Malnutrition related child morbidity and mortality: A space-time based analysis using Kilifi County Hospital Data 2002 to 2015

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A RESEARCH REPORT SUBMITTED TO THE SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN BIOSTATISTICS

November, 2017
DECLARATION

I, KM Wambui, student No: 1504769 declare that this research report is my own work. It is being submitted for the degree of Master of Science in Epidemiology in the field of Biostatistics at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

KM Wambui November 2017
DEDICATION

This research is dedicated to my loving mum Wambui and Mwai’s family at large for the uncontinued prayers and support during the research period, *Kūgūrū nī īrata thī*, (Perseverance prevails).

To Jehova Ngai (THE MOST HIGH), all is unto you.
ABSTRACT

Background:
Globally malnutrition is an underlying cause of death and accounts for over 45% of under-5 mortality mainly resulting from diarrhoea and pneumonia. The post-2015 era has seen, more than 25% of Kenya’s population being food insecure, with considerable geographic and temporal disparities. Our primary aim was to understand the determinants of malnutrition related morbidity and mortality in the rural Kilifi HDSS, with a special focus on children admitted in Kilifi County Hospital (KCH) during 2002-2015.

Methodology:
Our study participants were all the children between the ages of 6 months to 15 years who were admitted two times or more at the KCH. The outcomes were derived from malnutrition-related admissions based on wasting (WHZ<-2) and oedema and the discharge outcome whether alive or died. There were 3114 children with a total of 7620 admissions for children with more than one admission.

In the exploratory data analysis, temporality and seasonality were determined using SARIMA time series models. Morans I index was used to investigate for the presence of spatial autocorrelation. SatScan was used to identify the spatial clusters of malnutrition related admissions and mortality. To understand mortality patterns, geo-additive logistic models were fitted to the KCH data. Mixed effects negative binomial models with separate space and temporal random effects were fit using the Maximum Likelihood and Bayesian Estimation procedures. The Bayesian methods were used to estimate the spatial parameters using Markov Chain Monte Carlo (MCMC) assisted with either Metropolis Hastings or Integrated Nested Laplace Approximations (INLA).
ABSTRACT

Results:
There were 17,740 children observed over the period of study and 4.01% of those died. A total of 23,347 admission events were observed of which 7,128 were malnutrition related. Out of the 17,740 children admitted, 3,114 had one or more admission event. A seasonal hike in the May to July month was identified for malnutrition admission. Children with more than one admission, (7620 admissions) ~24%(n=1858) had a malnutrition event and 6.24% of them died. Spatial hotspots clusters were identified in the North and South of the creek and areas near Kilifi Town was identified as cold spots. Children with two or more severe diseases are more likely to have a malnutrition admission event and females are less likely to be admitted with malnutrition. There was a protective effect as the children grew older and also as their body weights increased. The males had a higher risk of death compared to the females and a year increase in age reduced the risk of death by 15%.

Conclusion:
A better understanding of the factors that contribute to malnutrition attributable admission and mortality can be used to advocate for and develop earlier and more appropriate responses. Additionally, this can provide an indication of future trends and the potential impact of interventions. Importantly, including spatial and temporal random effects biostatistical modelling can help reduce bias reporting and help understand better the patterns of morbidity and mortality. Campaigns providing food and/or vitamin or other supplements can contribute to reducing morbidity and ultimately deaths in Kenyan children and building more health facilities to reduce the distance of travel to care is highly recommendable.
ACKNOWLEDGEMENTS

The achievement and realization of this research project has been through the mentorship of my supervisor **Associate Prof Eustasius Musenge**. I am very grateful for the professional and personal advice he accorded me. As you continue mentoring many more, may blessings come your way.

Secondly I thank Sub-Saharan African Consortium for Advanced Biostatistics (SSACAB) training programme for funding me to advance my career in Bio-statistics. All the lectures, administrators and staff at the School of Public Health my gratitude for the support during the course period. My classmates; especially Biostatistics cohort Karimi, Chidumwa and Kaunda thank you for making the course fun and enjoyable.

Special thanks to KEMRI-Wellcome Trust for providing me with data for my masters especially David Amadi , Prof. James Berkley and Prof. Greg Fegan.

Special gratitude to my mum Wambui Mwai for the support and prayers during my course work and my career path.

Finally without you God, I could not have made it. **Siyabonga**

**Úgĩ wa mündũ ūmwe ndûrũmaga** (A single mans ability cannot till all fields)
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• **KHDSS** - Kilifi Health and Demographic Surveillance System

• **KCH** - Kilifi County Hospital

• **MySQL** - My Structured Query Language

• **WHZ** - Weight for Height Z Scores

• **WHO** - World Health Organisation

• **LRTI** - Lower Respiratory Tract Infection

• **CSF** - Cerebrospinal fluid

• **UNICEF** - United Nations Children’s Fund

• **MODIS** - Moderate Resolution Imaging Spectroradiometer

• **EVI** - Enhanced Vegetation Index

• **SD** - Standard Deviation

• **ARIMA** - AutoRegressive Integrated Moving Average

• **SARIMA** - Seasonal AutoRegressive Integrated Moving Average

• **ACF** - Autocorrelation Function

• **PACF** - Partial autocorrelation function

• **AR1** - Auto Regressive order 1

• **MLE** - Maximum Likelihood Estimation

• **MCMC** - Markov chain Monte Carlo
• **INLA** - Integrated Nested Laplace Approximations

• **DIC** - Deviance Information Criterion

• **GLM** - Generalised Linear Models
CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Background

1.1.1 Burden of Malnutrition

Malnutrition is a vital underlying cause of death and accounts for 45% of childhood mortality and morbidity by increasing susceptibility to major infections like diarrhoea and pneumonia (1,2). Among hospitalised children with malnutrition, in the absence of suitable treatment, the case-fatality rates range from 30% to 40% (1,3,4). Majorly, it affects childhood development and increases the risk of other diseases in adulthood. These malnutrition related outcomes can significantly affect the socio-economic productivity in their adult life (5). Sub-Saharan Africa and Asia remain the areas with the highest prevalence of malnutrition. Specifically, in Sub-Saharan Africa, malnutrition has been reported to be among the leading risk factors in populations health (1,2,6).

In East and Southern Africa, research estimates have shown that approximately 40%, 30% and 6% of children under five are stunted, underweight and wasted respectively (7). In patients with multiple infections and malnutrition have been shown to complicate the management
of patients, therefore leading to a higher case-fatality in hospitals (3,8). Malnutrition remains a major contributor to inpatient morbidity and mortality among children in rural areas in Kenya, despite the incentives to overcome malnutrition. Malnutrition has also been associated with increased inpatient costs and increased risk of inpatient mortality (3,9,10).

In Kenya, considerable geographic disparities of the food insecure population have been reported (11). Food inavailability has been shown to increase the risk of malnutrition potentially. Nonetheless, malnutrition is the result of a much broader range of risk factors. The UNICEF malnutrition conceptual framework (Appendix 7) shows a wide spectrum of determinants that worsen malnutrition leading to a vicious cycle (2).

1.1.2 Spatial-temporal analysis in sub-Saharan Africa

Spatial-temporal Bayesian models have been applied in different health research studies especially in malaria and other infectious diseases in sub-Saharan Africa (SSA). Spatial models in SSA have importantly contributed to understanding the spread of malaria and a potential role for alerts on epidemics. According to a review done by Gebreslasie et al., he describes the importance of spatial models in the study of epidemiology and the transmission risk of malaria in Africa (12).
Multivariate and Semi-Parametric Bayesian spatial models have also been applied to understand the risk and spatial variation of HIV in Africa (13,14). This modelling approach of spatial multivariate and semi-parametric models shows the adaptability and viability of spatial models in understanding HIV in sub-Saharan Africa (SSA) (13,14).

Malnutrition has been shown to be heterogeneous spatially although very little of this work has been done in sub-Saharan Africa. Lack of detailed spatial data at administrative and homestead levels has been a major limitation for residence centred investigation of malnutrition. According to a review of SSA spatial analysis on malnutrition, most of them applied spatial regression models at a meso level, but few studies used the Bayesian spatial modelling approach (15). In Somalia, Kinyoki et al. observed a clear seasonal variation in wasting in under 5s due to variations in climate, food security and diseases. Bayesian hierarchical space–time models using stochastic partial differential equation (SPDE) was used in Somalia (16).

Malnutrition being a compounded phenomenon, using joint spatial-temporal models can give a better understanding of this issue. Spatial analysis allows health research to integrate health, environmental and population data. This allows them to investigate the relationship between these
factors at different scales (17).

1.1.3 Advantages of Bayesian spatial models

The main advantage of Bayesian modelling approach is the ability to incorporate prior information on the parameters used in the models. This method offers a better way over the classical regression models by allowing concurrent modelling of spatial-temporal autocorrelation while still estimating the usual fixed effects. In spatial models, Bayesian models over the frequentist modelling approach make it possible to include the intrinsic Gaussian CAR prior distribution to represent the shared spatial components. Modelling of shared spatial components using the frequentist approach can also be cumbersome and computer intensive (13, 18, 19).

1.2 Problem statement

Malnutrition remains a serious challenge in public health and has been linked to an increased number of deaths and morbidity of children. This accounts for approximately 50% of global deaths in under-fives, which enhances the risk of infectious diseases. Conversely, infections aggravate malnutrition by different reasons leading to increased number of admissions
and a longer length of hospital stay ($1,6,20,21$). Malnutrition has also been reported to interact with various components of the environment potentially increasing the risk of malnutrition and low birth weight ($22,23$).

Shortage of data on detailed geographic, temporal, household and homestead level is a major setback in research on malnutrition related morbidity and association with potential risk factors ($15$).

1.3 Justification of the study

According to a review done by Marx et al., little research has been done on spatial-temporal malnutrition attributable mortality and morbidity. Some studies have associated this with a lack of detailed geographic household and homestead level data ($15,24$). Non-bayesian based methods are the most commonly used approaches to the analysis of malnutrition attributable morbidity and mortality, and they are limited in the manner they handle large data set, temporal and spatial random effects ($25,26$).

It is now feasible to map malnutrition attributable mortality and morbidity status at high spatial resolutions using Bayesian approach due to the availability of georeferenced data. Additionally, recent developments and accessibility of modern statistical tools together with advances in
computing speeds offer opportunities for fitting spatial-temporal models that converge quickly without loss of predictive precision (27). This will provide a better understanding of space-time variation of morbidity and mortality associated with malnutrition to improve the prevention, early detection and outcome of diseases in malnourished children.

1.4 Literature review

1.4.1 Child malnutrition morbidity and mortality studies

Currently, Asia Latin America and sub-Saharan Africa hosts two-thirds of the world’s malnourished children, and it is responsible for over 50% of under-five mortality (1,28). In a study done in a rural area in Kenya, malnutrition accounted for a higher rate of inpatient morbidity and mortality. Bejon et al. concluded that despite the great effort to fight malnutrition, the malnutrition attributable fraction for hospital mortality was over 50% and not a significant change noted in East Africa since 1980’s. Middle Upper Arm Circumference (MUAC) was a better marker for malnutrition compared to the other conventional clinical definitions; wasting and stunting in this study (3).

In a longitudinal study conducted in East rural Ethiopia among under-5
years, wasting was observed to occur during the dry season though seasonality was not a significant covariate. This could have been a limitation of using a fixed effect model as stated in their paper to avoid variable omission bias (28). Enhanced vegetation index (EVI) was highly associated with all the malnutrition indicators according to a study done in Somalia. EVI unit increase in Somalia accounted for over 30% reduction in all the indicators (29). This study concluded that infections and seasonal variations are key drivers of malnutrition, but a spatial-temporal study similar to what we propose would help understand this better.

In Malawi, spatial patterns of childhood morbidity determined by Bayesian geo-additive models similar to those we propose revealed some urban agglomerations to be associated with a higher childhood morbidity, especially diarrhoea. Other significant factors were environmental, climatic factors and remoteness in some rural areas. Modelling was also controlled for geographic factors (30).

1.4.2 Spatial-temporal modelling utilisation in epidemiology

In a few studies done in Africa and other studies elsewhere, the available evidence suggests that malnutrition is spatially heterogeneous (30,31). A Malawi study suggested more emphasis be placed upon childhood
morbidity association with remoteness and geographic variation (30). In Brazil, malnutrition was associated with primary diagnosis at admission and was shown to be higher in different regions (20). Non-random clustering of infant mortality due to malnutrition and diarrhoea deduced from verbal autopsy (VA) was observed in rural South Africa (32).

Geographical variability has also been seen in hospital admissions using non-separable spatial-temporal models (33). Since malnutrition amplify common life-threatening infections that lead to admissions, understanding the spatial and temporal patterns of the childhood malnutrition attributable mortality and morbidity can be of great importance (15,31). Developing models that will help better estimate the impacts of geographical variation on population changes in health has been recommended by various authors (23,34,35). Bayesian space–time geostatistical models and structured additive logistic regression models have been used to predict and estimate the risk factors of malaria in sub-Saharan Africa respectively (36,37).

Noor et al. applied the Bayesian spatial-temporal models to show how a reduction in transmission of malaria has been achieved and also predicted the malaria burden in SSA for the period between 2000 and 2010 (36). This
is complimented by Chirombo et al. using structured additive models which showed similar results in Malawi with second order random walk priors for their continuous variables (37).

Bayesian Poisson zero-inflated models using Integrated Nested Laplace Approximation (INLA) approach for inference were used to identify protective factors for HIV/TB child mortality (38). This was applied on the mortality outcome variable, which had a Poisson distribution similar to the morbidity outcome in this study. Inverse probability weighting combined with prediction models were used to obtain the statistics and spatial epidemiology of the prevalence of HIV in Malawi (13). This approach applied Bayesian multivariate models to jointly model and map the HIV risks (13). In Kenya, a spatial variation of HIV infections was observed using Bayesian Spatial Semi-Parametric model showing the adaptability and viability of spatial models in understanding HIV in SSA (14).

In Somalia, a Bayesian approach was applied to understand the spatial-temporal distribution of wasted children. The study showed a seasonality patterns in the prevalence of wasting recommending consideration of seasons implementation of nutrition programs (16). Ricardo et al., identified clusters of severe anaemia and malnutrition were
identified as one of the factors contributing to the spatial heterogeneity of anaemia risk \[39\].

### 1.4.3 Child malnutrition morbidity and mortality determinants

Agricultural production, food prices, food availability and food security remain important determinants of malnutrition in sub-Saharan Africa. However, while malnutrition exacerbates common life-threatening infections, these infections themselves cause growth faltering and without a sufficient recovery period can worsen malnutrition \[1,3,6,8,23\]. Thus, diseases, especially diarrhoea, are a key driver of malnutrition. Recently, it has also become clear that chronic intestinal inflammation, known as environmental enteric dysfunction (EED), is widespread in the developing countries and is an important mediator of stunting \[1,40\].

### 1.4.4 Hospital based models

Kazembe et. al. used semiparametric regression model with data from Zomba district hospital to show the risk of dying in hospital is lower in the dry season but high for those referred to the hospital. Significant difference was observed in both structured and unstructured spatial effects. The health facility effects revealed considerable differences by type of facility
or practice offered (41). In Tanzania, prompter care-seeking behaviour, improved quality of care at health facilities and better adherence to treatment was recommended after analysing hospital data to understand the malaria attributable mortality (42). This shows the importance of georeferenced data in informing important epidemiological policies and design of interventions.

Most of the malnutrition studies have used survey or household data. Therefore, we propose to map the mortality attributable to malnutrition and malnutrition related morbidity using the available georeferenced household data for admitted children in the paediatric ward at county Hospital in Kilifi and their non-admitted counterparts in the Kilifi Health and Demographic Survey System (KDHSS) (43). This should better our understanding of the variation of malnutrition attributable mortality and malnutrition related morbidity.

1.5 Research question

Is there a variation in malnutrition attributable mortality and malnutrition related morbidity space-time patterns among children admitted in Kilifi county Hospital from 2002-2015, Kenya?
1.6 Aim and objectives of the study

1.6.2 Study aim

To investigate the variability in childhood morbidity and mortality attributable to malnutrition in Kilifi county between 2002 and 2015 using space-time models.

1.6.3 Study objectives

a) To describe the spatial-temporal trends of malnutrition related morbidity and mortality in Kilifi county, Kenya between 2002 and 2015.

b) To investigate the space-temporal variations in malnutrition related morbidity in Kilifi county, Kenya between 2002 and 2015.

c) To investigate the spatial variations of impact factors for malnutrition attributable mortality patterns in Kilifi county, Kenya between 2002 and 2015.
CHAPTER 2: METHODOLOGY

Introduction

This chapter describes the study site, design and population of the data used for this research project. Additionally, we describe the data collection and management process for the different statistical approaches used to analyse the data. The analysis was done in three main phases, exploratory data analysis, temporal investigation and spatial-temporal models. Time series models were used for investigating temporality. Moran I and Kulldorff statistics that were used to investigate spatial auto correlation, hotspots and coldspots respectively are introduced for the exploratory analysis. Finally, we present Bayesian spatial-temporal negative binomial model and geo-additive logistic model for the inferential statistics. In this analysis we used WHZ and oedema as our malnutrition defining variables since the children were aged between 6 months to 15yrs and MUAC is a reliable malnutrition marker for children below 60 months (3,44).
2.1 The Kilifi Health and Demographic Surveillance System (KHDSS)

The KHDSS was launched in 2000 in Kilifi County which is located in the Coastal region of Kenya as shown on Figure~2.1. The area is a semi-arid area with subsistence farming being the main economic activity for the population in this region. The study area was mainly set to define rates of mortality, migration and fertility. KHDSS has 15 administrative locations and 40 sub-locations. Special 4-monthly visits are done to the households to record any death, migration and birth event.

Figure 2.1: The location of the KHDSS and the different dispensaries and the main Hospital
We utilise data from the Kilifi County Hospital (KCH) paediatric ward admissions. KCH is the main referral hospital in this region, and 80% of the admissions come from KHDSS. The hospital is located in the middle of KHDSS which was launched in 2000 to capture the majority of the inpatient details at KCH paediatric ward. The area has approximately 280,000 residents with almost 4000 paediatric admissions per year. The mortality and morbidity events at the hospital are synchronised real time with the population register updated by 4-monthly visits to the households (43).

2.2 Study Design and Data Management

Our study design was a retrospective cohort observational study. To understand malnutrition related morbidity, our outcome was the number of malnutrition related admissions over the period of 2002 to 2015. Our cases for the mortality were children who had a death outcome and malnutrition as the main predictor variable (3).

The mortality and morbidity events captured at the hospital are integrated with the population register updated by 4-monthly visits to the households. The linkage of the surveillance data and admissions data is done real time with the matching of individuals at the point of admissions by the field
workers. The data is then de-identified by assigning a unique identifier and a corresponding person identifier for the KHDSS residents. A MySQL 5.7 database updated by the medical officers at KCH using a web based PHP 5.3.19 application. The medical officers update the medical background of each admission with a unique identifier and a corresponding person identifier for the KHDSS residents (43,45,46).

2.2.1 Data Quality

A team of qualified field workers trained on using the KHDSS surveillance system do the matching of the data on real-time admissions. Each field worker has a unique username to access the web based system and the matching procedures of the individuals is explained elsewhere (43). Qualified medical and clinical officers enter the history and clinical examination of the patients in the system after matching has been done by the field workers. The data quality checks on the clinical measurements are implemented ensure values entered into the system are within the expected range. The database has a daily backup, and each event or record entered into the system has a unique event identifier and an audit trail.
2.3 Study Population

The study utilised data of children admitted in KCH from 2002 to 2015 and aged between 3 months and 13 yrs who live in KHDSS and were health system users. The highest number of admission events was 20, but for the morbidity outcome, we selected up to 11 admission events. This was considered in the modelling approach.

2.3.1 Inclusion Criteria

We included children who lived within the KHDSS and were admitted in Kilifi county hospital between 2002-2015. The age limit for the children was 3 months to 13 years. The household geolocations for the participant was a requirement to be included in the analysis.

2.3.2 Exclusion Criteria

We excluded children with unknown discharge outcome and the malnutrition status was unknown at admission. Trauma admission events were also excluded from the analysis. Children with missing person identifier were excluded from the analysis.
2.4 Outcome and Explanatory Variables

The outcome variables used to define a malnutrition related admission were Weight for Height Z-score (WHZ) for children under-5 years or BMI for age Z-score for children over 5 years and the presence of nutritional oedema.
at admission. The Weight for Height Z-score was calculated using the 2006 WHO child growth standards (47) and the BMI for age Z-score was calculated using WHO growth reference for school-aged children (48). The weight of the children during admission was done using an electronic scale (Weylux; H Fereday and Sons, London, United Kingdom). The heights of the children were measured with a wall-mounted scale except for children with less than two years whose length was measured using a calibrated board. Wasting which is low WHZ (WHZ < -2) or low BMI for age Z-score (BMIZ < -2) is one of the key indicators of malnutrition and is related to illness or food insecurity (49). Oedema is a clinical sign of undernutrition which may include swelling of the feet, skin and hair changes (3). Nutrition oedema is recorded by the medical officers at KCH during admission.

Child severe illness was defined as a child admitted with either gastroenteritis, LRTI, blood and CSF culture positive, malaria and fever or meningitis (3). Other factors affecting malnutrition related morbidity and mortality were selected using the UNICEF malnutrition conceptual framework guidance (2). The conceptual framework defines the immediate causes of undernutrition to be individual related, i.e., diseases and inadequate dietary intake and the underlying causes to be the environmental and household factors as shown in Appendix 7.
Additional covariates that are associated with malnutrition morbidity were identified by a stepwise analysis based on a generalised linear regression model and also those that have a biologically plausible relationship \((2,50)\). The environmental predictor variables were extracted from the Moderate Resolution Imaging Spectroradiometer (MODIS) using the MODISTools and MODIS package in R version 3.3.2 \((51–53)\). To extract values from the Kilifi EVI and Rainfall Raster files, the values interpolated from the values of the four nearest raster cells of each admission coordinate provided \((54)\).

The immediate and underlying factors of undernutrition were considered in this analysis.

2.5 Exploratory Data Analysis

The summary statistics, frequency tables of the demographic characteristics were done using the repeated measures tabulation and frequency statistics. The summaries are created from the panel data of the number of admissions and the monthly time variable. Continuous variables are summarised with sample size \((n)\), overall and between means, between, within and overall standard deviations of the panel data. Categorical variables are summarised as counts and percentages of overall, between and within components of the panel data.
2.5 Exploratory Data Analysis

2.5.1 Temporal Exploratory Data Analysis

To explore the temporal patterns, the data were defined as a regular time series data using monthly time points of counts of malnutrition related admissions and mortality. A line plot of the time series data was done for the period 2002-2015. Augmented Dickey-Fuller unit-root was used to test for stationarity; the null hypothesis is that the series has no root or there is no trend in the model. The stationary series is then examined on the Auto-Correlation Function (ACF) for the MA lags, and Partial Auto-Correlation Function (PACF) for the AR lags. This was followed by fitting Autoregressive integrated moving average (ARIMA) and seasonal ARIMA models (51,55). The Seasonal ARIMA is useful where a time series data shows a periodic pattern that reoccurs with about the same intensity in a year. This makes it adequate for the admissions data since admissions in a hospital seems to follow a pattern.

The time series orders autoregression, integration and moving-average of 1,0,1 respectively were selected using the table of the autocorrelations with Bartlett’s statistic (51). Seasonality was determined using the same approach with pointwise confidence intervals also based on Bartlett’s formula and selected the peaks.
In general the seasonal autoregressive moving average model is defined as:

\[
\text{ARIMA } (p, d, q) \ (P, D, Q)_s
\]

\[
\uparrow \quad \uparrow
\]

where \( s \) is the number period per season. SARIMA is an \( \text{ARIMA} (p, d, q) \) model whose residuals at \( \ell_t \) are \( \text{ARIMA} (P, D, Q) \).

In general SARIMA model with period \( s \) is defined as;

\[
(1 - \varphi_p L)(1 - \theta_1 L^s)(1 - L)(1 - L^s)y_t = (1 + \varphi_p L)(1 + \Theta_1 L^s)\ell_t
\]

\[
\uparrow \quad \uparrow \quad \uparrow \quad \uparrow \quad \uparrow
\]

\( \text{NS AR}(1) \quad \text{S AR}(1) \quad \text{NS D} \quad \text{SD} \quad \text{NS AR}(1) \quad \text{S AR}(1) \)

(Eqn:1)

NS - Non-seasonal, AR - Auto Regressive, S- Seasonal, D -Difference

By definition \( \text{ARIMA} (p, d, q) \ (P, D, Q)_s \) is fitted as

\[
\Theta (L^s) \varphi (L) (1 - L)^d (1 - L^s) \quad \text{and} \quad D Y_t = \Theta (L^s) \theta (L) \varepsilon_t \quad \text{where } L \text{ is the lag operator defined as } L^k = \frac{Y_{t-k}}{Y_t}, \quad \varphi (L) = 1 - \varphi_1 (L^1) - \varphi_2 (L^2) - \ldots - \varphi_p (L^p) \text{ is the polynomial function of order } p \text{ with a set number of}
\]
vector coefficients $\varphi \cdot \theta(L) = 1 - \theta_1(L^1) + \theta_2(L^2) + \ldots + \theta_q(L^q)$
is a moving average polynomial of order $q$ with a vector of coefficients $\theta$.

$\Theta(L^S) = 1 - \varphi_{S,1}L^S - \varphi_{S,2}L^{2S} - \ldots - \varphi_{S,P}L^{PS}$ and $\Theta(L^S) = 1 - \varphi_{S,1}L^S - \varphi_{S,2}L^{2S} - \ldots - \varphi_{S,Q}L^{QS}$ are seasonal parameters of order $P$ and $Q$ respectively that meet the stationarity assumption. $d$ is the number of differencing passes needed to stationarize the series, $D$ is the number of seasonal differences, and $\varepsilon_t$ are the error terms with mean zero and variance $\sigma^2$ (56,57).

The Portmanteau test is used to confirm the significance of the seasonality as a covariate. The Portmanteau test null hypothesis is there is no serial correlation using the white noise under the $\text{Chi}^2$ statistic (58). Our model was defined as; SARIMA$(p, d, q)(P, D, Q)_s$, where $s$ is the number of period per season. This was defined as SARIMA$(1,0,1)(1,0,1)_s$ and modelled as $\mu_t = \rho(y_{t-1}) + \theta\varepsilon_{t-1} + \varepsilon_t$ where $\rho$ and $\theta$ are the products of the seasonal parameters identified.

2.5.2 Spatial Exploratory Data Analysis

Maps of the prevalence of children admitted with malnutrition and the patients who died were done. The Global Moran I index was used
to calculate the measure of sublocations spatial autocorrelation or randomness or dispersion on malnutrition admission. A distance matrix of the sub-locations centroids was used to calculate the Morans I index (59,60). The Moran’s I index was calculated based on the large sample theory distribution of the index, which states that as the sample size increases the index tends to a normal distribution.

\[
I = \frac{n}{W} \sum_{i=1}^{n} \sum_{j=1}^{n} w_{i,j} z_i z_j \sum_{i=1}^{n} z_i^2
\]

(Eqn:2)

Where \( z_j \) is the deviation of a malnutrition admission from a sub-location \( z_i = Y_i - \bar{Y} \), \( w_{i,j} \) is the spatial weight between locations \( i \) and \( j \) and \( W = \sum_{i=1}^{n} \sum_{j \neq i}^{n} w_{i,j} \) is the aggregate of all spatial weights. The Moran I index is interpreted depending on the three outcomes; \( I > E(I) \) shows a positive autocorrelation implying clustering and \( I \approx 0 \) shows no spatial auto correlation and \( I < E(I) \) shows a negative autocorrelation implying a dispersed neighbouring value, where \( E(I) \) is the normally distributed population mean (38,61).

Local heterogeneity and clustering of malnutrition attributable mortality and morbidity were determined using SaTScan software to observe the hot and cold spots in Kilifi County. SaTScan applies the Kulldorff spatial scan
statistic which imposes a circular window and calculates the likelihood of observing the events inside and outside the study area. The circle with the maximum likelihood is defined as the most likely cluster (62,63).

2.6 Inferential Statistics

2.6.1 Spatial-Temporal Negative Binomial Model

Our outcome was defined as the counts of malnutrition related admissions until the person with the highest number of malnutrition related admissions. Secondly, the variance of the malnutrition related admissions was higher than the mean, so a negative binomial distribution fitted our count data well (25,32,64). The morbidity outcome data followed a negative binomial distribution; which is a generalisation of the Poisson distribution used to provide better epidemiological estimates of factors associated with malnutrition morbidity (25). The negative binomial spatial-temporal model was applied to achieve objective 2; to identify the spatial and temporal pattern of malnutrition admissions in Kilifi (64). We included children with at least two admissions events for the spatial-temporal negative binomial model due to computational requirements(65). The readmissions would also help investigate vulnerability due to malnutrition morbidity.
Model Definition

The definition of the negative binomial spatial model is

\[ y_{ijt} \mid \psi_{ijt}, \Omega \sim \pi \left( y_{ijt} \mid \psi_{ijt}; \Omega \right) \]  
\hspace{1cm} (Eqn:3)

For \( i = 1, 2, 3, \ldots, n_t = 3114, \) individuals data, \( j = 1, 2, 3, \ldots, q = 40, \) are the sub locations and \( t = 1, 2, 3, \ldots, p = 11 \) is the admission visit number. \( \Omega \) (used as \( \Omega \) thereafter) is a vector of parameters to be estimated and \( \psi_{ijt} \) is the linear predictor.

Where \( y = [y_{ijt}]_{n \times p} \) are the observed admission data which follow a negative binomial distribution of the form \( y_{ijt} \sim NegBinomial(p_{ijt}, r_{ijt}) \) (Eqn:4).

\[
p(y = [y_{ijt}] \mid p, r) = \binom{y_{ijt} - 1}{r - 1} p^r (1 - p)^{y_{ijt}}; y \geq r, r = 1, 2, 3...; 0 < p < 1
\]

where \( r = \frac{1}{\theta} \) and \( p_{ijt} = \frac{1}{1 + \theta \mu_{ijt}}. \)

Using our data and \( y \) is the number of admissions from each individual \( i, r \).
is the number of successful malnutrition admissions from sub-location \( j \) at admission \( t \), and \( p \) is the probability of a malnutrition admission.

The conditional mean is \( E(y_{ijt} | p, r) = \frac{r(1-p_{ijt})}{p_{ijt}} \) and conditional variance \( \text{var}(y_{ijt} | p, r) = \frac{r(1-p_{ijt})}{p_{ijt}^2} \).

Taking the natural logs from Eqn:4 above,

\[
\ln \left( \frac{y_{ijt} - 1}{r - 1} \right) + r \ln(p_{ijt}) + y_{ijt} \ln(1 - p_{ijt}) = \ln \left( \frac{y_{ijt} - 1}{r - 1} \right) + r \ln(p_{ijt}) + y_{ijt} \ln(1 - p_{ijt})
\]  

(Eqn:5)

And in general the exponential family form of a negative binomial is expressed as a member of the generalized linear model which has a link function and a cumulant as shown below;

\[
f(y; p, r) = \exp \left\{ y_{ijt} \ln(1 - p_{ijt}) + r \ln(p_{ijt}) + \ln \left( \frac{y_{ijt} - 1}{r - 1} \right) \right\}
\]  

(Eqn:6)

Since

\[
\left( \begin{array}{c} y_{ijt} - 1 \\ r - 1 \end{array} \right) = \frac{\Gamma(y_{ijt})}{\Gamma(y_{ijt} - r) \Gamma(r)}
\]
from $\Gamma(x) = (x - 1)!$ and $\begin{pmatrix} x \\ m \end{pmatrix} = \frac{x!}{m!(x-m)!}$ and using $r = \frac{1}{\theta}$ and $p_{ijt} = \frac{1}{1 + \theta \mu_{ijt}}$ from Eqn:4 above, and replace in Eqn:5, this gives

$$
= \ln \left( \frac{\Gamma(y_{ijt})}{\Gamma(y_{ijt} - \frac{1}{\theta}) \Gamma(\frac{1}{\theta})} \right) + \frac{1}{\theta} \ln \left( \frac{\theta \mu_{ijt}}{1 + \theta \mu_{ijt}} \right) + y_{ijt} \ln \left( 1 - \frac{1}{1 + \theta \mu_{ijt}} \right)
$$
(Eqn:7)

Then after taking the exponents, this can be expressed as;

$$
= \exp \left\{ \ln \Gamma(y_{ijt}) + y_{ijt} \ln \left( \frac{\theta \mu_{ijt}}{1 + \theta \mu_{ijt}} \right) - \ln \Gamma \left( y_{ijt} - \frac{1}{\theta} \right) + \frac{1}{\theta} \ln \left( \frac{1}{1 + \theta \mu_{ijt}} \right) - \ln \Gamma \left( \frac{1}{\theta} \right) \right\}
$$
(Eqn:8)

From the marginal of the joint distribution of the Poisson-Gamma, the Negative-Binomial distribution (66) can be expressed as follows;

$$
= \exp \left\{ c_0(\mu_{ijt}, \theta) + \ln \Gamma(y_{ijt}) - \ln \Gamma \left( y_{ijt} - \frac{1}{\theta} \right) - \ln \Gamma \left( \frac{1}{\theta} \right) \right\}
$$
(Eqn:9)

Where

$$c_0(\mu_{ijt}, \theta) = y_{ijt} \ln \left( \frac{\theta \mu_{ijt}}{1 + \theta \mu_{ijt}} \right) + \frac{1}{\theta} \ln \left( \frac{1}{1 + \theta \mu_{ijt}} \right)$$
\[ c_0 (\mu_{ijt}, \theta) = y_{ijt} \ln \left( \frac{\theta \mu_{it}}{1 + \theta \mu_{it}} \right) - \frac{1}{\theta} \ln (1 + \theta \mu_{it}) \]

Where \( \mu_{ijt} = \exp (\psi_{ijt}) = \log (E_{ijt}) + x_{ijt} \beta + \varphi_j + \vartheta_j + \gamma_t + \varepsilon_{ijt} \) with \( E_{ijt} \) as the ages of the children and is the exposure time variable, \( x_{ijt} \) are the covariates design matrix, \( \beta \) vector of fixed coefficients. And the INLA modelled latent variables for structured \( (\varphi_j) \) and unstructured \( (\vartheta_j) \) space and time \( (\gamma_t) \).

Our spatial-temporal model was fitted assuming the age of the child as the exposure variable and was fitted as follows

\[
\ln(\mu_{ijt}) = x_{ijt} \beta + \varphi_j + \vartheta_j + \gamma_t + \varepsilon_{ijt} + \log(E_{ijt})
\]  

(Eqn:10)

\[
\mu_{ijt} = \exp \left( x_{ijt} \beta + \varphi_j + \vartheta_j + \gamma_t + \varepsilon_{ijt} \right) \times E_{ijt}
\]  

(Eqn:11)

Under maximum likelihood estimation, the negative binomial form was expressed as (32,66)

\[
L (\mu_{ijt} | y_{ijt}, \theta) = \\
\prod_{i=1}^{n_t} \exp \left\{ c_0 (\mu_{ijt}, \theta) + \ln \Gamma \left( y_{ijt} - \frac{1}{\theta} \right) - \ln \Gamma (y_{ijt}) - \ln \Gamma \left( \frac{1}{\theta} \right) \right\}
\]  

(Eqn:12)
The log likelihood is obtained by taking the log of the likelihood; Eqn:12

$$\ell (\mu_{ijt}|y_{ijt}, \theta) =$$

$$\exp \left[ \sum_{i=1}^{n_t} \left\{ c_0 (\mu_{ijt}, \theta) + \ln \Gamma \left( y_{ijt} - \frac{1}{\theta} \right) - \ln \Gamma (y_{ijt}) - \ln \Gamma \left( \frac{1}{\theta} \right) \right\} \right]$$

(Eqn:13)

Considering values with the parameters, substituting $\mu_{ijt}$ with the linear predictor and $c_0 (\mu_{ijt}, \theta)$, the negative binomial log-likelihood from Eqn:13 the model coefficients can be expressed as

$$\propto \exp \left[ \sum_{i=1}^{n_t} \left\{ y_{ijt} \ln \left( \frac{\theta \exp(\psi_{ijt})}{1 + \theta \exp(\psi_{ijt})} \right) - \frac{1}{\theta} \ln (1 + \theta \exp(\psi_{ijt})) \right\} \right]$$

(Eqn:14)

Thus our model from Eqn:6 can be implemented using GLM with the link function being (66–68).

$$y_{ijt} \ln \left( \frac{\theta \exp(\psi_{ijt})}{1 + \theta \exp(\psi_{ijt})} \right)$$

Since the prior distribution of $\mu_{ijt}$ is a multivariate normal with a mean zero and a $\sum_{q \times q} = \Sigma_{40 \times 40}$ variance matrix, $\mu_{ijt} = MVN (0, \Sigma_{40 \times 40})$. The likelihood contribution for the $j^{th}$ sub location is obtained by integrating $\mu_{ijt}$ out of the joint probability density $f (y_{ijt}|\mu_{ijt}, \theta)$
\[
L (\Omega, \Sigma, \theta) = (2\pi)^{-\frac{q}{2}} |\Sigma|^{-\frac{1}{2}} \int f (y_{ijt} | \mu_{ijt}, \theta) \exp \left( \mu_{ijt} \sum^{-1} \frac{\mu_{ijt}}{2} \right) d\mu_{ijt}
\]
(Eqn: 15)

The above equation (Eqn: 15) has no closed form, and thus approximation method is used for Maximum likelihood estimation.

The spatial-temporal model with Bayesian approach estimation was defined as follows

\[
\text{Posterior} \left[ p(\text{parameters} | \text{data}) \right] \propto \text{Likelihood} \times \text{Priors}
\]

The posterior likelihood of our malnutrition admission data is defined as;

\[
L \left( \Omega \equiv \left\{ \beta, \phi, \varphi, \gamma \right\} | y_{ijt} \right) = \prod_{i=1}^{n} p (y_{ijt} | \Omega) \times p \left( \beta, \phi, \varphi, \gamma \right)
\]
(Eqn: 16)

The full conditional for our model is expressed as;

\[
p (\Omega | y_{ijt}) \propto L (y_{ijt} | \Omega) \times p \left( \beta_{k} \right) \times p \left( \phi_{j} | \tau_{e} \right) \times p \left( \varphi_{j} | \tau_{h} \right) \times p \left( \gamma_{t} | \tau_{e} \right)
\]
(Eqn: 17)
\begin{align*}
\quad = L (y_{ijt} | \Omega) \times p (\beta_{ik}) \times p (\phi_j | \tau_c) \times p (\tau_c) \times p (\tilde{\varphi}_j | \tau_h) \times p (\tau_h) \times p (\gamma_t | \tau_e)
\end{align*}
\quad \text{(Eqn:18)}

The prior for the beta coefficients for $k - 1$ predictors in the model is assumed to be $\beta_{ik} \sim iid N (\mu_{\beta}, \sigma_{\beta}^2)$ therefore
\begin{align*}
p (\beta_k) &= \frac{1}{\sqrt{2\pi\sigma_{\beta}^2}} \exp \left[ -\frac{1}{2} \left( \frac{\beta_k - \mu_{\beta}}{\sigma_{\beta}} \right)^2 \right] \quad \text{(Eqn:19)}
\end{align*}

\text{Spatial Components:}

The unstructured random effects $p (\varphi_j | \tau_h)$, where $\varphi_j \sim iid N (0, \frac{1}{\tau_h})$. Therefore
\begin{align*}
p (\varphi_j | \tau_h) &= \frac{1}{\sqrt{2\pi/\tau_h}} \exp \left[ -\frac{1}{2} \left( \varphi_j - 0 \right)^2 \right] \quad \text{(Eqn:20)}
\end{align*}

with a Gamma function prior used $\tau_h \sim \text{Gamma} (\alpha_h, \beta_h)$ expressed as
\begin{align*}
p (\tau_h) &= \frac{(\beta_h)^{\alpha_h}}{\Gamma (\alpha_h)} \tau_h^{\alpha_h - 1} \exp (-\beta_h \tau_h), \alpha_h > 0; \beta_h > 0 \quad \text{(Eqn:21)}
\end{align*}

Therefore the unstructured random effects prior in BUGS is expressed as;
\[ p(\psi_j|h) \times p(\tau_h) \propto \tau_h^{\alpha_h-1} \exp(-\beta_h \tau_h) \times \exp \left[ -\frac{1}{2} \left( \frac{\psi_j - 0}{\sqrt{\tau_h}} \right)^2 \right] \]

(Eqn:22)

Similarly in INLA the unstructured random effects \( \psi_j = f_{spat\_unst}(s_j) \) scaled with parameter \( \tau_h \).

In BUGS, a CAR prior is used for the structured spatial random effects, a CAR prior is used for the structured spatial random effects \( \phi_j \sim \text{CAR}(\tau_c) \) and a CAR prior given by prior is given as

\[ \phi_j | \phi_i, j \neq i, \tau_c \sim N \left( \frac{\phi_j}{\phi_j}, \frac{1}{\tau_c m_j} \right) \]

therefore

\[ p(\phi_j|\tau_c) = \frac{1}{\sqrt{2\pi \tau_c m_j}} \exp \left[ -\frac{1}{2} \left( \frac{\phi_j - \frac{\phi_j}{\sqrt{\tau_c m_j}}}{1} \right)^2 \right] \]

(Eqn:23)

Hence the likelihood of the neighbouring sub-locations is given as

\[ p(\phi_j|\tau_c) \propto \exp \left\{ -\tau_c \sum_{i=1}^{n_i} w_{ij}(\phi_j - \phi_i)^2 \right\} \]

(Eqn:24)

where \( w_{ij} \) denotes the adjacency matrix and \( i j \) shows that the sub location \( j \) is a neighbour of sub location \( i \) and \( m_j \) is the number of neighbours for sub
location $j$. A conjugate hyper prior of $\tau_c \sim \text{Gamma}(\alpha_c, \beta_c)$ is assumed

$$p(\tau_c) = \frac{(\beta_c)^{\alpha_c}}{\Gamma(\alpha_c)} \tau_c^{\alpha_c-1} \exp \left( -\beta_c \tau_c \right) , \alpha_c > 0; \beta_c > 0 \quad \text{(Eqn:25)}$$

Therefore;

$$p(\phi_j | \tau_c) \times p(\tau_c) \propto \exp \left\{ -\frac{\tau_c}{2} \sum_{i=1}^{n} w_{ij}(\phi_j - \phi_i)^2 \right\} \tau_c^{\alpha_c-1} \exp \left( -\beta_c \tau_c \right) \quad \text{(Eqn:26)}$$

In INLA, the structured temporal component $\phi_j = f_{\text{s}p} (s_j)$, a Besag CAR prior was used similar to CAR prior in BUGS, given as

$$s_j | s_i, j \neq i, \tau_c \sim N \left( \frac{1}{m_j \sum_j s_j}, \frac{1}{\tau_c m_j} \right) \quad \text{(Eqn:27)}$$

Where $\phi_j = (\phi_1, \phi_2, \phi_3, \ldots, \phi_{40})$, $m_j$ is the number of neighbours of sub location $j$, $j \sim i$ indicates that the two sub locations $j$ and $i$ are neighbours.

**AR(1) Temporal Component:**

The temporal component was only implemented using R-INLA only and a first order autoregressive model with normal first term prior was used.

$$\gamma_t = f_{\text{temp}}(y_t) \sim \text{AR}(1)$$ first order autoregressive model with normal
first term prior \( y_t = \rho y_{t-1} + \varepsilon_t \) (69,70) where

\[
y_1 = N \left( 0, \frac{1}{\tau_e (1 - \rho^2)} \right)
\]

\(|\rho| < 1\) for stationarity and \( \varepsilon_t \sim N(0, \tau_e^{-1} = \sigma_t^2) \) is the white noise process.

The auto regressive parameter is expressed as

\[
p(\rho|\sigma_t) = \frac{1}{\sqrt{2\pi \sigma_t^2}} \exp \left( -\frac{(y_t - \rho y_{t-1})^2}{2\sigma_t^2} \right)
\]

(Eqn:28)

Finally combining the likelihood and the prior to obtain our posterior distribution as shown in Eqn:43

\[
p(\Omega|y_{ijt}) \propto \exp \left[ \sum_{i=1}^{n_t} \{ y_{ijt} \ln \left( \frac{\theta \exp(\psi_{ijt})}{1 + \theta \exp(\psi_{ijt})} \right) - \frac{1}{\theta} \ln (1 + \theta \exp(\psi_{ijt})) \} \right] \times \frac{1}{\sqrt{2\pi \sigma_\beta}} \exp \left[ -\frac{1}{2} \left( \frac{\beta_k - \mu_\beta}{\sigma_\beta} \right)^2 \right] \times \tau_h^{\alpha_h-1} \exp(-\beta_h \tau_h) \times \exp \left[ -\frac{1}{2} \left( \frac{\vartheta_j - 0}{1/\sqrt{\tau_h}} \right)^2 \right] \times \exp \left\{ -\frac{\tau_c}{2} \sum_{i=1}^{n} w_{ij}(\phi_j - \phi_i)^2 \right\} \tau_c^{\alpha_c-1} \exp(-\beta_c \tau_c) \times \frac{1}{\sqrt{2\pi \sigma_t^2}} \exp \left( -\frac{(y_t - \rho y_{t-1})^2}{2\sigma_t^2} \right)
\]

(Eqn:29)

Where

\[
\exp(\psi_{ijt}) = \exp \left( x_{ijt} \beta + \phi_i + \vartheta_j + \gamma_t + \varepsilon_{ijt} \right)
\]
This combination has no closed form; estimation is used to estimate the parameters. To solve for the parameters, we use the adapted Stochastic Partial Differential Equations (SPDE) in INLA, and the MCMC with Metropolis- Hastings algorithms approaches in WinBUGS (25,32,71).

In our implementation, combination of the unstructured $\varphi_j = f_{s{\text{pat\_unst}}} (s_j)$ and the structured $\varphi_j = f_{s{\text{pat}}} (s_j)$ priors was modelled as a convolution-prior resulting to a Besag-York-Mollie model. The model is a union of a Besag model Eqn:27 and iid model Eqn:22. This BYM model allows to get the posterior marginal of the sum of structured Besag and unstructured iid spatial components (72).

A negative binomial Bayesian hierarchical space-time model was implemented through an adapted Stochastic Partial Differential Equations (SPDE) approach to produce continuous maps of malnutrition attributable morbidity at level 5 spatial resolution. This approach was selected over the Markov Chain Monte Carlo (MCMC) due to its suitability for Gaussian Markov Random Fields (GMRF) and its computing capability of temporal models (26,27,69,73,74).
2.6.2 Spatial Logistic Model

Our outcome for objective 3 was the discharge outcome of the patient, whether discharged alive or dead. A Bayesian geo-additive spatial logit model with the death as the outcome with a logit link function is fitted to determine the malnutrition attributable mortality. This was considered over the count model since the mortality outcome was fitted as a binomial outcome to allow adjusting for the individual admission effects.

Model Definition

Since our outcome is binary the general distribution is;

\[
y_i = \begin{cases} 
1 & \text{if there was a death} \\
0 & \text{otherwise} 
\end{cases}
\]

Then the likelihood of death is a binomial distribution (a sequence of Bernoulli trials) in general defined as;

\[
L (x_{ij}, y_{ij} | p_{ij}) = L \{Y_{ij} = y_{ij}\} = \binom{r_{ij}}{y_{ij}} p_{ij}^{y_{ij}} (1 - p_{ij})^{r_{ij} - y_{ij}} \tag{Eqn:30}
\]

Where \( p_{ij} \) represents the probability of the subject \( i \) from sub-location \( j \) who has a covariate vector \( x_{ij} \) and \( y_{ij} = 1 \) indicates death or alive if it takes value zero.
The $r_{ij}$ are total admissions with a mean $E(y_{ij}) = \mu_{ij} = r_{ij}p_{ij}$ and the variance is $\text{var}(y_{ij}) = \delta_{ij} = r_{ij}p_{ij}(1 - p_{ij})$.

Considering that a logistic regression model can be defined as follows with cluster-level random effects $\sim_{ij}$.

$$\logit(p_{ij}(x_{ij})) = x_{ij}\beta + \phi + \varphi_{j} + \epsilon_{ij} \quad \text{(Eqn:31)}$$

Then making $p_{ij}$ the subject of the formula, then logistic model was modelled as

$$\ln \left( \frac{p_{ij}}{1 - p_{ij}} \right) = x_{ij}^{T}\beta + \phi + \varphi_{j} + \epsilon_{ij} \quad \text{(Eqn:32)}$$

Considering the binomial mixed-effects model, for the sub location clusters, $j = 1, 2, 3, \ldots, 40$ the conditional distribution of $y_{j} = (y_{j1}, y_{j2}, \ldots, y_{jn_{j}})^{T}$ given a set of sub location level random effects $\sim_{ij}$; expressed as

$$f(y_{ij}|\mu_{ij}) = \prod_{i=1}^{n_{j}} \left[ \binom{r_{ij}}{y_{ij}} \left\{ H(\psi_{ij}) \right\}^{y_{ij}} \left\{ 1 - H(\psi_{ij}) \right\}^{r_{ij}-y_{ij}} \right] \quad \text{(Eqn:33)}$$

Where $\psi_{ij} = x_{ij}^{T}\beta + z_{ij}u_{j}$

Then, exponentiation and log transformation of $H(\psi_{ij})$, this can be written as,
\[
H\left(\psi_{ij}\right) = \frac{\exp\left(x_{ij}\beta + \phi_j + \vartheta_j + \varepsilon_{ij}\right)}{1 + \exp\left(x_{ij}\beta + \phi_j + \vartheta_j + \varepsilon_{ij}\right)} = \frac{\exp\left(\psi_{ij}\right)}{1 + \exp\left(\psi_{ij}\right)}
\]  
(Eqn:34)

From Eqn:32

\[
= \exp\left\{\ln\left(\frac{r_{ij}}{y_{ij}}\right) + y_{ij}\ln\left(H\left(\psi_{ij}\right)\right) + (r_{ij} - y_{ij})\ln\left(1 - H\left(\psi_{ij}\right)\right)\right\}
\]  
(Eqn:35)

Expanding the brackets inside the exponent and simplifying we obtain

\[
= \prod_{i=1}^{n_j} \exp\left\{\ln\left(\frac{r_{ij}}{y_{ij}}\right) + y_{ij}\ln\left(\frac{\exp\left(\psi_{ij}\right)}{1 + \exp\left(\psi_{ij}\right)}\right) + (r_{ij} - y_{ij})\ln\left(\frac{1}{1 + \exp\left(\psi_{ij}\right)}\right)\right\}
\]  
(Eqn:36)

\[
= \prod_{i=1}^{n_j} \exp\left\{\ln\left(\frac{r_{ij}}{y_{ij}}\right) + y_{ij}\ln\left(\exp\left(\psi_{ij}\right)\right) - r_{ij}\ln\left(1 + \exp\left(\psi_{ij}\right)\right)\right\}
\]  
(Eqn:37)

\[
= \prod_{i=1}^{n_j} \exp\left\{\ln\left(\frac{r_{ij}}{y_{ij}}\right) + y_{ij}\psi_{ij} - r_{ij}\ln\left(1 + \exp\left(\psi_{ij}\right)\right)\right\}
\]  
(Eqn:38)
= \exp \left\{ \sum_{i=1}^{n_j} \left[ y_{ij} \psi_{ij} - r_{ij} \ln \left( 1 + \exp \left( \psi_{ij} \right) \right) + \ln \left( \frac{y_{ij}}{\psi_{ij}} \right) \right] \right\} \quad \text{(Eqn:39)}

Let \( r_j = \left( r_{j1}, r_{j2}, \ldots, r_{jn_j} \right)^T \), \( y_j = \left( y_{j1}, y_{j2}, \ldots, y_{jn_j} \right)^T \) and \( \psi_j = \left( \psi_{j1}, \psi_{j2}, \ldots, \psi_{jn_j} \right)^T \) then

\[
c \left( y_j, r_j \right) = \sum_{i=1}^{n_j} \ln \left( \frac{r_{ij}}{y_{ij}} \right)
\]

which does not depend on the model parameters on Eqn:39 in compact form is thus expressed as

\[
f \left( y_j | u_j \right) = \exp \left[ \sum_{i=1}^{n_j} \left( y_{ij}' \psi_{ij} - r_{ij}' \ln \left( 1 + \exp \left( \psi_{ij} \right) \right) \right) + c \left( y_j, r_j \right) \right]
\quad \text{(Eqn:40)}
\]

Given that the prior distribution of the \( u_j = MVN \left( 0, \Sigma \right) \) is a multivariate normal with a mean zero and a \( \Sigma_{q \times q} = \Sigma_{40 \times 40} \) variance matrix. The likelihood contribution for the \( j^{th} \) cluster is obtained by integrating \( u_j \) out of the joint density \( f \left( y_j | u_j \right) \).

\[
L_j \left( \beta, \Sigma \right) = (2\pi)^{-\frac{q}{2}} |\Sigma|^{-\frac{1}{2}} \int f \left( y_j | u_j \right) \exp \left( -u_j' \Sigma^{-1} u_j \right) du_j
\quad \text{(Eqn:41)}
\]
\[ = \exp \{c(y_j, r_j)\} \left(2\pi\right)^{-\frac{q}{2}} |\Sigma|^{-\frac{1}{2}} \int \exp \left\{ h(\beta, \Sigma, u_j) \right\} du_j \quad \text{(Eqn:42)} \]

Where

\[
h(\beta, \Sigma, u_j) = y_j^\prime \psi_j - r_j^\prime \ln \left(1 + \exp(\psi_j)\right) - u_j^\prime \Sigma^{-1} u_j
\]

And for convenience in the arguments of \(h(.)\) we suppress the dependence on the observable data \((y_j, r_j, x_j, z_j)\).

The above equation has no closed form and has to be approximated for the maximum likelihood estimation using mean–variance adaptive Gauss–Hermite quadrature and Laplacian approximation crossed random-effects models (75).

The model fit within STATA does not cater for spatial random effects as such we extended this to the Bayesian framework such that the link function predictor \(\psi_j\) is extended such that

\[
\psi_j^* = x_{ij}\beta + z_{ij} u_j + \varepsilon_{ij}
\]

Letting \(z_{ij} u_j = \theta_j + \phi_j\)

The spatial Bayesian model is defined as follows

\[ Posterior[p(\text{parameters}|\text{data})] \propto \text{Likelihood} \times \text{Priors} \]
The full conditional for our model can be expressed as

\[
p\left(\Omega \equiv \{\beta, \phi, \psi\} \mid y_{ij}\right) \propto P\left(\Omega \mid y_{ij}\right) = \]

\[
L\left(y_{ij}, x_{ij} \mid \Omega\right) \times p\left(\beta_{k} \mid \phi_{i}ight) \times p\left(\phi_{j} \mid \tau_{c}\right) \times p\left(\psi_{j} \mid \tau_{h}\right)
\]

\[
= L\left(y_{ij} \mid \Omega\right) \times p\left(\beta_{k} \mid \phi_{i}\right) \times p\left(\phi_{j} \mid \tau_{c}\right) \times p\left(\tau_{c}\right) \times p\left(\psi_{j} \mid \tau_{h}\right) \times p\left(\tau_{h}\right) \quad \text{(Eqn:43)}
\]

The prior for the beta coefficients in the model is \(\beta_{k} \sim iid \ N\left(\mu_{\beta}, \sigma_{\beta}^{2}\right)\), as defined in Eqn:19.

The unstructured random effects \(p\left(\psi_{j} \mid \tau_{h}\right)\), where \(\psi_{j} \sim iid \ N\left(0, \frac{1}{\tau_{h}}\right)\) with a Gamma function prior used \(\tau_{h} \sim Gamma\left(\alpha_{h}, \beta_{h}\right)\) was defined as shown in equation Eqn:22 above.

A CAR prior is used for the structured spatial random effects \(\phi_{j} \sim CAR\left(\tau_{c}\right)\) and a CAR prior is given as \(\phi_{j} \mid \phi_{i}, j \neq i, \tau_{c} \sim N\left(\frac{\phi_{j}}{\phi_{i}}, \frac{1}{\tau_{em,j}}\right)\) with a conjugate hyper prior of \(\tau_{c} \sim Gamma\left(\alpha_{c}, \beta_{c}\right)\) assumed. The pdf is as described in equation Eqn:26 and a similar approach with a Besag prior as shown in Eqn:27.

Combining the equations for our posterior distribution as shown in Eqn:43.
\[ p(\Omega|y_{ij}) \propto \exp \left[ \sum_{i=1}^{n_j} \left( \frac{y'_j \psi_{\sim ij}}{r'_j} \ln \left( 1 + \exp \left( \psi_{\sim ij} \right) \right) \right) \right] \times \frac{1}{\sqrt{2\pi \sigma^2_{\beta}}} \exp \left[ -\frac{1}{2} \left( \frac{\beta_k - \mu_{\beta}}{\sigma_{\beta}} \right)^2 \right] \times \tau_h^{\alpha_h - 1} \exp(-\beta_h \tau_h) \times \exp \left[ -\frac{1}{2} \left( \frac{\vartheta_j - 0}{1/\sqrt{\tau_h}} \right)^2 \right] \times \exp \left\{ -\frac{\tau_c}{2} \sum_{i=1}^{n} w_{ij} (\phi_j - \phi_i)^2 \right\} \tau_c^{\alpha_c - 1} \exp(-\beta_c \tau_c) \]

(Eqn:45)

Where

\[ \psi_{\sim ij} = \exp \left( x_{ij} \beta + \phi_j + \vartheta_j + \varepsilon_{ij} \right) \]

The above equation also has no closed form and has to be approximated.

To approximate for the parameters we use the adapted Stochastic Partial Differential Equations (SPDE) in INLA and the MCMC with Metropolis-Hastings algorithms approaches (26,27,69,73,74).

The estimated parameters we then used to calculate the mortality attributable fraction. To calculate the confidence intervals for the attributable fractions, the ordinary bootstrap with 1000 iterations was used (3,76).
We adopted both multilevel models and Bayesian approach for model estimation. The advantage of Bayesian models over the multilevel models is the combination of the prior information with the data through Bayes theorem to obtain posterior distributions as shown in section 2.6.1 and 2.6.2. Convergence of the MCMC and SPDE approach was monitored using the trace plots. For model comparison and best fit, we use the Deviance Information Criterion (DIC), where the small DIC was considered better. DIC is defined as $-\bar{D}(\theta) + pD$ where $\bar{D}(\theta) = E[D(\theta)|y]$ which is the posterior mean of the deviance, $D(\theta)$. $pD$ is the difference in the posterior mean deviance and the deviance evaluated at the posterior mean of the parameters, $pD = \bar{D}(\theta) - D(E(\theta|y))$. The posterior mean of the deviance is used to assess the best model fit and $pD$ penalizes for number of parameters in the model, and values between 5-10 indicates the model fits better \cite{71,77}.

2.9 Ethical Clearance

The project utilises data from KHDSS which was received in an anonymised format. The study is approved by the KEMRI (Kenya Medical Research
Institute) Scientific Steering Committee in Kilifi (78). Ethical approval under clearance certificate number M1611104 was received from the Human Research Ethics Committee of the University of the Witwatersrand. The certificate is in Appendix 1.
CHAPTER 3: RESULTS

3.1 Introduction

In this chapter, we show the results of the analysis of the KHDSS admissions data for the period between 2002-2015. Temporal and spatial exploratory analysis using time series and hotspot analysis respectively are presented. We adjusted for the potential confounders, spatial-temporal random effects and other associated factors.

Inferential analysis of the spatial-temporal negative binomial model and spatial logistic model for objective 2 and objective 3 respectively are presented, but we discuss the models of best fit only. Firstly we present the exploratory analysis and then the inferential statistics.

3.2 Exploratory Data Analysis

3.2.1 Temporal Exploratory Data Analysis

The temporal analysis was fitted using monthly data for the period from April 2002 to December 2015. The auto correlation function (ACF) and partial auto correlation function (PACF) of the monthly transformed series using data from 2002 to 2015 show the peaks at different periods as shown
in Appendix 3 for morbidity. A significant serial correlation (seasonality) of 7 months was observed in children admitted with malnutrition and 4 months was observed for non-malnutrition admissions. We report the admission pattern that was unique for malnutrition related admissions. This was confirmed with a significant (p<0.001) Portmanteau test for white noise. An Autoregressive of order 1 (AR1) was selected to be used in the spatial-temporal model which fitted the observed data well as shown in Appendix 3.

Panels (A) and (B) of Figure~4.3 show graphs of the time series plots for the monthly malnutrition related admissions. A significant seasonality of July was observed for malnutrition related admissions, but in general, the malnutrition admissions decline over the period. The graphs show the prediction using SARIMA model. The Panel B of Figure~4.3 shows the non-malnutrition related admission. The red line on Figure~4.3 shows that the Auto Regressive of order 1 predicts the data well and this was implemented in the spatial-temporal model for malnutrition related admissions. The tables in Appendix 2 shows the monthly counts of malnutrition admissions and mortality for the period 2002 to 2015.
3.2.2 Spatial Exploratory Data Analysis

A Global Moran’s I index of 0.1 (p-value<0.001, sd=0.029) was observed. Based on the calculated Global Morans I index, we rejected the zero spatial autocorrelation hypothesis. This shows spatial clustering of the admissions from the different sub locations. The Kulldorff spatial scan statistic using SaTScan showed hotspots in the Northern and Southern areas of the Kilifi urban area. Areas closer to the main hospital (KCH) and Kilifi town were observed as cold spots of malnutrition related admissions as shown on the Figure~4.4 panel A. Four of the five hot spots and cold spots were significant (i.e. p<0.05), the cluster (Mwapula, Marere, Magogoni-K, Mdangarani, Vinagoni, Chivara) was the one observed not to be significant for malnutrition related admissions. The temporal clustering of malnutrition related admissions as shown in Appendix 4, kept on shifting.
over the periods but apparently similar regions were observed. Three mortality clusters we observed as shown on Figure~4.4 panel. We only did hotspot analysis for mortality, and the clusters close to urban Kilifi town was observed during the period 2002 to 2006, the other mortality hotspots were observed until 2008.

Figure 4.4: Malnutrition related hotspots (red shade) and coldspots (blue shade) in KHDSS 2002-2015, A- morbidity coldspots and hotspots and B- mortality hotspots
3.3 Bivariate Analysis

The data used was for the children aged 3 months to 15 years admitted in Kilifi County Hospital over the 14 years between 2002 and 2015 whose sub location data was available. This totalled to 23,483 admissions from 17,940 individuals across the 40 sub-locations in the KHDSS. Malnutrition related readmission analysis had 7,820 admission events from 3,114 children as shown on Table~4.1. In objective three we used the full set of data with 16,355 non-malnutrition related admissions and 7,128 malnutrition related admissions. The average age of the patients who died was higher than that of those who were discharged alive but had many numbers of admission days as shown on Table~4.1. The admissions that had a malnutrition was 30.24% of the total inpatient records of 2365 individuals. Out of the 1271 respondents who had a malnutrition admission in at least one of his or her admission, 73% of their admissions are a malnutrition related admission. The between column tells us that (1271/3114) 40.82% of the repeated admissions happened with the children being malnourished.

Males had a higher percentage (56.23% between males) of experiencing two or more admissions compared to the females (43.77% between females), which is also a similar case in the mortality outcome. Malaria
admissions happened 68% of the times in all admissions that occurred. At least 33% of the admissions had a malaria admission with a significant association in the cases and controls. Blood culture and CSF culture positive patients who died had a higher between percentage compared to those discharged alive as shown on Table~4.2 below.
Table 4.1: Characteristics of the study population for the continuous variables a bivariate analysis by mortality; SD(O,B,W) is the overall, within and between Standard Deviation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall</th>
<th>Alive</th>
<th>Died</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td></td>
<td>N (total admissions)</td>
<td>Mean</td>
<td>SD (O,B,W)</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (months)</td>
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<td>35.95</td>
<td>32.56</td>
<td>3114 (7621)</td>
</tr>
<tr>
<td>Admission Days</td>
<td>3113 (7780)</td>
<td>5.18</td>
<td>6.61</td>
<td>3113 (7591)</td>
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<td></td>
<td></td>
<td>4.95</td>
<td>4.45</td>
<td></td>
</tr>
<tr>
<td>Number of Admissions</td>
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<td>3.49</td>
<td>2.56</td>
<td>3114 (7621)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.59</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
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<td>3.22</td>
<td>2.27</td>
<td>3114 (7621)</td>
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<td></td>
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<td>10.96</td>
<td>4.69</td>
<td>3108 (7541)</td>
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<td></td>
<td></td>
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</tr>
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<td>85.17</td>
<td>19.06</td>
<td>3088 (7350)</td>
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<td></td>
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<td></td>
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<td>0.69</td>
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</tr>
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<td></td>
<td></td>
<td>0.06</td>
<td>0.05</td>
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</tr>
<tr>
<td>Rain (mm)</td>
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<td>31.92</td>
<td>44.30</td>
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<td></td>
<td></td>
<td>32.42</td>
<td>32.84</td>
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</tr>
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### Table 4.2: Categorical Characteristics of the study population; N-total number of individuals, Adm N - Total Admissions, (%B,%W) is the percentage between and within

<table>
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<tr>
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<td>82 (41.21;100)</td>
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<tr>
<td>Blood Culture</td>
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3.4 Spatial-Temporal Negative Binomial Model Fit and Diagnostics

3.4.1 Model fit results

Multivariable analysis was done adjusting for different random effects non-spatial, spatial and spatial-temporal. The age of the child at admission was used as the exposure duration (offset) variable, and the cumulative count of admissions was used as the temporal variable for more epidemiological intuitive results. The estimated coefficients are reported in Table~4.3 with 95% confidence interval based on the Maximum Likelihood Estimation (MLE) approach and 95% credible intervals for the Bayesian approach. As shown on Table~4.3 four models were fit, a multilevel model (MLE approach) adjusting for the sub-location random effects, a spatial model using Gibbs sampling and the INLA estimation procedure which has a better computational capability (79).

In general, the spatial-temporal model with a lower Deviance Information Criterion compared to non-spatial models was used to assess the best model fit. Bayesian spatial-temporal model using R-INLA was the model with the best fit with a DIC= 13640.20 which is the lowest among the spatial-temporal models but with a higher number of effective parameters \(pD = 35.50\) because of the extra temporal parameters.
### Table 4.3: Non-spatial and spatial multivariable Negative Binomial models.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficients (95% CI)</th>
<th>p-value</th>
<th>Mean (95% Cr.I)</th>
<th>Mean (95% Cr.I)</th>
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<tr>
<td>EVI</td>
<td>-0.48 (-0.98;0.02)</td>
<td>0.061</td>
<td>-0.6 (-1.81;-0.03)</td>
<td>-0.49 (-1.02;0.04)</td>
<td>-0.18 (-0.68;0.31)</td>
</tr>
<tr>
<td>Rainfall</td>
<td>0.04 (0.01;0.09)</td>
<td>0.059</td>
<td>0.04 (0;0.09)</td>
<td>0.03 (-0.01;0.08)</td>
<td>0.01 (-0.03;0.05)</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>-0.2 (-0.28;-0.13)</td>
<td>&lt;0.01</td>
<td>0.2 (0.12;0.27)</td>
<td>-0.15 (-0.22;-0.07)</td>
<td>-0.16 (-0.23;-0.09)</td>
</tr>
<tr>
<td>Severe Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.001 (-0.08;0.08)</td>
<td>0.927</td>
<td>0.01 (-0.09;0.07)</td>
<td>-0.08 (-0.16;0.0)</td>
<td>-0.04 (-0.12;0.03)</td>
</tr>
<tr>
<td>2</td>
<td>-0.06 (-0.26;0.14)</td>
<td>0.586</td>
<td>-0.07 (-0.28;0.13)</td>
<td>-0.21 (-0.42;0)</td>
<td>-0.12 (-0.32;0.07)</td>
</tr>
<tr>
<td>3</td>
<td>0.32 (-0.27;0.92)</td>
<td>0.286</td>
<td>0.31 (-0.3;0.93)</td>
<td>0.24 (-0.4;0.86)</td>
<td>0.22 (-0.38;0.77)</td>
</tr>
<tr>
<td>Total Admission</td>
<td>0.13 (0.11;0.14)</td>
<td>&lt;0.01</td>
<td>0.13 (0.11;0.14)</td>
<td>0.14 (0.13;0.16)</td>
<td>-0.02 (-0.04;0)</td>
</tr>
<tr>
<td>Admission Days</td>
<td>0.03 (0.02;0.03)</td>
<td>&lt;0.01</td>
<td>0.03 (0.02;0.03)</td>
<td>0.04 (0.03;0.04)</td>
<td>0.03 (0.03;0.03)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-0.06 (-0.21;-0.19)</td>
<td>&lt;0.01</td>
<td>-0.2 (-0.2;-0.19)</td>
<td>-0.08 (-0.09;-0.07)</td>
<td>-0.11 (-0.12;-0.1)</td>
</tr>
<tr>
<td>DIC (pD)</td>
<td>13169.33 (66.38)</td>
<td></td>
<td>14498.08 (25.03)</td>
<td>13640.2 (35.50)</td>
<td></td>
</tr>
</tbody>
</table>
The Bayesian spatial-temporal multi variable model showed some explanatory variables as determinants of child malnutrition re-admission which was consistent with the non-spatial models. The results are as shown on Table 4.3. The environmental variables were significantly associated with a malnutrition admission in the multilevel model, but a different observation in the spatial-temporal models. Rainfall increase was associated with a higher risk of malnutrition admission (RR=1.04; Cr.I=(1.01-1.09)) in the spatial model but after adjusting for the temporal component the interval of the level of significance changes (RR=1.02; Cr.I=(0.97-1.05)) in the spatial-temporal model. Similarly, adjusting for the spatial and temporal model changed the significance of the EVI variable in the model though it still showed a reduction of the risk of malnutrition admission. The weight of a child which is an important marker of malnutrition; we observed that an increase in weight of a child reduced the relative risk of admission by 20% (RR=0.89; Cr.I= (0.88-0.91)). The children with more admission days had a higher risk of malnutrition re-admission.

The Figure~4.5 shows the overall hot spots and cold spots which were consistent with the SaTScan results, but some sub-locations close to the Kilifi urban were identified as hotspots in this model. Areas with darker red
shows that they have a higher risk of admission with malnutrition and blue shades (in the coloured version) indicate less probability of a malnutrition admission. The temporal risk ratios map were generated after running the Bayesian spatial-temporal model and are as shown on the Figure~4.6. The maps were generated to explain differences in the temporal trend of malnutrition related admissions for the different sub-locations. The blue shades symbolise the cold spots; the red shades exhibits the hot spots for malnutrition related readmissions.
Figure 4.5: Malnutrition related hotspots (red shade) and coldspots (blue shade) in KHDSS 2002-2015, overall results from the Bayesian spatial-temporal model.
Figure 4.6: Malnutrition related hotspots (red shade) and coldspots (blue shade) in KHDSS 2002-2015, space-time interaction results from the Bayesian spatial-temporal model.
3.4.2 Model fit diagnostics

Using the final spatial-temporal model we investigated for the model convergence and correlation. As a way of showing the convergence graphically the model convergence we show posterior mean density plots Figure 4.7 and the WinBUGS model convergence graphs are shown in Appendix 5. The convergence graphs show a perfectly symmetrical pattern observed for the estimated parameters indicating that the model captured the true values very well (80).

![Figure 4.7: Posterior density plots for fixed effects of the NB spatiotemporal model](image)
3.5 Spatial Logistic Model Fit and Diagnostics

3.5.1 Model fit results

Multivariable analysis was done using non-spatial and spatial models for admission specific variables with WHZ scores being the main predictor, environmental variables and sub-location information. Table~4.4 shows the association between different admission predictors and mortality. The model with structured and unstructured random effects had a higher DIC due to the extra spatial parameters. We used the $pD$ that assesses the model complexity to select the most parsimonious model, which is the model with structured and unstructured random effects model as shown on Table~4.4.
Table 4.4: Spatial logistic model for mortality in Kilifi County Hospital, 2002-2015

<table>
<thead>
<tr>
<th>variables</th>
<th>Multi level model</th>
<th>Bayesian Multilevel Random Effects Model (INLA)</th>
<th>Bayesian Spatial Random Effects Model (INLA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficients (95% C.I)</td>
<td>p-value</td>
<td>Mean (95% Cr.I)</td>
</tr>
<tr>
<td>WHZ</td>
<td>-0.52 (-0.58;-0.46)</td>
<td>&lt;0.001</td>
<td>-0.22 (-0.26;-0.17)</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>0.08 (-0.1;0.25)</td>
<td>0.353</td>
<td>-0.1 (-0.23;0.03)</td>
</tr>
<tr>
<td>Severe Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.02 (-0.18;0.21)</td>
<td>0.45</td>
<td>-0.25 (-0.4;-0.11)</td>
</tr>
<tr>
<td>2</td>
<td>0.92 (0.61;1.23)</td>
<td>&lt;0.001</td>
<td>0.54 (0.29;0.78)</td>
</tr>
<tr>
<td>3</td>
<td>2.68 (2.13;3.23)</td>
<td>&lt;0.001</td>
<td>2.16 (1.69;2.62)</td>
</tr>
<tr>
<td>Total Admission</td>
<td>-0.28 (-0.37;-0.18)</td>
<td>0.89</td>
<td>-0.32 (-0.4;-0.24)</td>
</tr>
<tr>
<td>Admission Days</td>
<td>-0.02 (-0.03;0)</td>
<td>0.568</td>
<td>-0.01 (-0.02;0)</td>
</tr>
<tr>
<td>Time to Readmission</td>
<td>0.02 (0.01;0.02)</td>
<td>&lt;0.001</td>
<td>0.01 (0.001;0.02)</td>
</tr>
<tr>
<td>Age in Years</td>
<td>0.02 (-0.01;0.05)</td>
<td>0.188</td>
<td>0.01 (-0.01;0.03)</td>
</tr>
<tr>
<td>EVI</td>
<td>-0.18 (-1.36;0.99)</td>
<td>0.008</td>
<td>-0.39 (-1.29;0.5)</td>
</tr>
<tr>
<td>Rainfall</td>
<td>0.09 (0.01;0.18)</td>
<td>0.005</td>
<td>0.06 (-0.02;0.13)</td>
</tr>
<tr>
<td>Attributable Fraction</td>
<td>38.30 (35.64, 42.82)</td>
<td></td>
<td>24.91 (21.04, 30.84)</td>
</tr>
<tr>
<td>DIC (pD)</td>
<td>7690.56 (26.37)</td>
<td></td>
<td>7690.93 (22.41)</td>
</tr>
</tbody>
</table>
The model with unstructured and structured random effects model showed several predictors of mortality. WHZ which is one the determinant of malnutrition admission was strongly associated with mortality (p<0.001) and RR = -0.52 CrI= (-0.58;-0.46) in both spatial and non-spatial models respectively. The malnutrition attributable fraction for the non-spatial model was high than in the spatial model 38.30(C.I 35.64,42.82). The attributable fraction was lower in the spatial model, after adjusting for the spatial random effects 24.91(C.I = 21.04;30.84 ) but this was the most effective model with a $pD = 22.41$.

The weather variables and gender were significantly associated with mortality. The model shows high admission mortality when there is high rainfall, and EVI was significantly associated with a lower risk of admission mortality. The children who had a higher number of admissions and many admission days had a lower probability (~28% and 2% lower odds respectively) of death as shown on Table~4.4. The diagnostic plot for the posterior means are as shown on Figure~4.9

After adjusting for the spatial random effects, the attributable fraction differs by clusters as shown on Figure~4.8. The maps present the clustering of malnutrition attributable mortality after adjusting for the spatial random
effects. Areas on the south of the creek are observed to have a higher (more than 30%) mortality attributable to mortality. Gede location did not have an estimated fraction due to fewer numbers in from the region.

![Map showing mortality distribution](image)

Figure 4.8: Malnutrition attributable mortality in KHDSS, 2002-2015

### 3.5.2 Model fit diagnostics

The selected model which had the lowest $pD = 22.41$ was investigated for convergence and correlation. Posterior mean density plots on Figure 4.9 were used to show convergence graphically. The convergence graphs show a perfectly symmetrical pattern observed for the estimated parameters indicating that the model captured the true values very well.
(80).

Figure 4.9: Posterior density plots for fixed effects of the logistic spatial model
CHAPTER 4: DISCUSSION AND CONCLUSION

4.1 Introduction

This chapter discusses the key results from our analysis by comparing these with other studies. We also discuss the strength and limitations of the study. The two main models under discussion are the spatial-temporal model for morbidity and spatial model for mortality. We adjusted for potential confounders and other associated factors, adjusting for spatial and temporal for objective 2 and spatial only for objective 3.

In general, hotspots of malnutrition related admissions were found in North and South areas of the Kilifi town as shown on Figure 4.4. The mortality attributable to malnutrition had a spatial heterogeneity as it was observed in Figure 4.8 and the spatial model in section 3.3.

4.2 Spatial-Temporal Patterns of malnutrition related morbidity

A 19-year analysis done on Kilifi showed that a trend for neonatal admissions and severe diseases. Severe disease was defined as neonatal sepsis, prematurity, neonatal jaundice, neonatal encephalopathy, tetanus and neonatal meningitis. The severe diseases accounted for approximately
75% of the admissions, though seasonality of admissions was not reported (81). Stella et al. reported a seasonality during rainfall peaks for malaria admissions in the Kenya Coast (82). Malaria hotspots and hotspots within hotspots were also observed in the period between 2003 to 2011 (83). From our analysis, a seasonality of malnutrition related admissions was observed in Kilifi County hospital with peaks occurring in July.

The severity of disease was defined as the presence of either gastroenteritis, LRTI, blood and CSF culture positive, malaria and fever or meningitis. The explanatory variables; severe disease, admission weight, days of admission and environmental factors; EVI and rainfall were identified as significant factors from our model. In Somalia, infections and the Enhanced Vegetation Index were observed as key drivers of malnutrition (29). Similarly, in our analysis children with a higher number of severe diseases were associated with an increased risk of a malnutrition admission.

In Malawi, it was reported that remoteness, environmental factors and geographical factors were important drivers of children morbidity (30). Rainfall increased the risk of malnutrition admissions, but EVI was associated with the reduction of malnutrition admission. The malnutrition admissions mostly during the rainy season which was different from a
longitudinal malnutrition study done in Ethiopia where acute malnutrition happened during the dry seasons, though the season was not significant in their study (28). In our analysis, we combined both the spatial and temporal random effects and the environmental variables. In our analysis, rainfall increased the risk of a malnutrition related admission and the EVI index reduced the risk of a malnutrition related admission. This could be possibly be explained by the infections that occur during rainy seasons, i.e., diarrhoea, environmental enteropathy or malaria.

In Somalia, Damaris et al. observed a distinct seasonal variation in wasting of under 5 due to changes in climate, food security and diseases. The peaks of malnutrition were observed during the dry season and were reported to have an elevated effect for the rainy season (16). This can also be used to explain the peaks of malnutrition related re-admissions in Kilifi county hospital during the rainy season.

In a study done in Spain, malnutrition was significantly associated with the number of days a patient stayed in hospital thus increasing the cost of hospital stay (21). In our model, the length of hospital stay reduced the risk of a malnutrition admission. Additionally, higher time to readmission increased the risk of a malnutrition admission. Treatment of malnourished
children is considered an important factor for nutrition specific interventions and programs (1).

4.3 Spatial patterns malnutrition attributable mortality

The report for malnutrition attributable fractions in KHDSS report fractions for the whole study region (3). In our study, we build on the study to report location specific attributable fractions; having recognised the spatial heterogeneity in Kilifi HDSS. The importance of adjusting for spatial location in malnutrition prevalences is advised in a study done DR Congo in 2011 (31).

In our model WHZ was a strong predictor of mortality, a unit increase in WHZ score reduced the risk of death by approximately 20%. In a study done in Kilifi children aged 6 to 60 months malnutrition was a strong predictor of mortality with inpatient deaths attributable mortality reported as 19% using WHZ as the marker and 51% using MUAC (3).

In our spatial-temporal model, the inpatient mortality attributable fraction using WHZ was 21.98% with a confidence band of 18.73%-27.81%. The attributable fractions also showed a spatial heterogeneity as shown on Figure~4.8. Most children are treated in the community, and most of the
mortality occurs without a hospital admission, so the reported attributable fractions might be a lower estimate. Similarly, the maps show spatial variation in attributable fractions emphasising on the role of location in malnutrition related modelling (31).

Children who were older had a lower risk of death adjusting for the location and WHZ which is comparable to what was reported in a Tanzanian study where the prevalence of malnutrition decreased in older children (8). Children who had a higher number of admission days had a lower risk of a malnutrition admission in our model. The environmental factors were not significantly associated with mortality in both the multilevel and spatial-temporal models.

4.4 Computational aspects of Spatial-Temporal Modelling

The data we use for our analysis was imbalanced; some individuals had more admission events than others at different times. A better computing speed for approximation was needed. To handle this we also excluded individuals who had a single admission event for a reduced computing time. Sabrina et al. in 2014 review recommended the importance of combining spatial and temporal components in understanding the compounded
phenomenon of malnutrition (15). With the different recommendations of spatial models to get an improved understanding of malnutrition; some of them require higher computing resources for an imbalanced and large data sets (15,84). In our models, we utilise a spatial-temporal and spatial model to understand malnutrition related admissions and malnutrition attributable mortality using KHDSS data.

In most spatial-temporal models with imbalanced data, the temporal components are fitted as a random effect or a Bayesian generalised linear mixed model is implemented (71,84,85). We performed the latter in our analysis; a spatial-temporal negative binomial model, which is a family of GLM using a Bayesian approach. In the spatial mortality model, we did not include the temporal component since mortality is not a changing covariate for the individuals.

Due to the complexity of our data set over 23,000 admissions with 17,000 individuals, we utilised the nested Laplace approximation to handle our spatial-temporal model. The R-INLA interface provided an interface to handle the spatial-temporal negative binomial model with a better computing capability. This is similar to what Musenge et al. in 2013 utilised. In the analysis, they used Integrated Nested Laplace
Approximation (INLA) to fit spatial models with Gaussian Markov Random Fields which had better computing time over MCMC (38). This approach has also been applied in other health research methods and has been shown to give faster and accurate results of posterior estimates (27,36,69).

4.5 Strengths and limitations of the study

The strength and limitations of the results and discussion in this research project are discussed in four broad categories;

• Exposures and outcomes classification
• Modelling approach to catering for confounding and effect modification
• sub-Saharan Africa relevance of the results
• Computational requirements

4.5.1 Exposures and outcomes classification

A major drawback in the utilisation of Negative Binomial model over the truncated Negative Binomial model in modelling the morbidity variable due to lack of implementations truncated negative binomial (TNB) in INLA or BUGS packages (86). The main interest for our modelling was to adjust for the spatial and temporal random effects so we considered
the spatial-temporal negative binomial model over the truncated negative binomial. New approaches which would consider TNB in INLA implementation would further help in modelling this.

4.5.2 Modelling approach to catering for confounding and effect modification

Detailed spatial-temporal data has been a major drawback in understanding the epidemiology of malnutrition (15). One of the strengths of the data points used in this analysis is that they are consistently corrected, updated, and a proper audit trail is in place. However, in our modelling, selection bias may have occurred since we selected individuals who had two or more admissions and kept the admissions events up to the highest number of a malnutrition admission for objective 2. This was handled by using a negative binomial regression model which caters for this (66). Additionally, we used geo-additive regression models to cater for multiple confounding variables and also catered for time-varying covariates in the spatial-temporal model.

Bayesian models helped in catering for the complex structured data for inpatient admissions in KCH. This approach helped in adjusting for geographical location confounding and including the prior information on the distribution of the data.
4.5.3 sub-Saharan Africa relevance of the results

The results from our analysis show the importance of adjusting for the spatial random effects and spatial covariates. This is comparable to what other studies have shown in sub-Saharan Africa, especially temporality of admissions and spatial heterogeneity (29,31,82).

Environmental variables, EVI and rainfall, have been shown to be key drivers of malnutrition and infectious diseases. In Somalia, Kenya and the Democratic Republic of Congo, EVI was shown to reduce the risk of malnutrition in children. However, temporality was not considered in the different projects (29,31,82). Similarly, this was observed in our spatial-temporal models.

Logistic regression has been applied in different studies to estimate attributable fraction (3,76,87) but few studies adjust and report spatially adjusted attributable fractions. In our spatial model for mortality, we adjusted for spatial random effects, and as shown in section 3.3, heterogeneity of attributable fractions is observed.
4.6 Conclusion

4.5.4 Computational requirements

Bayesian inference using MCMC required high computing capabilities compared to the Laplace Approximation in handling imbalanced data. This led to fitting the spatial-temporal Bayesian models in INLA alone. This was due to the complex structure of the data. We treated the spatial component as a random effect without considering the temporality of the locations since children of age 6 months to 15 years rarely migrate.

Computational capability was one of the things required for bulk download of MODIS data for rainfall and EVI. The MODIS reprojection process for EVI was a challenge but using an R Slurm Job was a better way to handle this (53,88). Slurm job is an open source platform that clusters large jobs with a scheduling system in Linux clusters. This helps in performance and also notifications of jobs when done (88).

4.6 Conclusion

A better understanding of the spatial and environmental factors that contribute to malnutrition related re-admissions can be used to advocate for and develop earlier and more appropriate responses and provide an indication of future trends and the potential impact of interventions.
Admission with malnutrition is an important marker of re-admission, understanding the spatial risk distribution can be used to understand mechanisms of post discharge mortality. This would also help in the research of tremendous costs associated with the treatment of morbidity that could be prevented through better child nutrition.

Campaigns providing food and or vitamin or other supplements can help reduce deaths in Kenyan children and building more health facilities to reduce the distance of travel to care is highly recommendable.

The developments of spatial-temporal models account for individual, location and temporal aspects in health-related data analysis. As we have observed, spatial-temporal Bayesian models provide better fitting models compared to non-spatial models. Especially in targeted interventions, maps produced from Bayesian models can be of great importance to policy makers and financing organisations.

Studies considering malnutrition related interventions should consider time and locations in their approach. Available health care significantly reduce the risk of malnutrition as we have observed, so having medical facilities closer and evenly distributed can help reduce the burden of mortality and morbidity.
A more sustainable solution would be to empower and equip smaller facilities. This is drawn from our results that those closer to the Kilifi Hospital were most likely not to die and also not to be readmitted in relation to other health facilities.
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77. Spiegelhalter DJ, Best NG, Carlin BP, Linde A van der. Bayesian measures of model complexity and fit. Journal


APPENDICES

Appendix 1 - Plagiarism declaration report

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _______________ (Student number: ___) am a student registered for the degree of ____________ in the academic year ___2016/2017_____.

I hereby declare the following:

❖ I am aware that plagiarism (the use of someone else’s work without their permission and/or without acknowledging the original source) is wrong.

❖ I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

❖ I have followed the required conventions in referencing the thoughts and ideas of others.

❖ I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: _________________________ Date: 7 September 2017
Clearance Certificate

R14/49 Mr Wambui Kennedy Mwai

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1611104

NAME: Mr Wambui Kennedy Mwai

(Principal Investigator)

DEPARTMENT: School of Public Health

Kilifi County Hospital (KCH) Paediatric Ward, Kenya

PROJECT TITLE: Space-Time Patterns of Child Mortality and Morbidity Attributable to Malnutrition in Kilifi County during 2002-2015, Kenya: A Retrospective Case Control

DATE CONSIDERED: 25/11/2016

DECISION: Approved

CONDITIONS: South African Human Research Ethics Committees (HRECs) have no standing outside South Africa. Ethics approval is also required from local HRECs in Kenya

SUPERVISOR: Eustasius Musenge

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/11/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/were authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES
## Appendix 2 - Number of malnutrition admission cases by month.

Table 16.5: Number of malnutrition admission cases by month in KCH admissions from KHDSS, 2002-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sep</th>
<th>Oct</th>
<th>Nov</th>
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Table 16.6: Number of deaths by month in KCH admissions from KHDSS, 2002-2015

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<th>Mar</th>
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<td>5</td>
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</tr>
<tr>
<td>2015</td>
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<td>8</td>
<td>5</td>
<td>9</td>
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<td>2</td>
<td>4</td>
<td>2</td>
<td>7</td>
<td>55</td>
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<tr>
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<td>66</td>
<td>60</td>
<td>108</td>
<td>90</td>
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<td>85</td>
<td>56</td>
<td>85</td>
<td>68</td>
<td>86</td>
<td>955</td>
</tr>
</tbody>
</table>
Appendix 3 - Time series plots

Figure 16.10: A partial autocorrelation function calculated for both cases and controls

Figure 16.11: A test of AR1 for the temporal variable used in the Spatial - Temporal model.
Appendix 5 - Winbugs diagnostic plots for convergence.

alpha2 -alpha10 shows our covariates in the model.
Appendix 3 - Analysis Codes

The full codes are available at https://github.com/Keniajin/msc_thesis_2017

C.1 Morbidity Analysis

C.1.1 Stata Multi-level model

```
menbreg cumulative_count EVI_VALUE rain_mm i.nsex i.severe_disease total_admission ///
\nadmdays nweight , exposure(nagem) nolog || sublocs:
```

C.1.2 WinBUGS Model

```
model {

  for (i in 1:N) {

    # Likelihood
    cumulative_count[i] ~ dnegbin(p[i], r)
    p[i] <- r / (mu[i] + r)
    log(mu[i]) <-
      alpha[5] * equals(severe_disease[i], 1) + alpha[6] * equals(severe_disease[i], 2) +

  }
}
```

```
##########
# Priors #
##########

# r
r ~ dcat(pi[])
```

## 1:11 is the number of successful admissions
for (i in 1:7) {
    pi[i] <- 1 / 7
}

### Define the priors for the model parameters specification

# Baseline Covariate Coefficient

alpha[1] ~ dflat()

for (j in 2:10) {
    alpha[j] ~ dnorm(0, 0.001)
}

# Bivariate CAR Prior for Phi -- Spatial Main Effects

Phi[1:40] ~ car.normal(adj[], weights[], num[], tau)  # num specifies no. of neighbors

for (i in 1:sumNumNeigh) {
    weights[i] <- 1
}

### prior for tau

tau ~ dgamma(0.5, 0.0005)

}#end model

C.1.3 Bayesian Multilevel Spatial Random Effects Model (INLA)

## Mapping

## coloring the spplot

```r
# Model 1
```
Appendix 3 - Analysis Codes

# replicate the final model in STATA spatial unstructured DIC

formulaUH0 <- cumulitive_count ~ EVI_VALUE + rain_mm + gender +
    severe_disease + total_admission + admdays + nweight + f(Adj_ID,
    model = "iid", prior = "normal", param = c(0, 0.001), initial = 1)

resultUH0 <- inla(formulaUH0, family = "nbinomial", data = admData2,
    control.compute = list(dic = TRUE, cpo = TRUE), E = log(nagem),
    control.predictor = list(compute = TRUE))

## summary in 3 decimal places
summary(resultUH0)
exp(resultUH0$summary.fixed)

## write the files to a CSV
write.csv(data.frame(resultUH0$summary.fixed), "results1_14504_36.csv")

pdresultUH0 <- resultUH0$dic$p.eff

## summary in 3 decimal places
summary(resultUH0)

C.1.4 Spatial Model -INLA

## Load the packages in the above code
#
#'
  #\_Model 2\_  
#
########################################################################
# Model
########################################################################

# spatial model structured and unstructured without
# to compare with Winbugs DIC 14498.08 PD 25.03

formulaUHB <- cumulitive_count ~ EVI_VALUE + rain_mm +
    gender + severe_disease + total_admission + admdays +
    nweight + f(Adj_ID, model = "bym", graph = klf.adj,
    scale.model = TRUE, hyper = list(prec.unstruct = list(prior = "loggamma"),


param = c(0.0111, 0.001)), prec.spatial = list(prior = "loggamma",
param = c(0.0011, 0.001)))
resultUHB <- inla(formulaUHB, family = "nbinomial",
data = admData2, control.compute = list(dic = TRUE,
cpo = TRUE), E = log(nagem), control.predictor(compute = TRUE))
summary(resultUHB)
pdresultUHB <- resultUHB$dic$p.eff  #25.03
exp(resultUHB$summary.fixed)
## save the file to csv
write.csv(data.frame(resultUHB$summary.fixed), "results2_14498.08.csv")

C.1.5 Spatial Temporal Model -INLA

#################################### M0del

#################################### 3#############################################

#################################### spatial model structured and unstruetured with

#################################### the temporal component included

formulaUH <- cumulitive_count ~ EVI_VALUE + rain_mm +
            gender + severe_disease + total_admission + admdays +
nweight + f(Adj_ID, model = "bym", graph = klf.adj,
            scale.model = TRUE, hyper = list(prec.unstruct = list(prior = "loggamma",
            param = c(0.0111, 0.001)), prec.spatial = list(prior = "loggamma",
            param = c(0.0011, 0.001)))) + f(count_adm,
            model = "ar1")
resultUH <- inla(formulaUH, family = "nbinomial", data = admData2,
            control.compute = list(dic = TRUE, cpo = TRUE),
            E = log(nagem_int), control.predictor(compute = TRUE))
summary(resultUH)
pdresultUH <- resultUH$dic$p.eff  #35.50
exp(resultUH$summary.fixed)
write.csv(data.frame(resultUH$summary.fixed), "nm_results2_13640.2.csv")

#### The computation of the posterior mean for the
### random effects is performed in two steps as we have more than one parameter: we extract the marginal posterior distribution for each element of the random effect

csi <- resultUH$marginals.random$Adj_ID[1:40]

## then apply the exponential transformation and calculate the posterior mean for each of them using the lapply function.

zeta <- lapply(csi, function(x) inla.emarginal(exp, x))

## define the cut offs for your risk ratio

zeta.cutoff <- c(0.83, 0.9, 0.95, 0.999, 1, 1.01, 1.05, 1.1, 1.2)

# Transform zeta in categorical variable

cat.zeta <- cut(unlist(zeta), breaks = zeta.cutoff, include.lowest = TRUE)

# Create a dataframe with all the information needed for the map

maps.cat.zeta <- data.frame(unique(admData2$Adj_ID), cat.zeta = cat.zeta)

# Add the categorized zeta to the kilifi spatial polygon

data.kilifi <- attr(kilifi_sub, "data")

attr(kilifi_sub, "data") <- merge(data.kilifi, maps.cat.zeta, by.x = "Adj_ID", by.y = "unique.admData2.Adj_ID.")
C.2 Mortality Analysis

C.2.1 Stata Multi-level model

```stata
xtmelogit noutcome whz06 i.nsex i.severe_disease EVI_VALUE rain_mm //
total_admission admdays timeTR age_yr || sublocs: , nolog
```

C.2.2 Bayesian Multilevel Random Effects Model (INLA)

```r
formulaMorta0 <- noutcome ~ whz06 + nsex + severe_disease + EVI_VALUE +
  rain_mm + total_admission + admdays + timeR + age_yr + f(Adj_ID,
  model = "iid", prior = "normal", param = c(0, 0.001), initial = 1)
```
# f(count_adm, model = 'ar1', replicate = Adj_ID3)
resultMorta0 <- inla(formulaMorta0, family = "binomial", data = admData,
                      control.compute = list(dic = TRUE, cpo = TRUE),
                      control.predictor(compute = TRUE))
summary(resultMorta0)

C.2.3 Bayesian Spatial Random Effects Model (INLA)

formulaMorta <- noutcome ~ whz06 + nsex + severe_disease +
                EVI_VALUE + rain_mm + total_admission + admdays +
                timeR + age_yr + f(Adj_ID, model = "bym", graph = klf.adj,
                scale.model = TRUE, hyper = list(prec.unstruct = list(prior = "loggamma",
                     param = c(1, 0.001)),
                prec.spatial = list(prior = "loggamma",
                     param = c(1, 0.001))))

# f(count_adm, model = 'ar1', replicate = Adj_ID3)
resultMorta <- inla(formulaMorta, family = "binomial",
                   data = admData, control.compute = list(dic = TRUE,
                   cpo = TRUE), control.predictor(compute = TRUE))
summary(resultMorta)
Appendix 7 - UNICEF Conceptual Framework

The UNICEF conceptual framework, which the nutrition community has been using for programming for the past 25 years, identifies three levels of causes of undernutrition.

Figure 16.12: UNICEF Conceptual Framework for malnutrition