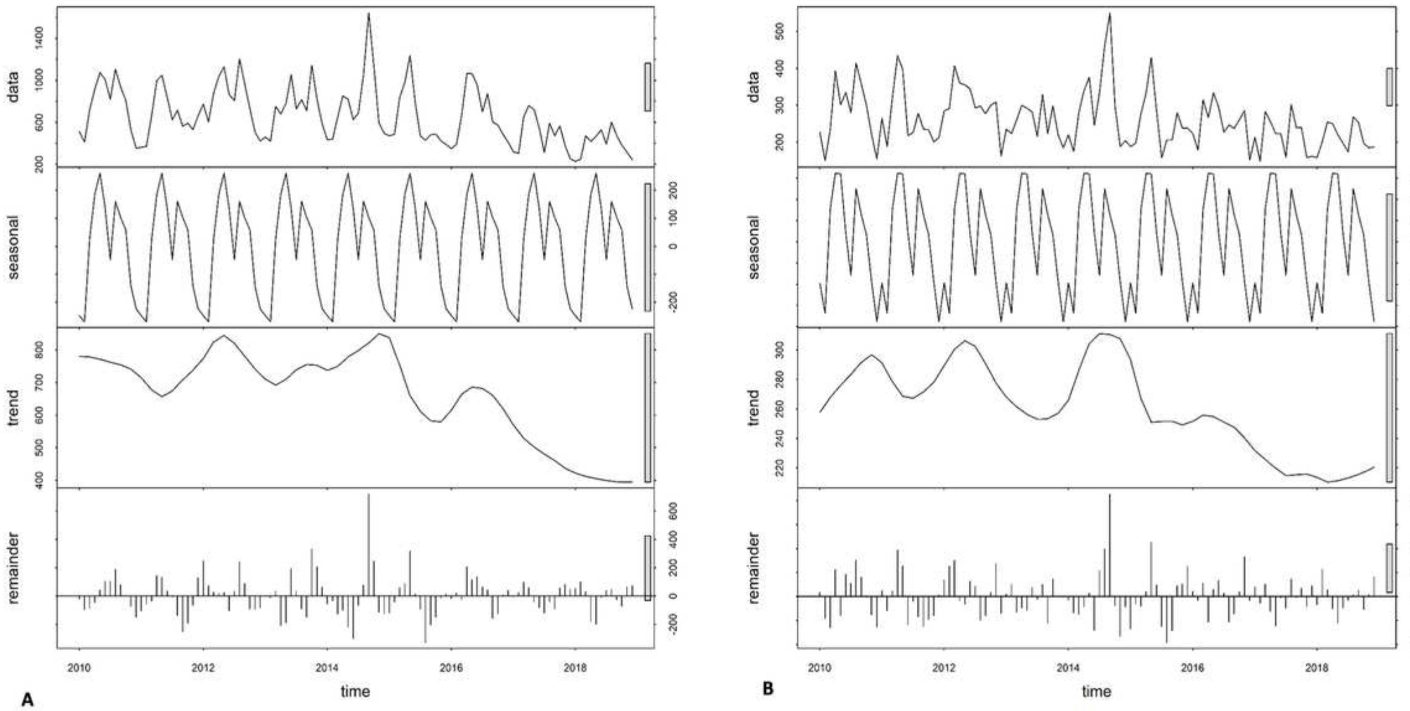

Figure 2

Decomposed monthly cases of pneumonia: (a) under 5 years and (b) 5 years and older during the study period, 2010-2018.

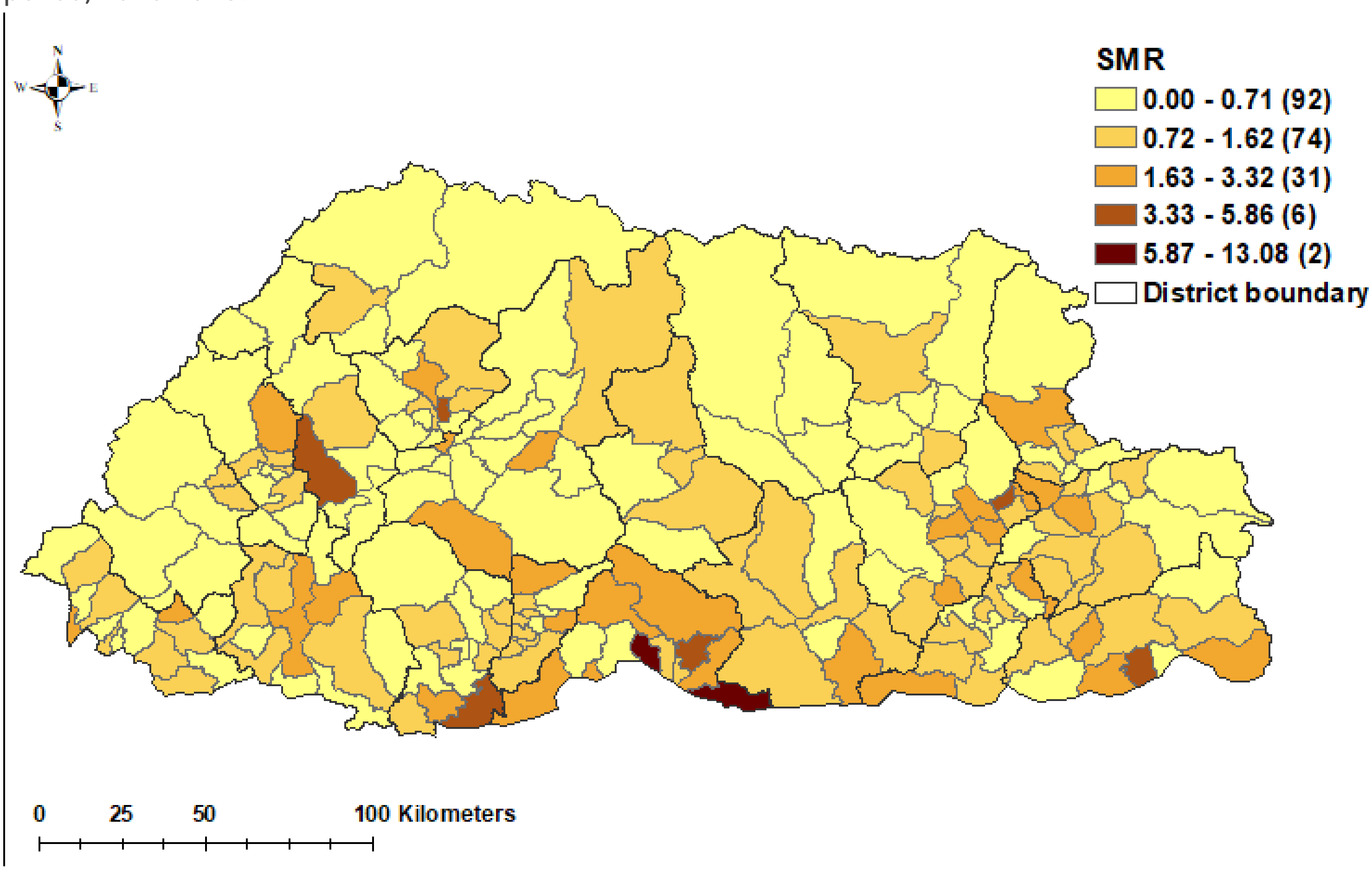

Figure 3

Crude standardized morbidity ratios (SMR) of pneumonia by sub-districts the study period, 2010-2018.

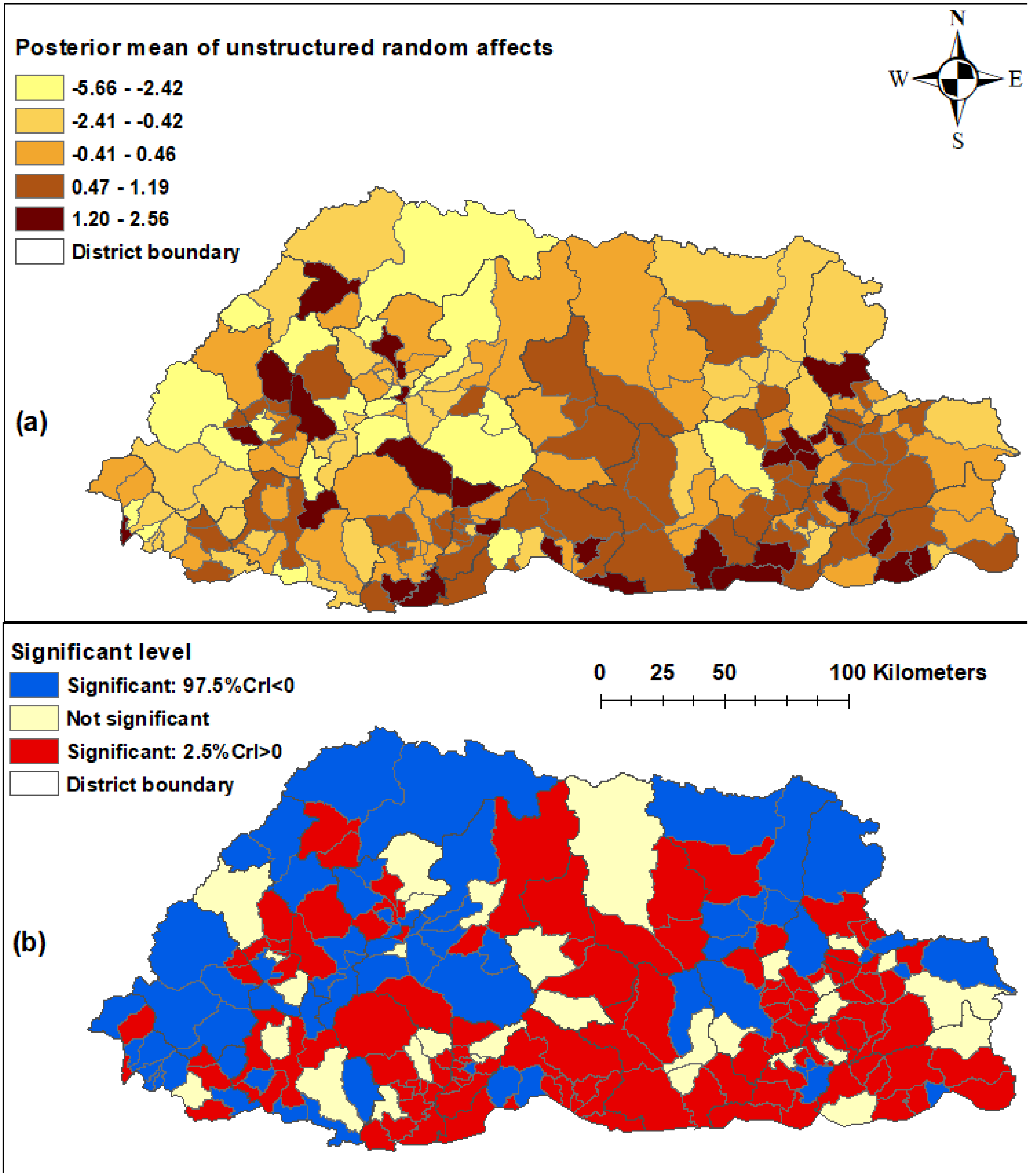

Figure 4

(a) Spatial distribution (b) significance map of the posterior means of unstructured random effects of pneumonia in Bhutan, 2010-2018.

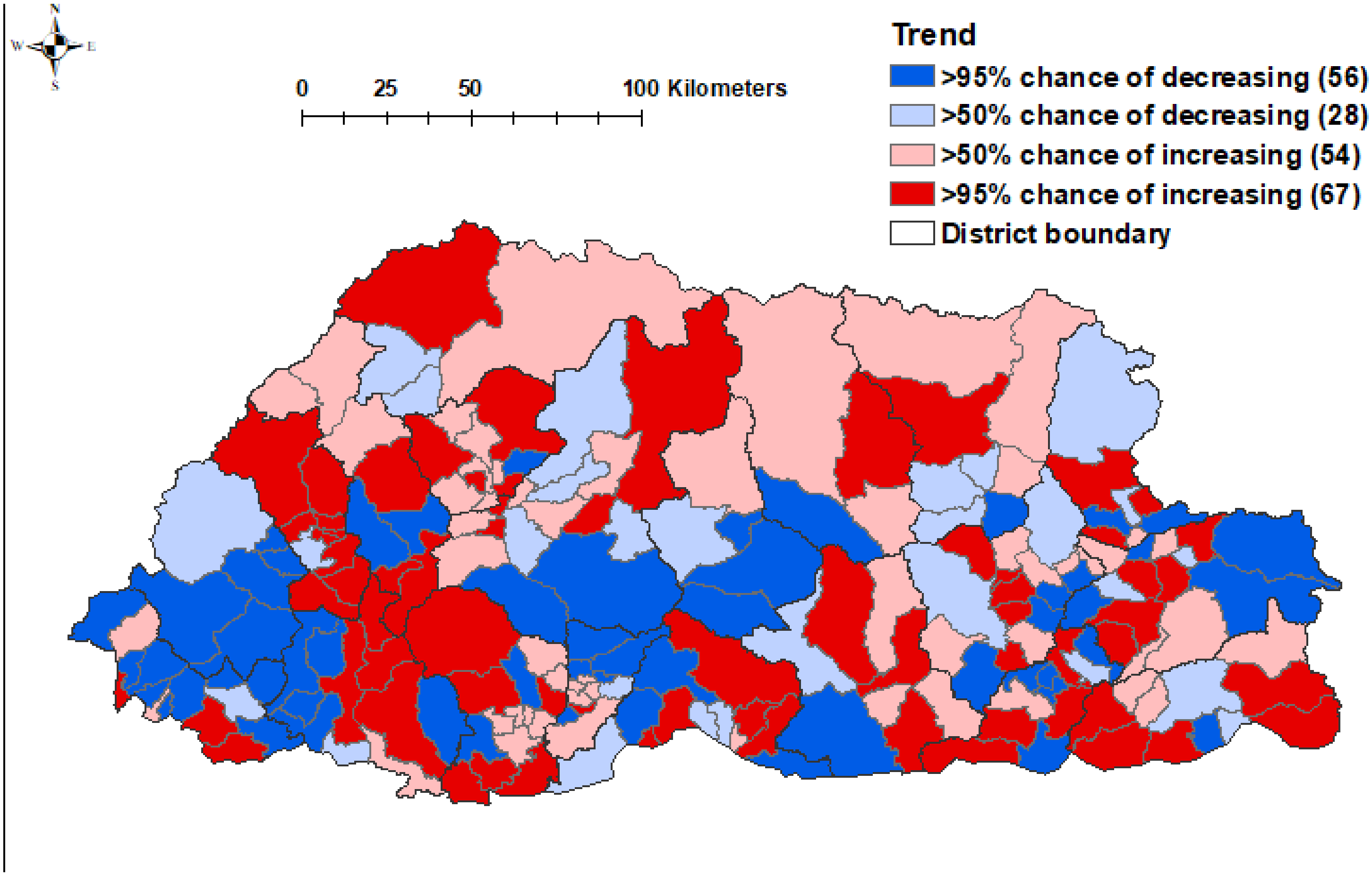

Figure 5

Trend of pneumonia by sub-districts of Bhutan during the study period, 2010-2018.

Supplementary Files

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