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Modeling the impact of vaccination on the epidemiology of measles in a metapopulation

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MODELING THE IMPACT OF VACCINATION ON THE EPIDEMIOLOGY OF MEASLES IN A METAPOPULATION

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A Dissertation Submitted in Partial Fulfilment of the Requirements for the Degree of Master's in Mathematical and Computer Sciences and Engineering of the Nelson Mandela African Institution of Science and Technology

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ABSTARCT

In this research, a metapopulation model is formulated as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. An expression for the effective reproduction number R_C for the metapopulation system and R_{Ci} $(i = 1,2)$ for the two patches when there are no individual movements between them are derived using the next generation approach for controlling the disease. The disease-free equilibrium is computed and proved to be locally and globally asymptotically stable if $R_C < 1$ and unstable if $R_C > 1$. We show that when there are no movements between the two patches, there exists at least one endemic equilibrium for all $R_{Ci} > 1$ and bifurcation analysis of the endemic equilibrium point proves that forward (supercritical) bifurcation occurs in each patch. Sensitivity analysis of the basic reproduction number R_0 for metapopulation system is performed and we found that movement rates from patch 2 to patch 1 tend to increases measles infection in a metapopulation while movement rates from patch 1 to patch 2 tend to decrease measles infection in a metapopulation. Numerical simulation results are also presented to validate analytical results and to show the impact of vaccination on incidence and prevalence of measles in the metapopulation.

DECLARATION

I, Leopard C. Mpande do hereby declare to the Senate of Nelson Mandela African Institution of Science and Technology that this dissertation is my own original work and that it has neither been submitted nor being concurrently submitted for degree award in any other institution.

Leopard C. Mpande _____

Name and signature of candidate **Date**

The above declaration is confirmed

Dr. Damian Kajunguri

Name and signature of supervisor 1 _____

Date

Dr. Emmanuel Mpolya _____

Name and signature of supervisor 2 **Date**

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CERTIFICATION

The undersigned certify that have read and found this dissertation acceptable by the Nelson Mandela African Institution of Science and Technology.

Dr. Damian Kajunguri

Name and Signature of Supervisor 1 _____

Date

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Dr. Emmanuel Mpolya _____

Name and Signature of Supervisor 2 Date

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DEDICATION

To my parents Mr. Constantine G. Mpande and Mary S. Titus.

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LIST OF ABBREVIATIONS AND SYMBOLS

DFE-Disease Free Equilibrium

EE-Endemic Equilibrium

MCSE-Mathematical and Computer Science and Engineering

NM-AIST-Nelson Mandela African Institution of Science and Technology

WHO.-World health organization

$\boldsymbol{R_0}$- Basic Reproduction Number

$\boldsymbol{R_C}$-Effective Reproduction Number

$\boldsymbol{R_{Ci}}$-Effective reproduction number in patch *i*

$\boldsymbol{R_{0i}}$-Basic reproduction number in patch *i*

CHAPTER ONE

Introduction

This chapter gives brief background information on measles disease, illustrates the problem statement, objectives, explains the significance of addressing the study problem, and gives the structure of the dissertation and the different lists of publication.

1.1 Background Information

Measles is a contagious disease and is due to infection of Paramyxovirus of the genus Morbillivirus (Ochoche *et al*., 2014; Onyejekwe *et al*., 2014). An incubation period for measles is found somewhere between 9 and 12 days and its infectivity period is found between 4 and 9 days (Doungmo Goufo *et al*., 2014). Globally, the disease is said to be one of the most prominent causes of death among young children, despite the presence of an effective vaccine (WHO, 2014). Measles is easily transmitted by coughing and sneezing, especially when someone stays in direct contact with an infected nasal secretions (WHO, 2014). It has been pointed out that in the year 2013 there were 145 700 measles induced deaths globally, which is equivalent to 400 deaths every day or 16 deaths every hour (WHO, 2014).

Measles cases occur if there is no high coverage of vaccination (Gahr *et al*., 2014). The high number of cases occur in places where there is an aggregation of individuals who have not been vaccinated or infected by the disease (WHO, 2001). Measles has a basic reproduction number of the range 6 to 45 which implies that the mean number of secondary infections caused by a single infected individual in a susceptible population is found somewhere between 6 and 45 (Ejima *et al*., 2012).

The earliest sign of measles is usually a high fever, which begins about 10 to 12 days after exposure to the virus, and lasts 4 to 7 days. A runny nose, a cough, red and watery eyes, and small white spots inside the cheeks can develop in the initial stage. After several days, a rash erupts, usually on the face and upper neck. Over about 3 days, the rash spreads, eventually reaching the hands and feet. The rash goes on for 5 to 6 days, and then fades. On average, the rash occurs 14 days after exposure to the virus within a range of 7 to 18 days (WHO, 2014).

No specific antiviral treatment exists for measles virus. Severe complications from measles can be avoided through supportive care that ensures good nutrition, adequate fluid intake and treatment of dehydration with WHO-recommended oral rehydration solution. This solution

replaces fluids and other essential elements that are lost through diarrhea or vomiting. Antibiotics should be prescribed to treat eye and ear infections, and pneumonia (WHO, 2014). Several studies have been done on the use of mathematical models to control measles (Abubakar *et al*., 2003; Adewale *et al*., 2014; Momoh *et al*., 2013; Fred *et al*., 2014; Mossong *et al*., 2000; Ochoche *et al*., 2014; Tessa, 2009) . These studies respectively, studied the effect of vaccination (Momoh et al., 2013) and area (Adewale *et al*., 2014) on transmission dynamics of measles, estimated basic reproduction number for measles (Mossong *et al*., 2000), studied control of measles by vaccination incorporating two phases of infectiousness (Ochoche *et al*., 2014), used bifurcation theory on the mathematical model to study measles dynamics (Abubakar *et al*., 2003), and predicted an optimal vaccine coverage level needed to control measles (Fred *et al*., 2014; Tessa, 2006). There are also other studies which use metapopulation models to control measles (Arino *et al*., 2006; Arino, 2009; Doungmo Goufo *et al*., 2014; Salmani *et al*., 2006; Xia *et al*., 2004). These models play an important role in studying disease epidemics because they can describe the dynamics of individuals between patches which may be cities, towns, and so forth. The studies respectively, presented a system of $4p$ ordinary differential equations to describe disease spread in an environment divided into p patches and extended their system to include cross infection between several patches and keeping track of both the current patch and the patch in which an individual usually resides (Arino *et al*., 2006; Arino, 2009), presented a fractional SEIR metapopulation system modelling the spread of measles by considering 4 distinct patches which are cities (Doungmo Goufo *et al*., 2014), proposed a metapopulation model for regional measles dynamics on the basis of a gravity coupling model and a time series susceptible-infected-recovered (TSIR) model for local dynamics (Xia *et al*., 2004), formulated a disease transmission model as a system of ordinary differential equations for a population with individuals traveling between discrete geographic patches (Salmani *et al*., 2006).

In this study, we propose a metapopulation mathematical model as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. Our metapopulation model consists of two regions one with high measles infection (patch 1) and the other region with a low measles infection (patch 2) and movement of individuals between the patches in all direction at constant rates is considered.

1.2 Research Problem

Several studies have been done for example (Momoh *et al*., 2013; Doungmo Goufo *et al*., 2014; Ochoche *et al*., 2014; Mossong *et al*., 2000; Fred *et al*., 2014) among others to address measles epidemic dynamics but the disease still persist despite the availability of interventions. Only few of them tried to consider measles epidemic in a metapopulation. Doungmo Goufo et al., 2014 studied the spread of measles in a city metapopulation, but did not consider the impact of vaccination. Thus, there is a need to assess the impact of vaccination on the disease epidemic in a metapopulation. Therefore, this study aims to study the impact of vaccination on epidemiology of measles in a metapopulation.

1.3 Research Justification

i. The study improves current knowledge and attitudes related to measles and its complications, prevention and treatment.
ii. This work acts as a platform for further research on measles spread in a metapopulation.
iii. The study will be useful for policy makers to establish programs and suitable plans and control of the disease.
iv. The model will help healthcare sector to quantify the effect of vaccination to the spread of the disease.

1.4 Objectives

1.4.1 Main objective

The main objective of this research is to model the impact of vaccination on the epidemiology of measles in a metapopulation.

1.4.2 Specific objectives

The specific objectives were:

i. To formulate a mathematical model for studying the impact of vaccination on the epidemiology of measles in a metapopulation.
ii. To analyze the stability of disease free and endemic equilibrium points for measles metapopulation model.
iii. To perform sensitivity analysis of various parameters of the model.

1.5 Research Questions

The research questions are:-

i. How can the mathematical model for studying the impact of vaccination on the epidemiology of measles in a metapopulaton be formulated?

ii. What is the stability of the disease free and endemic equilibrium point?

iii. How can the sensitivity analysis of the basic reproduction number with respect to model parameters be performed?

1.6 Dissertation outline

This dissertation consists of four chapters.

Chapter one includes the introduction of the problem and literature reviews that are closely related to this study.

Chapter two is based on the paper: *Modelling and sensitivity analysis for dynamics of measles in a metapopulation incorporating vaccination,* Leopard C. Mpande, Damian Kajunguri and Emmanuel Mpolya. The paper is accepted for publication in the American journal of Computational and Applied Mathematics. This chapter consists of model formulation, derivation of the effective and basic reproduction number as well as an analysis of the reproduction number of the measles metapopulation model which incorporates vaccination as a control strategy. The chapter also discusses sensitivity analysis of the basic reproduction number with respect to model parameters.

In **chapter three**, we present the second paper having the title: *Modelling and stability analysis for measles metapopulation model with vaccination,* Leopard C. Mpande, Damian Kajunguri, and Emmanuel Mpolya. The paper is published in the journal of Applied and Computational Mathematics. In this chapter, a clear stability analysis is done for the model formulated in chapter two.

In **chapter four** we conclude the dissertation by having a general discussion, conclusion and recommendation.

CHAPTER TWO

MODELLING AND SENSITIVITY ANALYSIS FOR DYNAMICS OF MEASLES IN A METAPOPULATION INCORPORATING VACCINATION[1]

Abstract

In this chapter, a metapopulation model is formulated as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. An expression for the effective reproduction number R_C for the metapopulation system and R_{Ci} $(i = 1,2)$ for the two patches when individual movements between them do not exist are derived using the next generation approach. Numerical simulations of the reproduction numbers show that vaccination is the effective way to fight against measles in a metapopulation. Sensitivity analysis of the basic reproduction number for the metapopulation system is performed and we found that rates of movement from patch 2 to patch 1 tend to increase measles infection in a metapopulation while rates of movement from patch 1 to patch 2 tend to decrease measles infection in a metapopulation.

Keywords: Vaccination, Metapopulation, Measles, Sensitivity analysis.

2.1 Introduction

Measles is a contagious disease and is due to infection of Paramyxovirus of the genus Morbillivirus (Ochoche *et al*., 2014; Onyejekwe *et al*., 2014). An incubation period for measles is found somewhere between 9 and 12 days and its infectivity period is found between 4 and 9 days (Doungmo Goufo *et al*., 2014). Globally, the disease is said to be one of the most prominent causes of death among young children despite the presence of an effective vaccine (WHO, 2014). Measles is easily transmitted by coughing and sneezing, especially when someone stays direct contact with an infected nasal secretions (WHO, 2014). It has been pointed out that in the year 2013 there were 145 700 measles induced deaths globally, which is equivalent to 400 deaths every day or 16 deaths every hour (WHO, 2014).

[1] This chapter is based on the accepted manuscript

Leopard C. Mpande, Damian Kajunguri, and Emmanuel A. Mpolya, "Modeling and Sensitivity Analysis for dynamics of Measles in a Metapopulation incorporating Vaccination," *American Journal of Computational and Applied Mathematics*.

Measles cases occur if there is no high coverage of vaccination (Gahr *et al*., 2014). The higher number of cases occur in places where there is an aggregation of individuals who have not been vaccinated or infected by the disease (WHO, 2001). Measles has a basic reproduction number of the range 6 to 45 which implies that the mean number of secondary infections caused by a single infected individual in a susceptible population is found somewhere between 6 and 45 (Ejima *et al*., 2012).

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In this study, we proposed a metapopulation mathematical model as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. Our

metapopulation model consists of two regions one with high measles infection (patch 1) and the other region with a low measles infection (patch 2) and movement of individuals between the patches in all direction at constant rates is considered.

2.2 Model Formulation

In this section we formulate a measles metapopulation model incorporating vaccination as a control strategy. Our model consists of two patches, where each patch is divided into the following epidemiological classes for $i = 1,2$: Susceptible S_i, Vaccinated V_i, Exposed E_i, Infected I_i, and Recovered R_i. We assume that individuals mix homogeneously. Recruitment is assumed to be through birth at a constant rate π_i. Natural mortality rate $\mu_i = \mu$ is constant for all patches. We assume one dose of vaccination for susceptible individuals at a rate $\theta_i = \theta$. Once an individual is vaccinated, he or she goes to recovered class with permanent immunity at a constant rate $\sigma_i = \sigma$. The average number of effective contacts of an infectious individual per unit time is β_i, and standard incidence is assumed. The exposed individuals move from exposed class to infectious class at a rate $\delta_i = \delta$. The infectious individuals recover permanently after treatment at a rate $\eta_i = \eta$. Our metapopulation model represents two regions, patch 1 with high measles infection and patch 2 with a low measles infection with an assumption of individual movements between patches in both directions at equal rates as shown in figure 1. The forces of infections for each patch are given by $\lambda_1 = \frac{\beta_1 I_1}{N_1}$ and $\lambda_2 = \frac{\beta_2 I_2}{N_2}$ respectively.

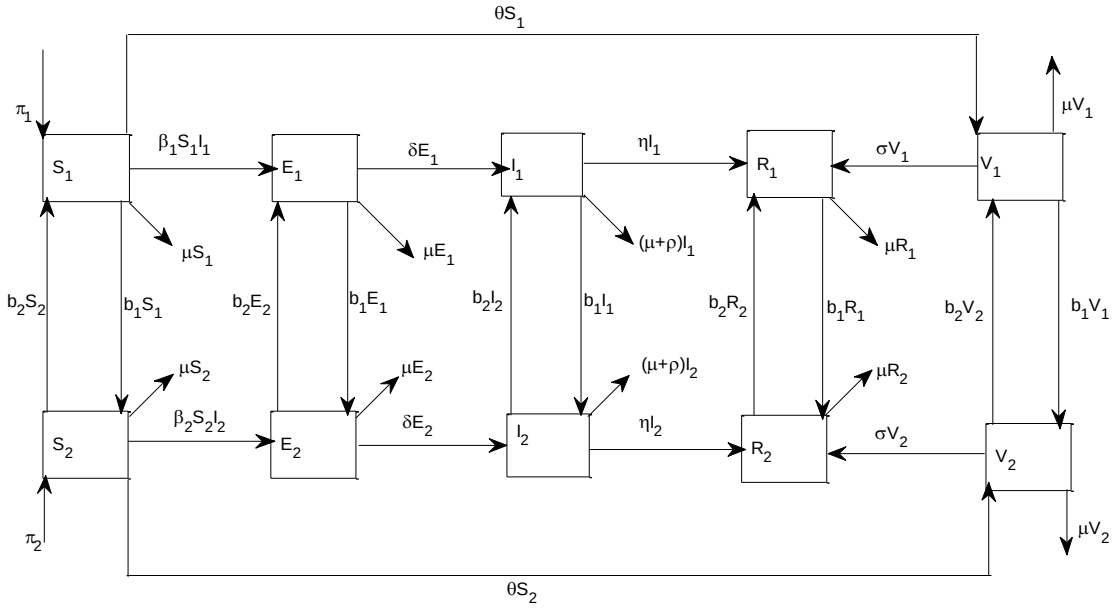


Figure 1. Flow diagram showing measles transmission dynamics in a metapopualtion with vaccination in patches 1 and 2.

Table 1.Parameters used in the model formulation and their description

Parameter	Description
π_i	Per capita birth rate in patch *i.*
β_i	Contact rate (the average number of adequate contacts per person per unit time) in patch *i.*
δ	The rate of progression from latent class to infectious class in patch *i.*
θ	Vaccine coverage rate in patch *i.*
η	Recovery rate of treated infectious individuals in patch *i.*
μ	Per capita natural mortality rate in patch *i.*
ρ	Disease induced death rate in patch *i.*
σ	Recovery rate of vaccinated individuals in patch *i.*

From the description of the dynamics of measles and with the aid of the compartmental diagram in Figure 1, we have the following set of differential equations.

$$\frac{dS_1}{dt} = \pi_1 - \lambda_1 S_1 + b_2 S_2 - (\mu + \theta + b_1) S_1$$

$$\frac{dS_2}{dt} = \pi_2 - \lambda_2 S_2 + b_1 S_1 - (\mu + \theta + b_2) S_2$$

$$\frac{dV_1}{dt} = \theta S_1 + b_2 V_2 - (\mu + \sigma + b_1) V$$

$$\frac{dV_2}{dt} = \theta S_2 + b_1 V_1 - (\mu + \sigma + b_2) V_2$$

$$\frac{dE_1}{dt} = \lambda_1 S_1 + b_2 E_2 - (\mu + \delta + b_1) E_1 \qquad (1)$$

$$\frac{dE_2}{dt} = \lambda_2 S_2 + b_1 E_1 - (\mu + \delta + b_2) E_2$$

$$\frac{dI_1}{dt} = \delta E_1 + b_2 I_2 - (\mu + \rho + \eta + b_1) I_1$$

$$\frac{dI_2}{dt} = \delta E_2 + b_1 I_1 - (\mu + \rho + \eta + b_2) I_2$$

$$\frac{dR_1}{dt} = \eta I_1 + \sigma V_1 + b_2 R_2 - (\mu + b_1) R_1$$

$$\frac{dR_2}{dt} = \eta I_2 + \sigma V_2 + b_1 R_1 - (\mu + b_2) R_2$$

with initial conditions $S_i(0) > 0$, $E_i(0)$, $I_i(0)$, $R_i(0), V_i(0) \geq 0$ and $\sum_{i=1}^{2}(E_i(0) + I_i(0)) > 0$ for $i = 1,2$ (Arino, 2009; Arino *et al*., 2006; Salmani *et al*., 2006).

Here, $N_i = S_i + E_i + I_i + R_i + V_i$ is the total population in each patch and satisfies $\frac{dN_i}{dt} = \pi_i - \mu N_i - \rho I_i$. The total population size in all patches is $N(t) = \sum_{i=1}^{2} N_i(t)$.

Let $\Pi = \sum_{i=1}^{2} \pi_i$. The following two lemmas show that the model is well posed and that all variables lie in the interval $[0, M]$ where $M = \max\left\{N(0), \frac{\Pi}{\mu}\right\}$.

Lemma 1: The solution for the model system (1) is positively invariant in the positive orthant $\mathbb{R}_+^{10}$

Proof. Suppose that initially, all variables are non-negative. We use the method of contradiction to prove this Lemma as done in (Ejima *et al*., 2012; Ngwenya, 2009).

Consider the first equation. Assume there exist a time t_1 such that $S_1(t_1) = 0$, $S_1'(t_1) < 0$ and $S_1(t) > 0$ for $0 < t < t_1$.

But we have $S_1'(t_1) = \pi_1 + b_2 S_2 > 0$ which is a contradiction to the assumption $S_1'(t_1) < 0$. This implies that S_1 remains positive for all t. Similarly, it can be shown that for all $i = 1,2$, the variables S_2, E_i, I_i, R_i and V_i remain positive for all t. Hence solutions remain non-negative for nonnegative initial conditions. Therefore the model is considered to be mathematically and epidemiologically well-posed. Basing on biological considerations, model system (1) will be studied in the region

$\Omega = \{(S_1, S_2, V_1, V_2, E_1, E_2, I_1, I_2, R_1, R_2) \in \mathbb{R}_+^{10}: S_1 + S_2 + V_1 + E_1 + E_2 + I_1 + I_2 + R_1 + R_2 \leq \frac{\Pi}{\mu}\}$.

Lemma 2: Consider the system (1) with nonnegative initial conditions. Assume that for all $i = 1,2$, the variables $S_i(t)$, $E_i(t)$, $I_i(t)$, $V_i(t)$, and $R_i(t)$ remain non-negative, then $N_i(t)$ remain positive, and the total population $N(t)$ is bounded above for $t \geq 0$.

Proof. Assume non-negative initial conditions.

For all $i = 1,2$, we have $\frac{dS_i(t)}{dt} \geq -(\mu + \beta_i + \theta + b_i)S_i$.

Thus $S_i(t) \geq S_i(0)^{-(\mu+\beta_i+\theta+b_i)t}$ for $t \geq 0$ which shows that $S_i(t) > 0$ provided $S_i(0) > 0$. Thus, $N_i(t) > 0$ provided that $S_i(0) > 0$.

By summing all the equations we have $\frac{dN}{dt} = \frac{d(\sum_{i=1}^{2} N_i)}{dt} = \sum_{i=1}^{2}(\pi_i - \mu N_i - \rho I_i) \leq \Pi - \mu N$.

If at a certain time t_1, $N(t_1) = \frac{\Pi}{\mu}$, then $\frac{dN}{dt} =\leq 0$ at t_1, so $N(t)$ is non-increasing at t_1. Thus $N(t)$ is bounded above by M (Salmani *et al*., 2006).

The right hand sides of (1) are continuously differentiable, hence basic theorems (Perko, 2000) can be used to show that there is a unique solution to the system with given non-negative initial conditions and that this solution exists for all $t \geq 0$. Therefore the model is considered to be mathematically and epidemiologically well-posed.

2.3 Model analysis

The model system (1) is analysed qualitatively to give better understanding of the impact of vaccination on the epidemiology of measles.

2.3.1 Disease Free Equilibrium (DFE), P_0

The metapopulation model is at equilibrium if the time derivatives are zero. In the case of system (1), the metapopulation model is at a disease free equilibrium if $E_i = I_i = R_i = 0$ for all i = 1,2. Thus, at a disease free equilibrium we have $N_i = S_i + V_i$.

Solving the system (1), we get a disease-free equilibrium point $P_0 = (S_1^0, S_2^0, V_1^0, V_2^0, 0, 0, 0, 0, 0, 0)$ where

$$S_1^0 = \frac{\pi_2 b_2 + \pi_1(\mu+\theta+b_2)}{(\mu+\theta+b_1)(\mu+\theta+b_2)-b_1 b_2}, S_2^0 = \frac{\pi_1 b_1 + \pi_2(\mu+\theta+b_1)}{(\mu+\theta+b_1)(\mu+\theta+b_2)-b_1 b_2},$$

$$V_1^0 = \frac{\theta b_2 S_2^0 + \theta(\mu+\sigma+b_2)S_1^0}{(\mu+\sigma+b_1)(\mu+\sigma+b_2)-b_1 b_2}, \text{ and } V_2^0 = \frac{\theta b_1 S_1^0 + \theta(\mu+\sigma+b_1)S_2^0}{(\mu+\sigma+b_1)(\mu+\sigma+b_2)-b_1 b_2}$$

2.3.2 The Effective Reproduction Number, R_C

Stability of equilibrium can be analyzed using the basic reproduction number (Castillo-Chavez *et al*., 2002; Hethcote, 2000; Anderson *et al*., 1991). The basic reproduction number R_0 is the expected number of secondary cases produced by a typical infective individual introduced into a completely susceptible population, in the absence of any control measure. A general method for computing R_0 is the next generation method (Diekman *et al*., 1990; Van den driessche *et al*., 2002). Mathematically, R_0 is the spectral radius of the so-called next generation matrix. Here, we compute the control reproduction number, denoted by R_C, to describe the average number of secondary cases generated by primary cases under specified controls such as vaccination (Hethcote, 2000; Anderson *et al*., 1991). Using the method described by (Van den Driessche *et al*., 2002), we use $\mathcal{F}$ to denote the rates of the appearance of new infections in each compartment; $\mathcal{V} = \mathcal{V}^+ + \mathcal{V}^-$, $\mathcal{V}^+$ being the vector of individual transfer rates into the particular compartment, and $\mathcal{V}^-$ the vector of individual transfer rates out of the particular compartment. The two vectors are given by

$$\mathcal{F} = \begin{bmatrix} \lambda_1 S_1 \\ \lambda_2 S_2 \\ 0 \\ 0 \end{bmatrix}, \text{ and } \nu = \begin{bmatrix} (\mu+\delta+b_1)E_1 - b_2 E_2 \\ (\mu+\delta+b_2)E_2 - b_1 E_1 \\ (\mu+\rho+\eta+b_1)I_1 - \delta E_1 - b_2 I_2 \\ (\mu+\rho+\eta+b_2)I_2 - \delta E_2 - b_1 I_1 \end{bmatrix}.$$

The next generation matrix is defined as FV^{-1}, where F and V are both the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ evaluated at disease free equilibrium with respect to exposed and infectious classes.
After some calculations we found

$$F=\begin{bmatrix} 0 & 0 & \frac{\beta_1 S_1^0}{S_1^0+V_1^0} & 0 \\ 0 & 0 & 0 & \frac{\beta_2 S_2^0}{S_2^0+V_2^0} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \text{ and } V=\begin{bmatrix} \mu+\delta+b_1 & -b_2 & 0 & 0 \\ -b_1 & \mu+\delta+b_2 & 0 & 0 \\ -\delta & 0 & \mu+\rho+\eta+b_1 & -b_2 \\ 0 & -\delta & -b_1 & \mu+\rho+\eta+b_2 \end{bmatrix}.$$

The next generation matrix FV^{-1}, has a nonzero eigenvalue corresponding to the spectral radius which represents the control reproduction number of the model as

$$R_C=\frac{\delta a\left(b_1b_2+df\right)+\delta b\left(b_1b_2+ce\right)+\delta\sqrt{\left(bb_1b_2+adf\right)^2+\left(ab_1b_2+bce\right)^2+4abb_1b_2\left(cd+ef\right)+\left(ab_1b_2-bce\right)\left(2adf-2bb_1b_2\right)}}{2\left(b_1b_2-cd\right)\left(b_1b_2-ef\right)} \tag{2}$$

where $c=\mu+\delta+b_1,\ d=\mu+\delta+b_2,\ e=\mu+\rho+\eta+b_1,\ f=\mu+\rho+\eta+b_2,\ a=\frac{\beta_1 S_1^*}{S_1^*+V_1^*}$, and $b=\frac{\beta_2 S_2^*}{S_2^*+V_2^*}$.

If $R_C<1$, the disease cannot invade the metapopulation and the infection will die out over a period of time, and also, if $R_C>1$, then an invasion is possible and infection can spread through the metapopulation. Generally, the larger the value of R_C , the more severe, and possibly widespread the epidemic will be.

When there is no vaccination in all patches, we set the parameters θ and σ to zero and we get $a=\beta_1$ and $b=\beta_2$. Thus we have the basic reproduction number

$$R_0=\frac{\delta\beta_1\left(b_1b_2+df\right)+\delta\beta_2\left(b_1b_2+ce\right)+\delta\sqrt{\left(\beta_2b_1b_2+\beta_1df\right)^2+\left(\beta_1b_1b_2+\beta_2ce\right)^2+4\beta_1\beta_2b_1b_2\left(cd+ef\right)+\left(\beta_1b_1b_2-\beta_2ce\right)\left(2\beta_1df-2\beta_2b_1b_2\right)}}{2\left(b_1b_2-cd\right)\left(b_1b_2-ef\right)} \tag{3}$$

where $c=\mu+\delta+b_1, d=\mu+\delta+b_2, e=\mu+\rho+\eta+b_1,$ and $f=\mu+\rho+\eta+b_2$.

The control reproduction number R_C, is less than the basic reproduction number R_0, and hence we conclude that the endemicity of infection is reduced when vaccination is applied to susceptible individuals in all two patches.

We now consider the case when there are no movements between the given two patches. This means that the parameters b_1 and b_2 become zero. Hence the control reproduction numbers for patches 1 and patch 2 are given in the form (for $i = 1,2$)

$$R_{Ci} = \frac{\beta_i \delta(\mu+\sigma)}{(\mu+\sigma+\theta)(\mu+\delta)(\mu+\rho+\eta)}. \qquad (4)$$

When there are no vaccination strategies, we set the parameter θ and σ equal to zero and hence the reproduction numbers for the two patches when there are no movements between them are given in the form (for $i = 1,2$)

$$R_{0i} = \frac{\beta_i \delta}{(\mu+\delta)(\mu+\rho+\eta)}. \qquad (5)$$

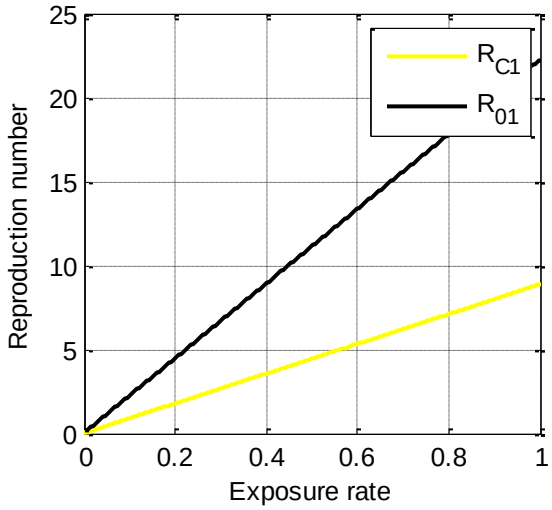
The comparison between reproduction numbers is not obvious analytically, so we opt for the numerical simulation to see how they behave. In order to support the analytical results, graphical representations showing the variations in reproduction numbers with respect to exposure rate will be provided

2.4 Simulation of reproduction numbers

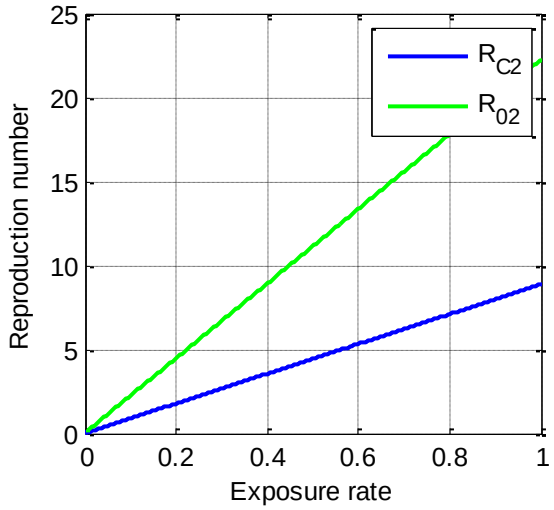
Most of the parameters were estimated and some were picked from the literature. The natural mortality was taken to be 0.02 as in (Ochoche *et al*, 2014), corresponding to a life expectancy of 50 years. The Recovery rate of vaccinated individuals was assumed to be varied in the range $0.52, 0.595, 0.68,$ and 0.769 (Momoh *et al*., 2013). We take a value of 0.52 in our model. The vaccination rate is varied for different values during simulations. We assume the movement rates to take the estimated values of 0.1 and 0.4 respectively which account on the average number of individuals travelling from one region to another. We assume contact rate in one region to be twice compared to another region. Thus the contact rates in the two regions are estimated to be 0.6 and 0.3 respectively. Per capita birth rates are estimated to take values of 250 and 245 respectively in the two regions. Other parameter values were also estimated in the same way.

Table 2.Parameters values for the model system (1)

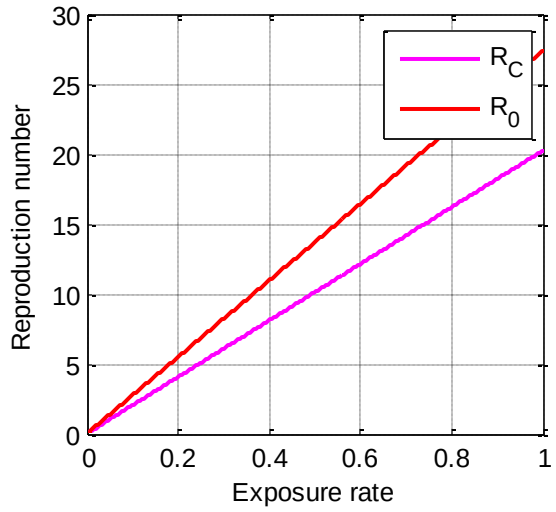
Parameter	Value	Source
π_1, π_2	250, 245	Estimated
β_1, β_2	0.6, 0.3	Estimated
δ	0.44	Estimated
θ	Variable	Estimated
η	0.024	Estimated
μ	0.01-0.6	Ochoche *et al*., 2014
ρ	0.01	Estimated
σ	0.52	Momoh *et al*., 2013
b_1, b_2	0.1, 0.4	Estimated



(a)



(b)



(c)

Figure 2. a and b respectively show variations in reproduction numbers for patch 1 and patch 2 when there are no individual movements between them and c shows variations in reproduction number for the metapopulation system when individual movements between the patches are allowed.

The basic reproduction numbers R_0, R_{01}, and R_{02} given in (3) and (5) respectively are obtained when there are no vaccination strategies to control the epidemic. We see these reproduction numbers are at the peak in both figures above, this implies that there is a high increase in reproduction numbers which result to the outbreak of measles infection.

The best case scenario occurs at control reproduction numbers R_C, R_{C1} and R_{C2}. We know that R_{C1} and R_{C2} are obtained when we give vaccinations to susceptible individuals in patch 1 and patch 2 respectively when there are no individual movements between them and R_C is obtained when vaccination is applied to the metapopulation system in which individual movements between the two patches exist. Thus, measles can be eradicated in the community if there is a widely coverage of vaccination.

2.5 Sensitivity analysis

In order to determine how best to reduce mortality and morbidity caused by measles infection in a metapopulation, it is useful to determine the relative importance of various factors which are accountable for transmission and prevalence of the disease (Makinde *et al*., 2011). Thus, in this

section we perform a sensitivity analysis of the basic reproduction number with respect to model parameters. This will enable us to discover parameters that have a high impact on the basic reproduction number and these parameters should be targeted for measles control. We follow the approach of (Mlay *et al*., 2014; Massawe *et al*., 2015; Chitnis *et al*., 2008; Makinde *et al*., 2011; Edward *et al*., 2014) by using the normalized forward sensitivity index, which is said to be computationally efficient (Kung'aro *et al*., 2014).

Definition 1.1: The normalized forward sensitivity index of R_0, that depends differentiable on a parameter Z, is defined as (Chitnis *et al*., 2008)

$$X_Z^{R_0} = \frac{\partial R_0}{\partial Z} \cdot \frac{Z}{R_0}.$$

For example, using the set of parameter values given in table 2, the sensitivity indices of R_0 with respect to parameters $\beta_1$and η are given as follows

$$X_{\beta_1}^{R_0} = \frac{\partial R_0}{\partial \beta_1} \cdot \frac{\beta_1}{R_0} = 0.89315025.$$

$$X_{\eta}^{R_0} = \frac{\partial R_0}{\partial \eta} \cdot \frac{\eta}{R_0} = -0.54446158.$$

Other indices can be obtained following the same procedure and tabulated below. We ordered the parameters from the most sensitive to the least.

Table 3. Sensitivity indices of model parameters to R_0

Parameter	Sensitivity index
β_1	+0.89315025
η	-0.54446158
μ	-0.24905810
ρ	-0.22685899
β_2	+0.10684997

b_1	-0.08794904
b_2	+0.08508616
δ	+0.02324150

The most sensitive parameters are contact rate β_1 and treated infectious individuals η. The least sensitive parameters are the movement rate from patch 2 to patch 1 (i.e. b_2), and the rate of progression from latent class to infectious class δ. Positive sensitivity index means that an increase or decrease of a given parameter value will lead to the increase or decrease of the basic reproduction number. Negative sensitivity index means that an increase or decrease of a given parameter value will lead to the decrease or increase of the basic reproduction number. For instance, the sensitivity index for η is -0.5444615 which implies that increasing the proportion of individuals who recover through treatment by 50%, decreases the value of R_0 by approximately 27.2% and hence lowering the endemicity of measles in a metapopulation. In contrast, decreasing η by 50%, increases the value of R_0 by 27.2% and hence increases the endemicity of the disease. On the other hand, the sensitivity index of b_2 is +0.08508616 which means that an increase of movements from the patch of low disease incidence (i.e. patch 2) to the patch of high disease incidence (i.e. patch 1) by 50% increases the value of R_0 by approximately 4.25% and hence increases the endemicity of the disease. Therefore, by considering these results, our study suggests that the combination of treatment to infected individuals and vaccination to susceptible individuals should be given high priority. Also, movement rates from patch 2 to patch 1 need to be controlled to prevent more spread of infections in the metapopulation.

2.6 Conclusion

In this chapter, we presented a mathematical model for the control of measles in a metapopulation by considering two regions (patches). We used estimated data and data from literature in numerical simulations. We started by showing nonnegativity of solutions to the metapopulation model, thereby addressing the problem of its well posedness. We used estimated data and data from the literature in numerical simulation. Sensitivity analysis of the basic reproduction number strongly

indicated that the spread of measles largely depends on the contact rate with an infected individual in patch 1 and treatment rate of infectious individuals. Furthermore, we showed that the spread of measles in our metapopualation model is directly proportional to the movement rate of individuals from patch 2 to patch 1 and it is inversely proportional to the movement rates of individuals from patch 1 to patch 2. This means that the movement rates from patch 2 to patch 1 increases measles infection in a metapopulation while movement rates from patch 1 to patch 2 tend to decrease measles infection in a metapopulation. Simulations of the reproduction numbers have proved that vaccination is the effective way to eradicate measles in a metapopulation.

CHAPTER THREE

MODELING AND STABILITY ANALYSIS FOR MEASLES METAPOPULATION MODEL WITH VACCINATION[2]

Abstract

In this chapter, a metapopulation model is formulated as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. The disease-free equilibrium is computed and proved to be locally and globally asymptotically stable if $R_C < 1$ and unstable if $R_C > 1$. We show that when there are no movements between the two patches, there exists at least one endemic equilibrium for all $R_{Ci} > 1$ and bifurcation analysis of endemic equilibrium point proves that forward (supercritical) bifurcation occurs in each patch. Numerical simulation results are also presented to validate analytical results and to show the impact of vaccination on the incidence and prevalence of measles in a metapopulation.

Keywords: Vaccination, Metapopulation, Measles, Bifurcation Analysis.

3.1 Introduction

Measles is a contagious disease and is due to infection of Paramyxovirus of the genus Morbillivirus (Ochoche *et al*., 2014; Onyejekwe *et al*., 2014). An incubation period for measles is found somewhere between 9 and 12 days and its infectivity period is found between 4 and 9 days (Doungmo Goufo *et al*., 2014). Globally, the disease is said to be one of the most prominent causes of death among young children, despite the presence of an effective vaccine (WHO, 2014). Measles is easily transmitted by coughing and sneezing, especially when someone stays in direct contact with an infected nasal secretions (WHO, 2014). It has been pointed out that in the year 2013 there were 145 700 measles induced deaths globally, which is equivalent to 400 deaths every day or 16 deaths every hour (WHO, 2014).

Measles cases occur if there is no high coverage of vaccination (Gahr *et al*., 2014). The high number of cases occur in places where there is an aggregation of individuals who have not been vaccinated or infected by the disease (WHO, 2001). Measles has a basic reproduction number of the range 6 to 45 which implies that the mean number of secondary infections caused by a

[2] This chapter is based on the research paper:

Leopard C. Mpande, Damian Kajunguri, and Emmanuel A. Mpolya, "Modeling and Stability Analysis for Measles Metapopulation Model with Vaccination," *Applied and Computational Mathematics*. Vol. 4, No. 6, 2015, pp. 431-444. doi:10.11648/j.acm. 20150406.16

single infected individual in a susceptible population is found somewhere between 6 and 45 (Ejima *et al*., 2012).

Several studies have been done on the use of mathematical models to control infectious diseases such as measles (Abubakar *et al*., 2003; Adewale *et al*., 2014; Momoh *et al*., 2013; Fred et al., 2014; Mossong *et al*., 2000; Ochoche *et al*., 2014; Tessa, 2009) . These studies respectively, studied the effect of vaccination (Momoh *et al*., 2013) and area (Adewale *et al*., 2014) on transmission dynamics of measles, estimated basic reproduction number for measles (Mossong et al., 2000), studied control of measles by vaccination incorporating two phases of infectiousness (Ochoche *et al*., 2014), used bifurcation theory on the mathematical model to study measles dynamics (Abubakar *et al*., 2003), and predicted an optimal vaccine coverage level needed to control measles (Fred *et al*., 2014; Tessa, 2006). There are also other studies which use metapopulation models to control infectious diseases such as measles (Arino *et al*., 2006; Arino, 2009; Doungmo Goufo *et al*., 2014; Salmani *et al*., 2006; Xia *et al*., 2004). These models play an important role in studying disease epidemics because they can describe the dynamics of individuals between patches which may be cities, towns, and so forth. These studies respectively, presented a system of $4p$ ordinary differential equations to describe disease spread in an environment divided into p patches and extended their system to include cross infection between several patches and keeping track of both the current patch and the patch in which an individual usually resides (Arino *et al*., 2006; Arino, 2009), presented a fractional SEIR metapopulation system modeling the spread of measles by considering 4 distinct patches which are cities (Doungmo Goufo *et al*., 2014), proposed a metapopulation model for regional measles dynamics on the basis of a gravity coupling model and a time series susceptible-infected-recovered (TSIR) model for local dynamics (Xia *et al*., 2004), formulated a disease transmission model as a system of ordinary differential equations for a population with individuals traveling between discrete geographic patches (Salmani *et al*., 2006).

In this study, we proposed a metapopulation mathematical model as a system of ordinary differential equations to study the impact of vaccination on the spread of measles. Our metapopulation model consists of two regions one with high measles infection (patch 1) and the other region with a low measles infection (patch 2) and movement of individuals between patches in all direction at constant rates is considered.

3.2 Model Formulation

In this section we formulate a measles metapopulation model which incorporates vaccination strategy. Our model consists of two patches, where each patch is divided into the following epidemiological classes for $i = 1,2$: Susceptible S_i, Vaccinated V_i, Exposed E_i, Infected I_i, and Recovered R_i. We assume that individuals mix homogeneously. Recruitment is assumed to be through birth at a constant rate π_i. Natural mortality rate $\mu_i = \mu$ is constant for all patches. We assume one dose of vaccination for susceptible individuals at a rate $\theta_i = \theta$. Once an individual is vaccinated, he or she goes to recovered class with permanent immunity at a constant rate $\sigma_i = \sigma$. The average number of effective contacts of an infectious individual per unit time is β_i, and standard incidence is assumed. The exposed individuals move from exposed class to infectious class at a rate $\delta_i = \delta$. The infectious individuals recover permanently after treatment at the rate $\eta_i = \eta$. Our metapopulation model represents two regions, patch 1 with high measles infection and patch 2 with a low measles infection with an assumption of individual movements between patches in both directions at equal rates as shown in figure 3. The forces of infections for each patch are given by $\lambda_1 = \frac{\beta_1 I_1}{N_1}$ and $\lambda_2 = \frac{\beta_2 I_2}{N_2}$ respectively.

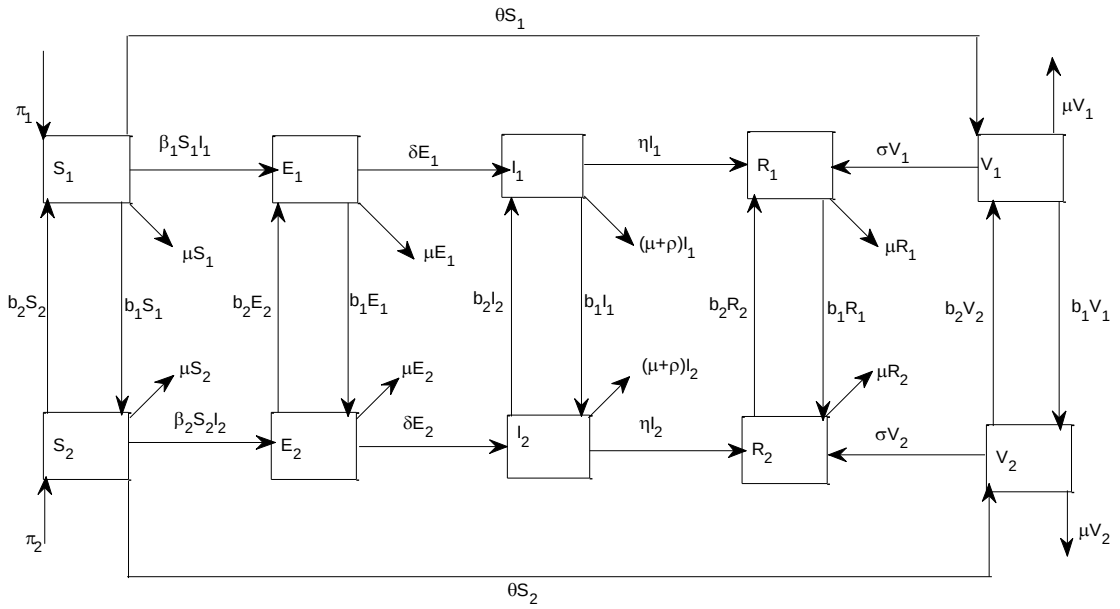


Figure 3. Flow diagram showing measles transmission dynamics in a metapopualtion with vaccination in patches 1 and 2.

Table 4. Parameters used in the model formulation and their description

Parameter	Description
π_i	Per capita birth rate in patch *i.*
β_i	Contact rate (the average number of adequate contacts per person per unit time) in patch *i.*
δ	The rate of progression from latent class to infectious class in patch *i.*
θ	Vaccine coverage rate in patch *i.*
η	Recovery rate of treated infectious individuals in patch *i.*
μ	Per capita natural mortality rate in patch *i.*
ρ	Disease induced death rate in patch *i.*
σ	Recovery rate of vaccinated individuals in patch *i.*

From the description of the dynamics of measles and with the aid of the compartmental diagram in Figure 1, we have the following set of differential equations.

$$\frac{dS_1}{dt} = \pi_1 - \lambda_1 S_1 + b_2 S_2 - (\mu + \theta + b_1) S_1$$
$$\frac{dS_2}{dt} = \pi_2 - \lambda_2 S_2 + b_1 S_1 - (\mu + \theta + b_2) S_2$$
$$\frac{dV_1}{dt} = \theta S_1 + b_2 V_2 - (\mu + \sigma + b_1) V_1$$
$$\frac{dV_2}{dt} = \theta S_2 + b_1 V_1 - (\mu + \sigma + b_2) V_2$$
$$\frac{dE_1}{dt} = \lambda_1 S_1 + b_2 E_2 - (\mu + \delta + b_1) E_1$$
$$\frac{dE_2}{dt} = \lambda_2 S_2 + b_1 E_1 - (\mu + \delta + b_2) E_2 \qquad (1)$$
$$\frac{dI_1}{dt} = \delta E_1 + b_2 I_2 - (\mu + \rho + \eta + b_1) I_1$$
$$\frac{dI_2}{dt} = \delta E_2 + b_1 I_1 - (\mu + \rho + \eta + b_2) I_2$$

$$\frac{dR_1}{dt} = \eta I_1 + \sigma V_1 + b_2 R_2 - (\mu + b_1) R_1$$

$$\frac{dR_2}{dt} = \eta I_2 + \sigma V_2 + b_1 R_1 - (\mu + b_2) R_2$$

with initial conditions $S_i(0) > 0, E_i(0), I_i(0), R_i(0), V_i(0) \geq 0$ and $\sum_{i=1}^{2}\big(E_i(0) + I_i(0)\big) > 0$ for $i = 1,2$ (Arino, 2009; Arino *et al*., 2006; Salmani *et al*., 2006).

Here $N_i = S_i + E_i + I_i + R_i + V_i$ is the total population in each patch and satisfies $\frac{dN_i}{dt} = \pi_i - \mu N_i - \rho I_i$.

The total population size in all patches is $N(t) = \sum_{i=1}^{2} N_i(t)$.

Let $\Pi = \sum_{i=1}^{2} \pi_i$.

The following two lemmas show that the model is well posed and that all variables lie in the interval $[0, M]$ where $M = \max\{N(0), \frac{\Pi}{\mu}\}$.

Lemma 1: The solution for the model system (1) is positively invariant in the positive orthant $\mathbb{R}_+^{10}$.

Proof. Assume that initially, all variables are non-negative. We use the method of contradiction to prove this Lemma as done in (Ejima *et al.*, 2012; Ngwenya, 2009).

Consider the first equation. Assume there exist a time $t_1$such that $S_1(t_1) = 0$, $S_1'(t_1) < 0$ and $S_1(t) > 0$ for $0 < t < t_1$.

But we have $S_1'(t_1) = \pi_1 + b_2 S_2 > 0$ which is a contradiction to the assumption $S_1'(t_1) < 0$. This implies that S_1 remains positive for all t. Similarly, it can be shown that for all $i = 1,2$, the variables S_2, E_i, I_i, R_i and V_i remain positive for all t. Hence solutions remain non-negative for nonnegative initial conditions. Therefore the model is considered to be mathematically and epidemiologically well-posed. Basing on biological considerations, model system (1) will be studied in the region

$\Omega = \{(S_1, S_2, V_1, V_2, E_1, E_2, I_1, I_2, R_1, R_2) \in \mathbb{R}_+^{10} : S_1 + S_2 + V_1 + V_2 + E_1 + E_2 + I_1 + I_2 + R_1 + R_2 \leq \frac{\Pi}{\mu}\}$.

Lemma 2: Consider the system (1) with nonnegative initial conditions. Assume that for all $i = 1,2$, the variables $S_i(t), E_i(t), I_i(t), V_i(t)$ and $R_i(t)$ remain non-negative, then $N_i(t)$ remain positive, and the total population $N(t)$ is bounded above for $t \geq 0$.

Proof. Assume non-negative initial conditions.

For all $i=1,2$, we have $\frac{dS_i(t)}{dt} \geq -(\mu+\beta_i+\theta+b_i)S_i$.

Thus $S_i(t) \geq S_i(0)^{-(\mu+\beta_i+\theta+b_i)t}$ for $t \geq 0$ which shows that $S_i(t) > 0$ provided $S_i(0) > 0$. Thus $N_i(t) > 0$ provided that $S_i(0) > 0$.

By summing all the equations we have $\frac{dN}{dt} = \frac{d(\sum_{i=1}^{2} N_i)}{dt} = \sum_{i=1}^{2}(\pi_i - \mu N_i - \rho I_i) \leq \Pi - \mu N$.

If at a certain time t_1, $N(t_1) = \frac{\Pi}{\mu}$, then $\frac{dN}{dt} =\leq 0$ at t_1, so $N(t)$ is non-increasing at t_1. Thus $N(t)$ is bounded above by M (Onyejekwe *et al*., 2015).

The right hand sides of (1) are continuously differentiable, hence basic theorems (Perko, 2000) can be used to show that there is a unique solution to the system with given non-negative initial conditions and that this solution exists for all $t \geq 0$. Therefore the model is considered to be mathematically and epidemiologically well-posed.

3.3 Model analysis

The model system (1) is analysed qualitatively to give better understanding of the impact of vaccination on the epidemiology of measles. From chapter two we have seen that the model (1) have various reproduction numbers as shown in (2), (3), (4) and (5). We now turn into discussing about various stability analysis of the model. We also provide a detailed discussion about various stability analysis of the patch models with and without individual movements between them.

3. 3. 1 Local Stability of the Disease-Free Equilibrium

We investigate the stability of the disease free equilibrium point $P_0 = (S_1^0, S_2^0, V_1^0, V_2^0, 0,0,0,0,0,0)$ as derived in chapter one by employing the method described in (Elbasha *et al*., 2006; Liao *et al*., 2013; Ngwenya, 2009; Tessa, 2006). Thus, we linearize the model system (1) by computing its Jacobian matrix J. The Jacobian matrix is computed at disease free equilibrium point by differentiating each equation in the system with respect to the state variables $S_1, S_2, V_1, V_2, E_1, E_2, I_1, I_2, R_1$ and R_2. We get

$$J(P_0)=\begin{bmatrix} -g & b_2 & 0 & 0 & 0 & 0 & -a & 0 & 0 & 0 \\ b_1 & -h & 0 & 0 & 0 & 0 & 0 & -b & 0 & 0 \\ \theta & 0 & -k & b_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \theta & b_1 & -l & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -c & b_2 & a & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & b_1 & -d & 0 & b & 0 & 0 \\ 0 & 0 & 0 & 0 & \delta & 0 & -e & b_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \delta & b_1 & -f & 0 & 0 \\ 0 & 0 & \sigma & 0 & 0 & 0 & \eta & 0 & -i & b_2 \\ 0 & 0 & 0 & \sigma & 0 & 0 & 0 & \eta & b_1 & -j \end{bmatrix},$$

where $a=\frac{\beta_1 S_1^0}{S_1^0+V_1^0}$, $b=\frac{\beta_2 S_2^0}{S_2^0+V_2^0}$, $c=\mu+\delta+b_1$, $d=\mu+\delta+b_2$, $e=\mu+\rho+\eta+b_1$,

$f=\mu+\rho+\eta+b_2$, $g=\mu+\theta+b_1$, $h=\mu+\theta+b_2$, $i=\mu+b_1$, $j=\mu+b_2$, $k=\mu+\sigma+b_1$, and

$l=\mu+\sigma+b_2$.

An equilibrium point $P_0=\left(S_1^0,S_2^0,V_1^0,V_2^0,0,0,0,0,0,0\right)$ is locally asymptotically stable if the Jacobian matrix has a negative trace and a positive determinant or if all of its eigenvalues have negative real parts [Liao *et al*., 2013; Fred *et al*., Mpeshe *et al*., 2009; Edward *et al*., 2014). Using the idea of (Elbasha et al., 2006; Liao et al., 2013) we write the jacobian matrix in the form

$J(P_0)=\begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix}$, where

$$J_{11}=\begin{bmatrix} -g & b_2 & 0 & 0 & 0 \\ b_1 & -h & 0 & 0 & 0 \\ \theta & 0 & -k & b_2 & 0 \\ 0 & \theta & b_1 & -l & 0 \\ 0 & 0 & 0 & 0 & -c \end{bmatrix},\ J_{12}=\begin{bmatrix} 0 & -a & 0 & 0 & 0 \\ 0 & 0 & -b & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ b_2 & a & 0 & 0 & 0 \end{bmatrix},\ J_{21}=\begin{bmatrix} 0 & 0 & 0 & 0 & b_1 \\ 0 & 0 & 0 & 0 & \delta \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma & 0 & 0 \\ 0 & 0 & 0 & \sigma & 0 \end{bmatrix}, \text{ and}$$

$$J_{22}=\begin{bmatrix} -d & 0 & 0 & 0 & 0 \\ 0 & -e & b_2 & 0 & 0 \\ \delta & b_1 & -f & 0 & 0 \\ 0 & \eta & \sigma & -i & b_2 \\ 0 & 0 & \eta & b_1 & -j \end{bmatrix}.$$

The disease-free equilibrium is locally asymptotically stable if and only if all the eigenvalues of the matrices J_{11} and J_{22} have negative eigenvalues. The eigenvalues of J_{11} are

$-c$, $-\frac{1}{2}(k+l)+\frac{1}{2}\sqrt{(k-l)^2+4b_1b_2}$, $-\frac{1}{2}(k+l)-\frac{1}{2}\sqrt{(k-l)^2+4b_1b_2}$, $-\frac{1}{2}(g+h)+\frac{1}{2}\sqrt{(g-h)^2+4b_1b_2}$,

and $-\frac{1}{2}(g+h)-\frac{1}{2}\sqrt{(g-h)^2+4b_1b_2}$.

It can also be shown that all eigenvalues of J_{22} are negative. Thus, it is clear that for $R_C < 1$, the DFE is locally asymptotically stable, so that the infection does not persist in the metapopulation and under this condition the endemic equilibrium point does not exist. The DFE is unstable for $R_C > 1$, and then the endemic equilibrium point exists and the infection persists in the metapopulation. Therefore we established the following Lemma.

Lemma 3. With nonnegative initial conditions the disease-free equilibrium of the system (1) is locally asymptotically stable if $R_C < 1$ and unstable if $R_C > 1$.

3.3.2 Global Stability of Disease Free Equilibrium Point (DFE)

In this section, we use the method developed in (Castillo-Chevez *et al*., 2002; Mukandavire et al., 2009; Ochoche *et al*., 2014) to analyse the global stability of disease free equilibrium point. We state two conditions which guarantee the global stability of the disease free equilibrium. The model system (1) can be written in the form

$$\begin{cases} \dfrac{dU}{dt} = F(U,I) \\ \dfrac{dI}{dt} = G(U,I),\ G(U,0)=0 \end{cases},$$

where $U \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $I \in \mathbb{R}^n$ denotes (its components) the number of infected individuals including latent, infectious, etc.

We use $P_0 = (U^0, 0)$ as a disease free equilibrium of this system. According to Barbalat (1959) the conditions H_1 and H_2 below must be met to guarantee local asymptotic stability.

H_1: For $\frac{dU}{dt} = F(U,0)$, U^0 is globally asymptotically stable (g.a.s).

H_2: $G(U,I) = AI - \hat{G}(U,I)$, $\hat{G}(U,I) \geq 0$ for $(U,I) \in \Omega$,

where $A = D_I G(U^0, 0)$ is an *M*-matrix (the off-diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. Considering our model system (1), we have

$$F(U,I) = \begin{bmatrix} \pi_1 - \frac{\beta_1 S_1 I_1}{N_1} + b_2 S_2 - (\mu + \theta + b_1) S_1 \\ \pi_2 - \frac{\beta_2 S_2 I_2}{N_2} + b_1 S_1 - (\mu + \theta + b_2) S_2 \\ \theta S_1 + b_2 V_2 - (\mu + \sigma + b_1) V_1 \\ \theta S_2 + b_1 V_1 - (\mu + \sigma + b_2) V_2 \\ \eta I_1 + \sigma V_1 + b_2 R_2 - (\mu + b_1) R_1 \\ \eta I_2 + \sigma V_2 + b_1 R_1 - (\mu + b_2) R_2 \end{bmatrix}, \quad G(U,I) = \begin{bmatrix} \frac{\beta_1 S_1 I_1}{N_1} + b_2 E_2 - (\mu + \delta + b_1) E_1 \\ \frac{\beta_2 S_2 I_2}{N_2} + b_1 E_1 - (\mu + \delta + b_2) E_2 \\ \delta E_1 + b_2 I_2 - (\mu + \rho + \eta + b_1) I_1 \\ \delta E_2 + b_1 I_1 - (\mu + \rho + \eta + b_2) I_2 \end{bmatrix},$$

$U^0 = \left(S_1^0, S_2^0, V_1^0, V_2^0, 0, 0\right)$, and $\Omega = \mathbb{R}_+^{10}$.

Now,

$$\frac{dU}{dt} = F(U,0) = \begin{bmatrix} \pi_1 + b_2 S_2 - (\mu + \theta + b_1) S_1 \\ \pi_2 + b_1 S_1 - (\mu + \theta + b_2) S_2 \\ \theta S_1 + b_2 V_2 - (\mu + \sigma + b_1) V_1 \\ \theta S_2 + b_1 V_1 - (\mu + \sigma + b_2) V_2 \\ 0 \\ 0 \end{bmatrix},$$

which clearly shows that $U^0 = \left(S_1^0, S_2^0, V_1^0, V_2^0, 0, 0\right)$ is globally asymptotically stable (g.a.s). So, the condition H_1 is satisfied.

For the second condition H_2 we have

$$\hat{G}(U,I)=\begin{bmatrix}\beta_1 I_1(1-\frac{S_1}{N_1})\\ \beta_2 I_2(1-\frac{S_2}{N_2})\\ 0\\ 0\end{bmatrix},\ A=\begin{bmatrix}-c & b_2 & \beta_1 & 0\\ b_1 & -d & 0 & \beta_2\\ \delta & 0 & -e & b_2\\ 0 & \delta & b_1 & -f\end{bmatrix},$$

where $c=\mu+\delta+b_1, d=\mu+\delta+b_2, e=\mu+\rho+\eta+b_1$ and $f=\mu+\rho+\eta+b_2$.

Since $0<S_1<N_1$ and $0<S_2<N_2$, it is clear that $\hat{G}(U,I)\geq 0$.

Now consider the right hand side of H_2.

$$AI-\hat{G}(U,I)=\begin{bmatrix}-c & b_2 & \beta_1 & 0\\ b_1 & -d & 0 & \beta_2\\ \delta & 0 & -e & b_2\\ 0 & \delta & b_1 & -f\end{bmatrix}\begin{bmatrix}E_1\\ E_2\\ I_1\\ I_2\end{bmatrix}-\begin{bmatrix}\beta_1 I_1(1-\frac{S_1}{N_1})\\ \beta_2 I_2(1-\frac{S_2}{N_2})\\ 0\\ 0\end{bmatrix},$$

$$=\begin{bmatrix}-cE_1+b_2E_2+\beta_1 I_1-\beta_1 I_1+\frac{\beta_1 S_1 I_1}{N_1}\\ b_1E_1-dE_2+\beta_2 I_2-\beta_2 I_2+\frac{\beta_2 S_2 I_2}{N_2}\\ \delta E_1-eI_1+b_2I_2\\ \delta E_2-fI_2+b_1I_1\end{bmatrix},$$

$$=\begin{bmatrix}\frac{\beta_1 S_1 I_1}{N_1}+b_2E_2-(\mu+\delta+b_1)E_1\\ \frac{\beta_2 S_2 I_2}{N_2}+b_1E_1-(\mu+\delta+b_2)E_2\\ \delta E_1+b_2I_2-(\mu+\rho+\eta+b_1)I_1\\ \delta E_2+b_1I_1-(\mu+\rho+\eta+b_2)I_2\end{bmatrix},$$

$$=G(U,I).$$

So the condition H_2 is also satisfied. Thus $P_0=(U^0,0)$ is globally asymptotically stable (g.a.s). Therefore, we have the following important Lemma.

Lemma 4. With non-negative initial conditions, the DFE of the model system (1) is globally asymptotically stable if $R_C < 1$ and unstable if $R_C > 1$.

3.3.3 Existence and Local Stability of Endemic Equilibrium (EE) Point, E^*

In the presence of infection the model system (1) has a non-trivial equilibrium point, known as endemic equilibrium point given by $E^* = (S_1^*, S_2^*, V_1^*, V_2^*, E_1^*, E_2^*, I_1^*, I_2^*, R_1^*, R_2^*)$. The endemic equilibrium is an equilibrium where at least one of the components E_i or I_i is nonzero (Chitnis *et al*., 2008; Ngwenya, 2009). We compute the endemic equilibrium point by setting the equations of the model system (1) to zero. Since the endemic equilibrium cannot be cleanly expressed in closed form, we find the conditions for its existence as done in (Massawe *et al*., 2015; Tumwiine *et al*., 2007). We can reduce the model by eliminating V_1, V_2, R_1 and R_2 to obtain the system

$$\begin{aligned}
\frac{dS_1}{dt} &= \pi_1 - \lambda_1 S_1 + b_2 S_2 - (\mu + \theta + b_1) S_1 \\
\frac{dS_2}{dt} &= \pi_2 - \lambda_2 S_2 + b_1 S_1 - (\mu + \theta + b_2) S_2 \\
\frac{dE_1}{dt} &= \lambda_1 S_1 + b_2 E_2 - (\mu + \delta + b_1) E_1 \\
\frac{dE_2}{dt} &= \lambda_2 S_2 + b_1 E_1 - (\mu + \delta + b_2) E_2 \qquad (2) \\
\frac{dI_1}{dt} &= \delta E_1 + b_2 I_2 - (\mu + \rho + \eta + b_1) I_1 \\
\frac{dI_2}{dt} &= \delta E_2 + b_1 I_1 - (\mu + \rho + \eta + b_2) I_2
\end{aligned}$$

For the existence of an endemic equilibrium the following condition must be satisfied

$E_1^* \neq 0$ or $E_2^* \neq 0$ or $I_1^* \neq 0$ or $I_2^* \neq 0$ i.e. $S_1^* > 0$ or $S_2^* > 0$ or $E_1^* > 0$ or $E_2^* > 0$ or $I_1^* > 0$ or $I_2^* > 0$.

Adding equations in the system (2) above at an endemic equilibrium we have

$$\pi_1 + \pi_2 - \mu(S_1^* + S_2^* + E_1^* + E_2^* + I_1^* + I_2^*) - \theta(S_1^* + S_2^*) - \rho(I_1^* + I_2^*) - \eta(I_1^* + I_2^*) = 0,$$

which is equivalent to

$$\mu(S_1^* + S_2^* + E_1^* + E_2^* + I_1^* + I_2^*) + \theta(S_1^* + S_2^*) + \rho(I_1^* + I_2^*) + \eta(I_1^* + I_2^*) = \pi_1 + \pi_2.$$

Since $\pi_1 + \pi_2 > 0$ and $\mu, \theta, \eta > 0$ we can observe that

$$\theta(S_1^* + S_2^*) > 0, \rho(I_1^* + I_2^*) > 0, \eta(I_1^* + I_2^*) > 0 \text{ and } \mu(S_1^* + S_2^* + E_1^* + E_2^* + I_1^* + I_2^*) > 0,$$

which implies

$S_1^* > 0$ or $S_2^* > 0$ or $E_1^* > 0$ or $E_2^* > 0$ or $I_1^* > 0$ or $I_2^* > 0$.

Therefore endemic equilibrium point E^* of the model exists.

The reduced model system given in (2) can be studied as means of attacking the model system (1) Thus, we will use this reduced model system for checking global stability of endemic equilibrium point in section 3.3.5. Since the disease free equilibrium is locally asymptotically stable as we have proved in section 3.3.1, this will imply local stability of the endemic equilibrium point for the model system (1). In the next section we are going to investigate the existence and local stability of endemic equilibrium point for patch 1and patch 2 when there are no individual movements between them using bifurcation analysis theory.

3.3.4 Stability Analysis Using Bifurcation Analysis

Bifurcation analysis plays an important role in disease control and eradication. In this section we study the existence and stability of endemic equilibrium point of the two patches when there exists no individual movements between them and determine the existence of either forward (supercritical) or backward (subcritical) bifurcation. When a forward bifurcation occurs then we guarantee that reducing basic reproduction number to a value less than one is a sufficient condition for disease eradication. On the other hand when a backward bifurcation occurs, an endemic equilibrium may also occur for $R_0 < 1$. This means that R_0 must be reduced further so as to avoid endemic states and ensures the eradication (Buonomo *et al*., 2011). We apply theorem 1 as done in (Bhunu *et al*., 2008; Castillo-Chavez *et al*., 2004; Mlay *et al*., 2014; Edward *et al*., 2014) which is based on the use of center manifold theory (Carr, 1981), to establish local stability of endemic equilibrium point corresponding to patch 1 and patch 2 respectively.

Considering patch 1 and patch 2 in isolation, we have the following model system (for $i = 1,2$)

$$\frac{dS_i}{dt} = \pi_i - \lambda_i S_i - (\mu + \theta) S_i$$

$$\frac{dV_i}{dt} = \theta S_i - (\mu + \sigma) V_i$$

$$\frac{dE_i}{dt} = \lambda_i S_i - (\mu + \delta) E_i \qquad (3)$$

$$\frac{dI_i}{dt} = \delta E_i - (\mu + \rho + \eta) I_i$$

$$\frac{dR_i}{dt} = \eta I_i + \sigma V_i - \mu R_i$$

It can be shown that for existence of endemic equilibrium in patch *i*, the system (3) must satisfy the equation $AI_i^{*2} + BI_i^{*2} = 0$

where $A = \beta_i(\mu + \delta)(\mu + \rho + \eta)$ and $B = (\mu + \delta)(\mu + \rho + \eta)(\mu + \theta)N_i - \beta_i \delta \pi_i$.

It follows that

$$B = \frac{(\mu + \rho + \eta + b_1)(\mu + \delta)((\mu + \rho + \eta)(\mu + \delta)(\mu + \theta)N_i - \pi_i \beta_i \delta)(1 - R_{0i})}{(\mu + \rho + \eta)(\mu + \delta) - \beta_i \delta}. \qquad (4)$$

From (4) it can be proved that a positive endemic equilibrium exists in patch i if $R_{0i} > 1$.

The model system (3) has effective reproduction number R_{Ci} and a basic reproduction number R_{0i} as defined from chapter two in (4) and (5) respectively.

For studying the direction of bifurcation we transform the system (3) by setting $S_i = x_1$, $V_i = x_2$, $E_i = x_3$, $I_i = x_4$, and $R_i = x_5$.

The model system (3) can be written in the form $\frac{dX}{dt} = F$ as follows

$$\frac{dx_1}{dt} = f_1 = \pi_1 - \frac{\beta_i x_1 x_4}{x_1 + x_2 + x_3 + x_4 + x_5} - (\mu + \theta)x_1$$

$$\frac{dx_2}{dt} = f_2 = \theta x_1 - (\mu + \sigma)x_2$$

$$\frac{dx_3}{dt} = f_3 = \frac{\beta_i x_1 x_4}{x_1 + x_2 + x_3 + x_4 + x_5} - (\mu + \delta)x_3 \qquad (5)$$

$$\frac{dx_4}{dt} = f_4 = \delta x_3 - (\mu + \rho + \eta)x_4$$

$$\frac{dx_5}{dt} = f_5 = \eta x_4 + \sigma x_2 - \mu x_5$$

We choose β_i as a bifurcation parameter. Solving for β_i when $R_{Ci} = 1$ we get

$$\beta_i = \beta^* = \frac{(\mu + \delta)(\mu + \sigma + \theta)(\mu + \rho + \eta)}{\delta(\mu + \sigma)}.$$

Theorem 1. (Castillo-Chavez *et al*., 2004).

Consider the general system of ordinary differential equations with a parameter β^* such that

$\frac{dx}{dt} = f(x, \beta^*),\ f: \mathbb{R}^n x \mathbb{R}$ and $f \in \mathbb{C}^2(\mathbb{R}^n x \mathbb{R})$

Without loss of generality we assume that $x = 0$ is an equilibrium point of the system. Thus $f(0, \beta^*) \equiv 0$ for all β^*.

1. $A = D_x f(0,0)$ is Jacobian (linearization) matrix of the system around the equilibrium $x = 0$ with β^* evaluated at 0. Zero is a simple eigenvalue of *A* and all other eigenvalues of *A* have negative real parts.
2. Matrix *A* has a (nonnegative) right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.
3. Let f_k denote the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),\ b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0)\ .$$

Then the local dynamics of the system around $x = 0$ are totally determined by the sign of a and b. In particular, if $a > 0, b > 0$ then a backward bifurcation occurs at $x = 0$.

i. $a > 0, b > 0$. When $\beta^* < 0$ with $|\beta^*| \ll 1, x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \beta^* \ll 1, x = 0$ is unstable and there exists a negative and locally asymptotically stable equilibrium.

ii. $a < 0, b < 0$. When $\beta^* < 0$ with $|\beta^*| \ll 1, x = 0$ is unstable; when $0 < \beta^* \ll 1, x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium.

iii. $a > 0, b < 0$. When $\beta^* < 0$ with $|\beta^*| \ll 1, x = 0$ is unstable and there exists a locally asymptotically negative stable equilibrium; when $0 < \beta^* \ll 1, x = 0$ is stable and a positive unstable equilibrium appears.

iv. $a < 0, b > 0$. When β^* changes from negative to positive, $x = 0$ changes its stability from stable to unstable. Correspondently, a negative unstable equilibrium becomes positive and locally asymptotically stable.

Remark. The requirement that *w* is non-negative is unnecessary (Castillo-Chavez *et al*., 2004). Clearly, at $\beta^* = 0$ a transcritical bifurcation takes place: more precisely, when $a < 0, b > 0$ such a bifurcation is forward; when $a > 0, b > 0$ the bifurcation is backward.

Now applying theorem 1, the Jacobian matrix of the system (5) at disease free equilibrium evaluated at $\beta_i = \beta^*$ is given by

$$J_0(\beta^*) = \begin{bmatrix} -(\mu+\theta) & 0 & 0 & \frac{-\beta^*(\mu+\sigma)}{\mu+\sigma+\theta} & 0 \\ \theta & -(\mu+\sigma) & 0 & 0 & 0 \\ 0 & 0 & -(\mu+\delta) & \frac{\beta^*(\mu+\sigma)}{\mu+\sigma+\theta} & 0 \\ 0 & 0 & \delta & -(\mu+\rho+\eta) & 0 \\ 0 & \sigma & 0 & \eta & -\mu \end{bmatrix}.$$

The eigenvalues of $J_0(\beta^*)$ are 0, $-\mu$, $-(\mu+\theta)$, $-(\mu+\sigma)$, and $-2\mu-\delta-\rho-\eta$.

Since 0 is a simple eigenvalue of $J_0(\beta^*)$ and all other eigenvalues have negative real parts, then assumption 1 of theorem 1 is verified.

The right eigenvector of $J_0(\beta^*)$ corresponding to zero eigenvalue is given by

$w = (w_1, w_2, w_3, w_4, w_5)^T$ where

$w_1 = -\frac{(\mu+\delta)^2(\mu+\rho+\eta)}{\delta(\mu+\theta)}$, $w_2 = -\frac{\theta(\mu+\delta)^2(\mu+\rho+\eta)}{\delta(\mu+\sigma)(\mu+\theta)}$, $w_3 = \frac{(\mu+\delta)(\mu+\rho+\eta)}{\delta}$, $w_4 = \mu+\delta$, and

$w_5 = -\frac{\sigma\theta(\mu+\delta)^2(\mu+\rho+\eta)}{\mu\delta(\mu+\sigma)(\mu+\theta)} + \frac{\eta}{\mu}(\mu+\delta)$.

The left eigenvector of $J_0(\beta^*)$ satisfying $w.v = 0$ is given by $v = (v_1, v_2, v_3, v_4, v_5)^T$ where

$v_1 = v_2 = v_5 = 0$, $v_3 = \frac{\delta}{(\mu+\delta)(\mu+\rho+\eta)+(\mu+\delta)^2}$, and $v_4 = \frac{\mu+\delta}{(\mu+\delta)(\mu+\rho+\eta)+(\mu+\delta)^2}$.

Considering system (3) and only nonzero components of the left eigenvector v, we compute the values of a and b at disease free equilibrium as defined in theorem 1 as follows.

The disease free equilibrium in patch i is given by

$$P_{0i} = \left(\frac{\pi_i}{\mu+\theta}, \frac{\pi_i\theta}{(\mu+\sigma)(\mu+\theta)}, 0, 0, 0 \right).$$

We consider the functions f_3 and f_4 as defined in (5). Associated nonzero partial derivatives at the disease fee equilibrium and $\beta_i = \beta^*$ are given by

$$\frac{\partial^2 f_3}{\partial x_1 \partial x_4} = \frac{(\mu+\delta)(\mu+\theta)(\mu+\rho+\eta)(1-\mu-\theta)}{\pi_i \delta}, \frac{\partial^2 f_3}{\partial x_2 \partial x_4} = -\frac{(\mu+\delta)(\mu+\sigma)(\mu+\theta)(\mu+\rho+\eta)}{\pi_i \delta},$$

$$\frac{\partial^2 f_3}{\partial x_3 \partial x_4} = \frac{\partial^2 f_3}{\partial x_2 \partial x_4}, \frac{\partial^2 f_3}{\partial x_4^2} = 2\frac{\partial^2 f_3}{\partial x_2 \partial x_4}, \frac{\partial^2 f_3}{\partial x_4 \partial x_5} = \frac{\partial^2 f_3}{\partial x_2 \partial x_4}, \text{ and } \frac{\partial^2 f_3}{\partial x_4 \partial \beta^*} = \frac{\mu+\sigma}{\mu+\sigma+\theta}.$$

It follows that

$$a = v_3 w_1 w_4 \frac{\partial^2 f_3}{\partial x_1 \partial x_4} + 2v_3 w_2 w_4 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 2v_3 w_3 w_4 \frac{\partial^2 f_3}{\partial x_3 \partial x_4} + v_3 w_4^2 \frac{\partial^2 f_3}{\partial x_4^2} + 2v_3 w_4 w_5 \frac{\partial^2 f_3}{\partial x_4 \partial x_5},$$

$$= 2v_3 w_1 w_4 \frac{\partial^2 f_3}{\partial x_1 \partial x_4} + 2v_3 w_2 w_4 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 2v_3 w_3 w_4 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 2v_3 w_4^2 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 2v_3 w_4 w_5 \frac{\partial^2 f_3}{\partial x_2 \partial x_4},$$

$$= -\frac{2(\alpha_1 - \alpha_2)(\mu+\delta)(\mu+\rho+\eta)}{\delta \mu \pi_i}. \quad (6)$$

$$b = v_3 w_4 \frac{\partial^2 f_3}{\partial x_4 \partial \beta^*},$$

$$= \frac{\delta(\mu+\sigma)(\mu+\delta)}{(\mu+\sigma+\theta)((\mu+\delta)(\mu+\rho+\eta)+(\mu+\delta)^2)} > 0, \text{ where} \quad (7)$$

$\alpha_1 = 2\mu^2\delta\rho + 2\mu^2\delta\eta + \delta^2\mu^2 + \delta^2\rho\mu + \delta^2\eta\mu + \mu^4 + \mu^3\rho + \mu^3\eta + 2\mu^3\delta$, and

$\alpha_2 = \mu^2\delta\rho\sigma + \delta^2\sigma\rho\theta + \mu^3\delta\rho + \delta^2\mu^2\rho + \mu^2\delta\rho\theta + \delta^2\mu\rho\theta + \mu\delta\rho\sigma\theta + \delta^2\mu\rho\sigma$.

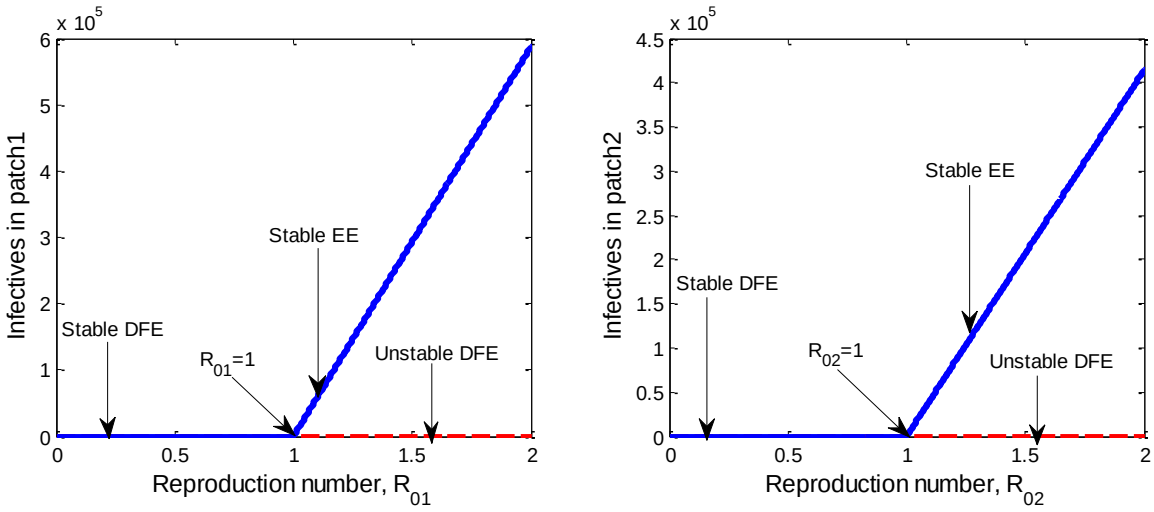
The sign of a in (6) depends on the sign of $\alpha_1 - \alpha_2$. If $\alpha_1 > \alpha_2$ then $a < 0$, and if $\alpha_1 < \alpha_2$ then $a > 0$. Thus we have the following theorem

Theorem 2.

($\boldsymbol{i}$) If $\alpha_1 > \alpha_2$ then patch i exhibit forward bifurcation at $R_{Ci} = 1$. When $\beta_i = \beta^*$ changes from negative to positive, the disease free equilibrium changes its stability from stable to unstable. Correspondently, a negative unstable endemic equilibrium becomes positive and locally asymptotically stable when $R_{Ci} > 0$.

($\boldsymbol{ii}$) If $\alpha_1 < \alpha_2$ then patch i exhibits backward bifurcation at $R_{Ci} = 1$. When $\beta^* < 0$ with $|\beta^*| \ll 1$, the disease free equilibrium is locally asymptotically stable and there exists a positive unstable endemic equilibrium; when $0 < \beta^* \ll 1$, the disease free equilibrium is unstable and there exists a negative and locally asymptotically stable endemic equilibrium.

The bifurcation diagrams for patch 1 and patch 2 are shown in figure 4*a* and *b* respectively.



(a) (b)

Figure 4. *a* and *b* shows the forward bifurcation diagrams for patch 1 and patch 2 respectively obtained from numerical simulations. DFE stands for disease free equilibrium and EE stands for endemic equilibrium. The two diagrams show that the disease free and endemic equilibria exchange stability when $R_{0i} = 1$ for $i = 1,2$. This means that the disease free equilibrium is locally asymptotically stable when $R_{0i} < 1$ and unstable when $R_{0i} > 1$. Furthermore, a unique endemic equilibrium exists for $R_{0i} > 1$ and it is locally asymptotically stable. So, the total number of infectious individual in each patch goes to a unique endemic equilibrium.

An implication of EE point being locally asymptotically stable is that the disease can still invade in the metapopulation and transmission dynamics can persist if control measures for the disease are not highly considered in each patch. Therefore, our study agrees that reducing the reproduction number R_{0i} to value less than one is a sufficient condition to eradicate the disease.

3.3.5 Global Stability of Endemic Equilibrium Point

In this section we analyse the global stability of the endemic equilibrium point E^* by constructing a suitable Lyapunov function. For simplicity, we consider the reduced model system (2) to prove for global stability. We employ the approach of (Korobeinikov *et al*., 2004) as it is used for many complicated epidemiological models. We consider the Lyapunov function of the form

$L = \sum k_i (P_i - P_i^* \ln(P_i))$, where

$k_i > 0$ (for $i = 1,2,3,\ldots,6.$) is a properly chosen positive constant in the given region. P_i is a population of compartment i and P_i^* is the equilibrium level. So we define the Lyapunov function as

$$L(S_1,S_2,E_1,E_2,I_1,I_2) = K_1(S_1 - S_1^* \ln(S_1)) + \quad K_2(S_2 - S_2^* \ln(S_2)) + K_3(E_1 - E_1^* \ln(E_1)) +$$

$$K_4(E_2 - E_2^* \ln(E_2)) + K_5(I_1 - I_1^* \ln(I_1)) + K_6(I_2 - I_2^* \ln(I_2)).$$

The time derivative of L is

$$\frac{dL}{dt} = K_1\left(1 - \frac{S_1^*}{S_1}\right)\frac{dS_1}{dt} + K_2\left(1 - \frac{S_2^*}{S_2}\right)\frac{dS_2}{dt} + K_3\left(1 - \frac{E_1^*}{E_1}\right)\frac{dE_1}{dt}$$

$$+K_4\left(1 - \frac{E_2^*}{E_2}\right)\frac{dE_2}{dt} + K_5\left(1 - \frac{I_1^*}{I_1}\right)\frac{dI_1}{dt} + K_6\left(1 - \frac{I_2^*}{I_2}\right)\frac{dI_2}{dt},$$

$$= K_1\left(1 - \frac{S_1^*}{S_1}\right)\left(\pi_1 - \frac{\beta_1 S_1 I_1}{N_1} + b_2 S_2 - (\mu + \theta + b_1)S_1\right) +$$

$$K_2\left(1 - \frac{S_2^*}{S_2}\right)\left(\pi_2 - \frac{\beta_2 S_2 I_2}{N_2} + b_1 S_1 - (\mu + \theta + b_2)S_2\right) +$$

$$K_3\left(1 - \frac{E_1^*}{E_1}\right)\left(\frac{\beta_1 S_1 I_1}{N_1} + b_2 E_2 - (\mu + \delta + b_1)E_1\right) + K_4\left(1 - \frac{E_2^*}{E_2}\right)\left(\frac{\beta_2 S_2 I_2}{N_2} + b_1 E_1 - (\mu + \delta + b_2)E_2\right) +$$

$$K_5\left(1 - \frac{I_1^*}{I_1}\right)\left(\delta E_1 + b_2 I_2 - (\mu + \rho + \eta + b_1)I_1\right) + K_6\left(1 - \frac{I_2^*}{I_2}\right)\left(\delta E_2 + b_1 I_1 - (\mu + \rho + \eta + b_2)I_2\right).$$

At an endemic equilibrium point E^* we have

$$\pi_1 = \frac{\beta_1 S_1^* I_1^*}{N_1} + (\mu + \theta + b_1)S_1^* - b_2 S_2^*, \pi_2 = \frac{\beta_2 S_2^* I_2^*}{N_2} + (\mu + \theta + b_2)S_2^* - b_1 S_1^*,$$

$$\mu + \delta + b_1 = \frac{1}{E_1^*}\left(\frac{\beta_1 S_1^* I_1^*}{N_1} + b_2 E_2^*\right), \mu + \delta + b_2 = \frac{1}{E_2^*}\left(\frac{\beta_2 S_2^* I_2^*}{N_2} + b_1 E_1^*\right), \ \mu + \rho + \eta + b_1 = \frac{1}{I_1^*}\left(\delta E_1^* + b_2 I_2^*\right)$$

and $\mu + \rho + \eta + b_2 = \frac{1}{I_2^*}\left(\delta E_2^* + b_1 I_1^*\right)$.

Therefore,

$$\frac{dL}{dt} = K_1\left(1 - \frac{S_1^*}{S_1}\right)\left(\frac{\beta_1 S_1^* I_1^*}{N_1} + (\mu + \theta + b_1)S_1^* - b_2 S_2^* - \frac{\beta_1 S_1 I_1}{N_1} + b_2 S_2 - (\mu + \theta + b_1)S_1\right) + K_2\left(1 - \frac{S_2^*}{S_2}\right)\left(\frac{\beta_2 S_2^* I_2^*}{N_2} +\right.$$

$$(\mu+\theta+b_2)S_2^* - b_1S_1^* - \frac{\beta_2 S_2 I_2}{N_2} + b_1S_1 - (\mu+\theta+b_2)S_2\Bigg) + K_3\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{\beta_1 S_1 I_1}{N_1} + b_2E_2 - \left(\frac{\beta_1 S_1^* I_1^*}{N_1} + b_2E_2^*\right)\frac{E_1}{E_1^*}\right),$$

$$+K_4\left(1-\frac{E_2^*}{E_2}\right)\left(\frac{\beta_2 S_2 I_2}{N_2} + b_1E_1 - \left(\frac{\beta_2 S_2^* I_2^*}{N_2} + b_1E_1^*\right)\frac{E_2}{E_2^*}\right) + K_5\left(1-\frac{I_1^*}{I_1}\right)\left(\delta E_1 + b_2I_2 - \left(\delta E_1^* + b_2I_2^*\right)\frac{I_1}{I_1^*}\right) +$$

$$K_6\left(1-\frac{I_2^*}{I_2}\right)\left(\delta E_2 + b_1I_1 - \left(\delta E_2^* + b_1I_1^*\right)\frac{I_2}{I_2^*}\right).$$

Simplification yields

$$\frac{dL}{dt} = -K_1\left(1-\frac{S_1^*}{S_1}\right)^2(\mu+\theta+b_1)S_1 - K_2\left(1-\frac{S_2^*}{S_2}\right)^2(\mu+\theta+b_2)S_2 + F(S_1,S_2,E_1,E_2,I_1,I_2),$$

where

$$F(S_1,S_2,E_1,E_2,I_1,I_2) = K_1\left(1-\frac{S_1^*}{S_1}\right)\left(1-\frac{S_1I_1}{S_1^*I_1^*}\right)\frac{\beta_1 S_1^* I_1^*}{N_1} -$$

$$K_1\left(1-\frac{S_1^*}{S_1}\right)\left(1-\frac{S_2^*}{S_2}\right)b_2S_2^* + K_2\left(1-\frac{S_2^*}{S_2}\right)\left(1-\frac{S_2I_2}{S_2^*I_2^*}\right)\frac{\beta_2 S_2^* I_2^*}{N_2} -$$

$$K_2\left(1-\frac{S_2^*}{S_2}\right)\left(1-\frac{S_1^*}{S_1}\right)b_1S_1^* + K_3\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{E_2^*}{E_2} - \frac{E_1}{E_1^*}\right)b_2E_2^* +$$

$$K_3\left(1-\frac{E_1^*}{E_1}\right)\left(\frac{S_1I_1}{S_1^*I_1^*} - \frac{E_1}{E_1^*}\right)\frac{\beta_1 S_1^* I_1^*}{N_1} + K_4\left(1-\frac{E_2^*}{E_2}\right)\left(\frac{E_1^*}{E_1} - \frac{E_2}{E_2^*}\right)b_1E_1^* + K_4\left(1-\frac{E_2^*}{E_2}\right)\left(\frac{S_2I_2}{S_2^*I_2^*} - \frac{E_2}{E_2^*}\right)\frac{\beta_2 S_2^* I_2^*}{N_2} +$$

$$K_5\left(1-\frac{I_1^*}{I_1}\right)\left(\frac{E_1}{E_1^*} - \frac{I_1}{I_1^*}\right)\delta E_1^* + K_5\left(1-\frac{I_1^*}{I_1}\right)\left(\frac{I_2}{I_2^*} - \frac{I_1}{I_1^*}\right)b_2I_2^*,$$

$$+K_6\left(1-\frac{I_2^*}{I_2}\right)\left(\frac{E_2}{E_2^*} - \frac{I_2}{I_2^*}\right)\delta E_2^* + K_6\left(1-\frac{I_2^*}{I_2}\right)\left(\frac{I_1}{I_1^*} - \frac{I_2}{I_2^*}\right)b_1I_1^*.$$

F is non-positive following the modified version of Barbalat's Lemma (Barbalat *et al*., 1959) or by following the approach of (McCluskey, 2006; Mukandavire *et al*., 2009). Thus, $F \leq 0$ for $S_1, S_2, E_1, E_2, I_1, I_2 > 0$. Hence $\frac{dL}{dt} < 0$ and is zero when $S_1 = S_1^*$, $S_2 = S_2^*$, $E_1 = E_1^*$, $E_2 = E_2^*$, $I_1 = I_1^*$, $I_2 = I_2^*$.

Therefore, the largest invariant set in Ω such that $\frac{dL}{dt} < 0$ is the singleton $\{E^*\}$ which is our endemic equilibrium point. By LaSalle's invariant principle (LaSaile, 1976) we conclude that E^* is globally asymptotically stable (g.a.s). Thus, we establish the following theory

Theorem 3. When $R_C > 1$ the endemic equilibrium point E^* is globally asymptotically stable in Ω.

3.4 Simulation and Discussion

The main objective of this study was to study the impact of vaccination on the spread of measles in a metapopulation. In order to support the analytical results, graphical representations showing the variations in parameters with respect to different state variables have been presented in this section. This is done by using a set of parameter values whose sources are mainly from literature as well as estimation in order to have more realistic simulation results. We will vary key parameters to investigate the impact of vaccination on the transmission dynamics of measles. The parameter values are shown in table 2.

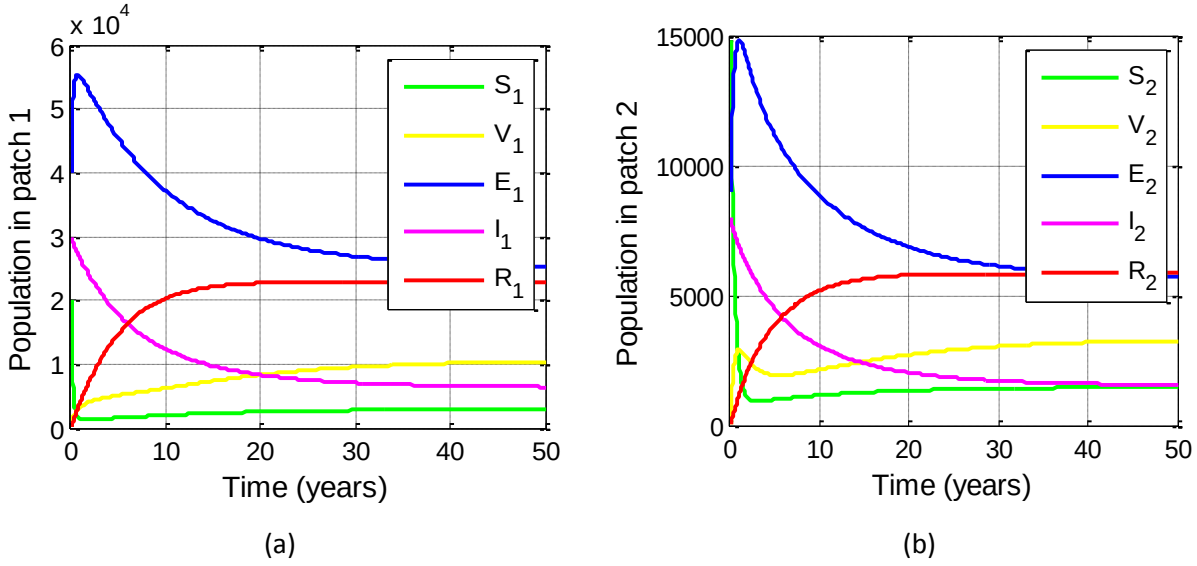


Figure 5. *a* and *b* shows variations of susceptible, vaccinated, exposed, infected and recovered individuals in patch1and patch 2 respectively when individual movements between them are allowed. The values of initial conditions are: $S_1 = 20\,000, S_2 = 14\,800, V_1 = V_2 = 0, E_1 = 40\,000, E_2 = 9000, I_1 = 30\,000, I_2 = 8000, R_1 = R_2 = 0$. We chose these values of initial conditions for the two

patches for simulation purposes, however other different values of initial conditions could also bring positive results.

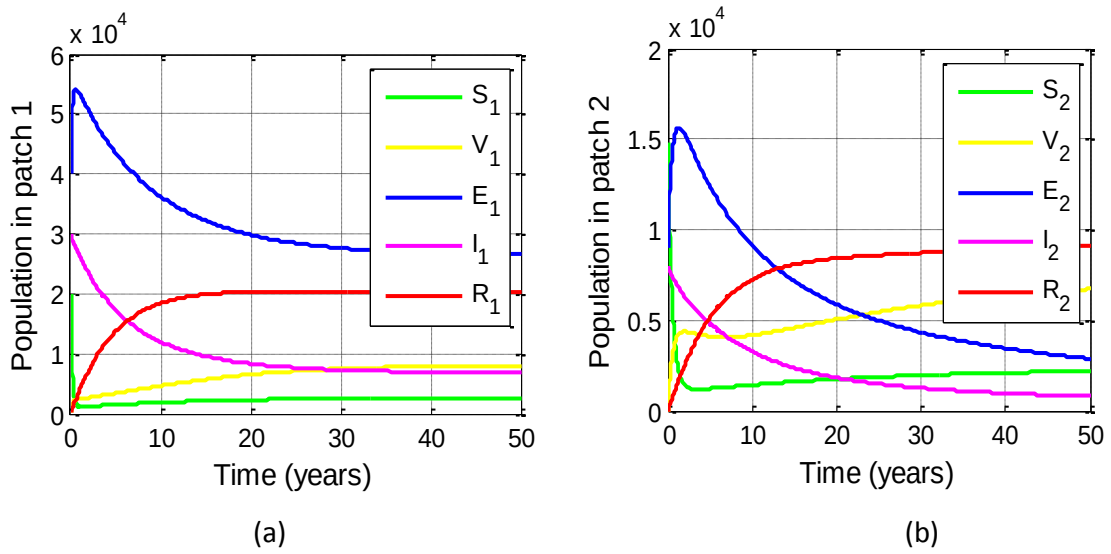


Figure 6. *a* and *b* shows variations of susceptible, vaccinated, exposed and recovered individuals in patch1and patch 2 respectively when individual movements between them are not allowed. Here we used the values of initial conditions as: $S_1 = 16\,000, S_2 = 12\,500, V_1 = V_2 = 0, E_1 = 35\,000, E_2 = 8000, I_1 = 20\,000, I_2 = 6500, R_1 = R_2 = 0$. We chose these values of initial conditions for the two patches for simulation purposes, however other different values of initial conditions could also bring positive results depicted by figure 6.

In figures 5 and 6 above we can see that the susceptible population in both patches decrease rapidly to lower levels with time due to high number of individuals who become vaccinated or exposed due to high contact rates. Exposed population increases more rapidly in patch 1 than in patch 2 due to high contact rates in patch 1. The exposed population later starts to decrease due to large number of individuals who become infected or vaccinated. In both patches, the infected population decreases with time due to high vaccination and treatment rates. On the other hand, due to treatment and vaccination, recovered population increases in both patches as shown in the figures 5 and 6 above.

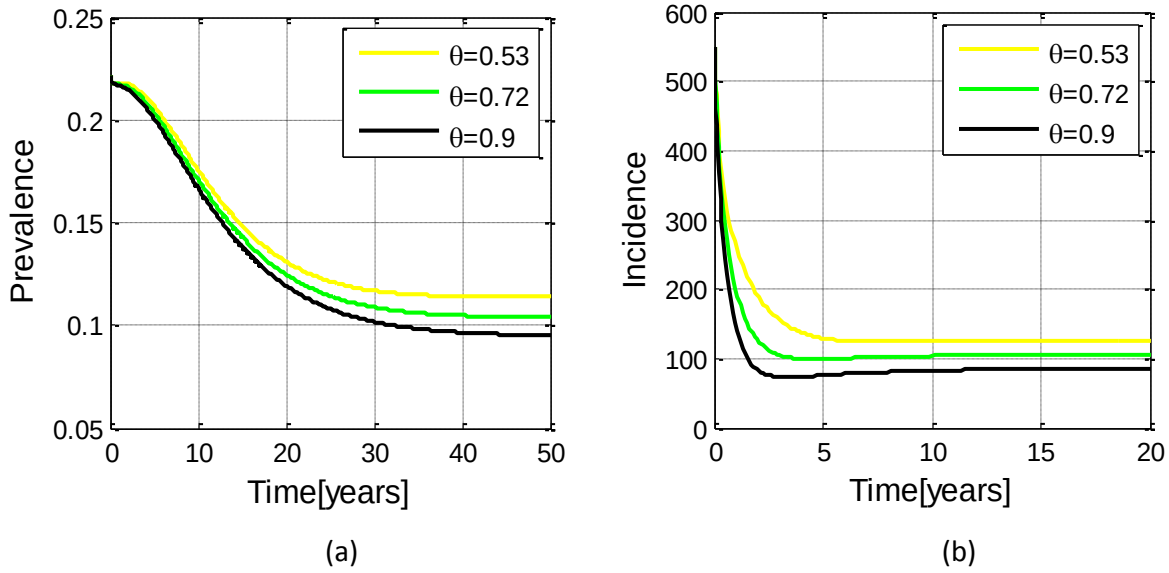


Figure 7. *a* and *b* respectively show measles prevalence and incidence in a metapopulation when the individual movements between the patches are allowed. The values of initial conditions are: $S_1 = 20\,000, S_2 = 14\,800, V_1 = V_2 = 0, E_1 = 40\,000, E_2 = 9000, I_1 = 30\,000, I_2 = 8000, R_1 = R_2 = 0$. We chose these values of initial conditions for the two patches for simulation purposes, however other different values of initial conditions could also bring positive results.

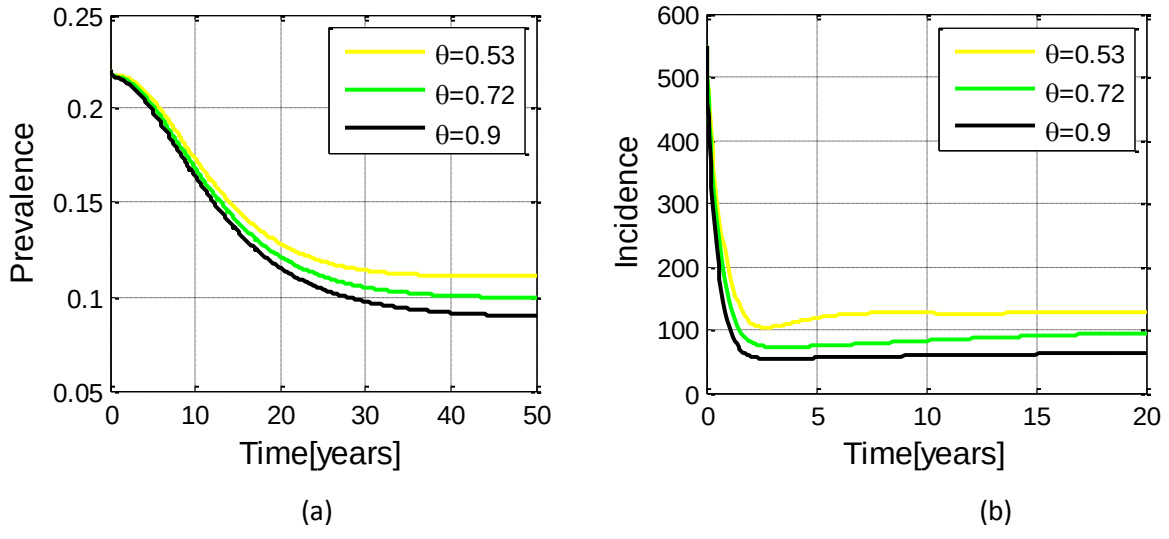


Figure 8. *a* and *b* respectively show measles prevalence and incidence in a metapopulation when the individual movements between the patches are not allowed. Here we have chosen the values of initial conditions as: $S_1 = 16\,000, S_2 = 12\,500, V_1 = V_2 = 0, E_1 = 35\,000, E_2 = 8000, I_1 =$

$20\,000, I_2 = 6500, R_1 = R_2 = 0$. We chose these values of initial conditions for the two patches for simulation purposes, however other different values of initial conditions could also bring positive results as shown the figure.

It can be observed that as vaccination rates increase, the measles prevalence and incidence also decrease. Thus figures 7 and 8 depicts positive impact of vaccination on measles prevalence and incidence in a metapopulation. Therefore, our study suggests higher vaccination coverage in all patches in order to eradicate the disease in a metapopulation.

3.5 Conclusion

In this chapter, we presented a mathematical model for the control of measles in a metapopulation by considering two regions (patches). We used estimated data and data from literature in numerical simulation. We started by showing nonnegativity of solutions to the metapopulation model, thereby addressing the problem of its well posedness. We proved that the disease equilibrium points of the model to be locally and globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. We performed bifurcation analysis of endemic equilibrium points of the two patches when there exist no movement of individuals between them and found that forward (supercritical) bifurcation occurs in both cases, which agrees with an intuition that reducing reproduction number to values less than one is a necessary and sufficient condition for disease eradication in the community (Buonomo *et al*., 2011; Van den Driessche *et al*., 2002). Simulation results of different epidemiological classes revealed that most of the individuals undergoing treatment or vaccination join the recovered class. Through simulations we also showed that vaccination has a positive impact on measles incidence and prevalence in a metapopulation.

CHAPTER FOUR
GENERAL DISCUSSION, CONCLUSION AND RECOMMENDATION

4.1 General Discussion

In this study, we presented and analysed a measles metapopulation model with vaccination. The main objective of the study was to investigate the impact of vaccination on the epidemiology of measles in a metapopulation. Both the basic and effective reproduction numbers were computed and used to assess the impact of vaccination by varying different epidemiological parameters. Qualitative analysis of the model was carried out and it was seen that the model had both the disease free equilibrium and endemic equilibrium point. Using the idea of next generation method and theorem by (Van den Driessche *et al*., 2002), it was found out that when the effective reproduction number is less than one, that is, $R_C < 1$, the disease free equilibrium point is locally asymptotically stable and unstable when the effective reproduction number is greater than one, that is, $R_C > 1$.

We determined the existence and stability of the endemic point using the Center Manifold Theorem (Carr J, 1981). We found out that in the absence of vaccination the effective reproduction number return to basic reproduction number (R_0). It was also observed that the models for patch 1 and patch 2 with vaccination both exhibits a forward bifurcation. Numerical simulations of the reproduction numbers were done as shown in Figure 2. Simulations of the various reproduction numbers enables us to understand that, high vaccination coverage to susceptible individuals should be attained so as to combat measles in a metapopulation. Also, we conclude that measles infected individuals should be given treatment so as to save their lives and at the same time limiting chances of spread of the disease.

We performed a sensitivity analysis on the basic reproduction number from which we have noted that the most sensitive parameters are the contact rate β_1, and treated infectious individuals η. Numerical simulations of the model have shown that, the combination of vaccination and treatment is the most effective way to combat measles in a metapopulation. Furthermore, we conducted numerical simulations for measles incidence and prevalence as seen in figures 7 and 8. We showed that vaccination coverage has a positive impact on both measles incidence and prevalence in a metapopulation.

4.2 Conclusion

We found that in order to control the disease prevalence and incidence it is vital to vaccinate susceptible individuals in both patches. Therefore it may be concluded that the most effective way to combat measles epidemiology is to vaccinate and treat individuals. Hence, education programs must reach all the community at all social levels, to increase the awareness about efficiency of vaccination and early treatment so as to control or minimize the disease in the community.

We also found that individual movements from patch 2 to patch 1 tend to increase measles infection in a metapopulation since these movements increase the reproduction number. Therefore, rules or regulations must be set by given authorities in order to minimize this flow of movement and to fight against the disease.

4.3 Recommendations

Measles eradication remains a big challenge in most developing countries. Thus, from the results of this work, it is recommended that:

1. Educational awareness campaigns should be conducted among the community to eliminate the illusion that vaccination has adverse side effects on their life. This will increase positive attitude towards vaccination and hence more newborns will be vaccinated against measles.
2. Quarantine of sick people should be a priority. For example sick children should not be allowed to attend school until they are recovered. Sick adults too should be quarantined and treated before they come in contact with other healthy individuals, this is because this disease transmits very fast on contact with an infected person.
3. The government should invest more fund on vaccination of measles, this is due to the fact that this research together with the previous ones have shown that the disease may be easily controlled when high coverage of vaccination is administered.
4. It is also recommended that rules or regulations must be set by given authorities in order to minimize the flow of infected individuals to different regions so as to fight against the disease.
5. Based on the model of this study, it is proposed that future work should consider the following:
    i. Carrying out cost-effectiveness analysis of the measles metapopulation model with vaccination.

ii. Age-structured, non-constant population model with vaccination is suggested to be formulated for further research.

iii. In practice the contact rate for each patch may change over time, thus it is useful to consider the contact rate for each patch as a function of time in the future work.

iv. We assumed one type of mobility for disease status in each patch. Thus, in future work it is recommended to consider different types of mobility depending on age or season. It is also recommended to consider where an individual resides as well as where an individual currently is.

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APPENDICES

APPENDIX 1: Variation in reproduction number for patch 1.

```
pi1=250;pi2=245;beta2=0.3;eta=0.024;mu=0.01;delta=0.44;rho=0.01;sigma=0.52;b1
=0.1;b2=0.4;theta=0.8;
beta1=0:0.001:1;
RC1=(delta*beta1*(mu+sigma))./((mu+sigma+theta)*(mu+delta)*(mu+rho+eta));
R01=(delta*beta1)./((mu+delta)*(mu+rho+eta));
plot(beta1, RC1,'y',beta1, R01,'k','linewidth',3)
xlabel('Exposure rate')
ylabel('Reproduction number')
legend('R_{C1}', 'R_{01}')
grid on
```

APPENDIX 2: Variation in reproduction numbers for patch 2.

```
pi1=250;pi2=245;beta1=0.6;eta=0.024;mu=0.01;delta=0.44;rho=0.01;sigma=0.52;b1
=0.1;b2=0.4;theta=0.8;
beta2=0:0.001:1;
RC2=(delta*beta2*(mu+sigma))/((mu+sigma+theta)*(mu+delta)*(mu+rho+eta));
R02=(delta*beta2)/((mu+delta)*(mu+rho+eta));
plot(beta2, RC2,'b',beta2, R02,'g','linewidth',3)
xlabel('Exposure rate')
ylabel('Reproduction number')
legend('R_{C2}', 'R_{02}')
grid on
```

APPENDIX 3: Variation in reproduction numbers for the metapopulation system.

```
pi1=250; pi2=245; beta1=0.6; beta2=0.3; eta=0.024; mu=0.01; rho=0.01;
sigma=0.52;
b1=0.1; b2=0.4; theta=0.8;
delta=0.44;
i=mu+theta+b1;
j=mu+theta+b2;
g=mu+sigma+b1;
h=mu+sigma+b2;
c=mu+delta+b1;
```

```
d=mu+delta+b2;
e=mu+rho+eta+b1;
f=mu+rho+eta+b2;
S1=((pi2*b2)+(pi1*j))/((i*j)-(b1*b2));
S2=((pi1*b1)+(pi2*i))/((i*j)-(b1*b2));
V1=((theta*b2*S2)+(theta*h))/((g*h)-(b1*b2));
V2=((theta*b1*S1)+(theta*g))/((g*h)-(b1*b2));
a=(beta1*S1)/(S1+V1);
b=(beta2*S2)/(S2+V2);
delta=0:0.001:1;
RC=((delta*a*((b1*b2)+(d*f))+delta*b*((b1*b2)+(c*e))+delta*(sqrt(((b*b1*b2)+(
a*d*f)).^2+((a*b1*b2)+(b*c*e)).^2+4*a*b*b1*b2*((c*d)+(e*f))+((a*b1*b2)-
(b*c*e))*((2*a*d*f)-(2*b*b1*b2))))))./(2*((b1*b2)-(c*d))*((b1*b2)-(e*f)));
R0=((delta*beta1*((b1*b2)+(d*f))+delta*beta2*((b1*b2)+(c*e))+delta*sqrt(((bet
a2*b1*b2)+(beta1*d*f)).^2+((beta1*b1*b2)+(beta2*c*e)).^2+4*beta1*beta2*b1*b2*
((c*d)+(e*f))+((beta1*b1*b2)-(beta2*c*e))*((2*beta1*d*f)-
(2*beta2*b1*b2)))))./(2*((b1*b2)-(c*d))*((b1*b2)-(e*f)));
plot(delta, RC,'m',delta, R0,'r','linewidth',3)
xlabel('Exposure rate')
ylabel('Reproduction number')
legend('R_C', 'R_0')
grid on
```

APPENDIX 4: Forward bifurcation in patch 1

```
%Figure 4. Forward bifurcation codes patch 1
R01_value=0:0.0001:2;
Root_array=zeros(length(R01_value),2);
% parameter values used
pi1=250;pi2=245;beta1=0.6;beta2=0.3;eta=0.024;mu=0.01;rho=0.01;sigma=0.52;
b1=0.1;b2=0.4;theta=0.8;delta=0.44;N1=7000;
for  i=1:length(R01_value);
    R01=R01_value(i);
    %Coefficients of quadratic equation
 beta1=(mu+delta)*(mu+sigma+theta)*(mu+rho+eta)/delta*(mu+sigma);
A=beta1*(mu+delta)*(mu+rho+eta);
B=(mu+rho+eta)*(mu+delta)*((mu+rho+eta)*(mu+delta)*(mu+theta)*N1-
pi1*beta1*delta)*(1-R01)./((mu+rho+eta)*(mu+delta)-beta1*delta);
C=0;
```

```
P=[A,B,C];
r =roots(P);
len=length(r);
for t=1:1:len
if (imag(r(t))~=0) || (real(r(t))<0);
Root_array(i,t)=0;
else
Root_array(i,t)=r(t);
end
end
end
f=1;
f=f+1;
R01_value_Cr=f;
for j=R01_value_Cr:length(R01_value)
Root_array(j,:)=sort(Root_array(j,:));
end
f1=R01_value_Cr;
while (Root_array(f1,1)~=0) ,f1=f1+1;
end
R01_value_Cr2=f1;
Zero_1st=R01_value(1,1:R01_value_Cr2-1); y_zero=zeros(1,length(Zero_1st));
Unstable=R01_value(1,R01_value_Cr:length(R01_value));
%figure(1)
plot(Unstable,Root_array(R01_value_Cr:length(R01_value),2),'b','LineWidth',3)
xlabel('Reproduction number, R_{01}','FontSize',12)
ylabel('Infectives in patch 1','FontSize',12)
hold off
%figure (2)
plot(R01_value,Root_array(:,1),'r--
',R01_value,Root_array(:,2),'b','LineWidth',3)
xlabel('Reproduction number, R_{01}','FontSize',12)
ylabel('Infectives in patch1','FontSize',12)
%ylim([0 1.5])
```

APPENDIX 5: Forward bifurcation in patch 2

```
%Figure 5. Forward bifurcation codes patch 2
R02_value=0:0.0001:2;
```

```
Root_array=zeros(length(R02_value),2);
% parameter values used
pi1=250;pi2=245;beta1=0.6;beta2=0.3;eta=0.024;mu=0.01;rho=0.01;sigma=0.52;b1=
0.1;b2=0.4;theta=0.8;delta=0.44;N2=5000;
for  i=1:length(R02_value);
    R02=R02_value(i);
    %Coefficients of quadratic equation
 beta2=(mu+delta)*(mu+sigma+theta)*(mu+rho+eta)/delta*(mu+sigma);
A=beta2*(mu+delta)*(mu+rho+eta);
B=(mu+rho+eta)*(mu+delta)*((mu+rho+eta)*(mu+delta)*(mu+theta)*N2-
pi1*beta2*delta)*(1-R02)./((mu+rho+eta)*(mu+delta)-beta2*delta);
C=0;
P=[A,B,C];
r =roots(P);
len=length(r);
for t=1:1:len
if (imag(r(t))~=0) || (real(r(t))<0);
Root_array(i,t)=0;
else
Root_array(i,t)=r(t);
end
end
end
f=1;
f=f+1;
R02_value_Cr=f;
for j=R02_value_Cr:length(R02_value)
Root_array(j,:)=sort(Root_array(j,:));
end
f1=R02_value_Cr;
while (Root_array(f1,1)~=0) ,f1=f1+1;
end
R02_value_Cr2=f1;
Zero_1st=R02_value(1,1:R02_value_Cr2-1); y_zero=zeros(1,length(Zero_1st));
Unstable=R02_value(1,R02_value_Cr:length(R02_value));
%figure(1)
plot(Unstable,Root_array(R02_value_Cr:length(R02_value),2),'b','LineWidth',3)
xlabel('Reproduction number, R_{02}','FontSize',12)
```

```
ylabel('Infectives in patch 2','FontSize',12)
hold off
%figure (2)
plot(R02_value,Root_array(:,1),'r--
',R02_value,Root_array(:,2),'b','LineWidth',3)
xlabel('Reproduction number, R_{02}','FontSize',12)
ylabel('Infectives in patch1','FontSize',12)
%ylim([0 1.5])
```

APPENDIX 6: Variations of susceptible, vaccinated, exposed, infected and recovered individuals in patch1and patch 2 respectively when individual movements between them are allowed.

```
function dy=META(~,y)
dy= zeros(size(y));
pi1=250;pi2=245;beta1=0.6;beta2=0.3;eta=0.024;mu=0.01;rho=0.01;sigma=0.52;
b1=0.1;b2=0.4;theta=0.8;delta=0.44
S1=y(1);
S2=y(2);
V1=y(3);
V2=y(4);
E1=y(5);
E2=y(6);
I1=y(7);
I2=y(8);
R1=y(9);
R2=y(10);
N1=S1+V1+E1+I1+R1;
N2=S2+V2+E2+I2+R2;
dy(1)=pi1-((beta1*S1*I1)./N1)+b2*S2-(mu+theta+b1)*S1;
dy(2)=pi2-((beta2*S2*I2)./N2)+b1*S1-(mu+theta+b2)*S2;
dy(3)=theta*S1+b2*V2-(mu+sigma+b1)*V1;
dy(4)=theta*S2+b1*V1-(mu+sigma+b2)*V2;
dy(5)=((beta1*S1*I1)./N1)+b2*E2-(mu+delta+b1)*E1;
dy(6)=((beta2*S2*I2)./N2)+b1*E1-(mu+delta+b2)*E2;
dy(7)=delta*E1+b2*I2-(mu+rho+eta+b1)*I1;
dy(8)=delta*E2+b1*I1-(mu+rho+eta+b2)*I2;
dy(9)=eta*I1+sigma*V1+b2*R2-(mu+b1)*R1;
dy(10)=eta*I2+sigma*V2+b1*R1-(mu+b2)*R2;
```

APPENDIX 7: Variations of susceptible, vaccinated, exposed, infected and recovered individuals in patch1and patch 2 respectively when individual movements between them are not allowed.

```
function dy=META_iso(~,y)
dy= zeros(size(y));
pi1=250;pi2=245;beta1=0.6;beta2=0.3;eta=0.024;mu=0.01;rho=0.01;sigma=0.52;
b1=0.1;b2=0.4;theta=0.8;delta=0.44
S1=y(1);
S2=y(2);
V1=y(3);
V2=y(4);
E1=y(5);
E2=y(6);
I1=y(7);
I2=y(8);
R1=y(9);
R2=y(10);
N1=S1+V1+E1+I1+R1;
N2=S2+V2+E2+I2+R2;
dy(1)=pi1-((beta1*S1*I1)./N1)-(mu+theta)*S1;
dy(2)=pi2-((beta2*S2*I2)./N2)-(mu+theta)*S2;
dy(3)=theta*S1-(mu+sigma)*V1;
dy(4)=theta*S2-(mu+sigma)*V2;
dy(5)=((beta1*S1*I1)./N1)-(mu+delta)*E1;
dy(6)=((beta2*S2*I2)./N2)-(mu+delta)*E2;
dy(7)=delta*E1-(mu+rho+eta)*I1;
dy(8)=delta*E2-(mu+rho+eta)*I2;
dy(9)=eta*I1+sigma*V1-mu*R1;
dy(10)=eta*I2+sigma*V2-mu*R2;
```

APPENDIX 9: Matlab code for plotting variations of susceptible, vaccinated, exposed, infected and recovered individuals in patch1and patch 2 respectively when individual movements between them are allowed.

```
clear all
close all
clc
tspan=[0 50];
```

```
y0=[20000, 14800, 0, 0, 40000, 9000, 30000, 8000, 0, 0];
[t, y]=ode45(@META,tspan,y0,[]);
figure (1)
plot(t,y(:,1), 'g',t,y(:,3), 'y',t,y(:,5), 'b',t,y(:,7), 'm',t,y(:,9),
'r','LineWidth',2);
xlabel('Time (years)','FontSize',11)
ylabel('Population in patch 1','FontSize',11)
legend('S_1','V_1','E_1','I_1','R_1')
grid on
hold on
figure (2)
plot(t,y(:,2), 'g',t,y(:,4), 'y',t,y(:,6), 'b',t,y(:,8), 'm',t,y(:,10),
'r','LineWidth',2);
xlabel('Time (years)','FontSize',11)
ylabel('Population in patch 2','FontSize',11)
legend('S_2','V_2','E_2','I_2','R_2')
grid on
hold off
```

APPENDIX 10: Matlab code for plotting variations of susceptible, vaccinated, exposed, infected and recovered individuals in patch1and patch 2 respectively when individual movements between them are not allowed.

```
clear all
close all
clc
tspan=[0 50];
y0=[16000, 12500, 0, 0, 35000, 8000, 20000, 6500, 0, 0];
[t, y]=ode45(@META_iso,tspan,y0,[]);
figure (1)
plot(t,y(:,1), 'g',t,y(:,3), 'y',t,y(:,5), 'b',t,y(:,7), 'm',t,y(:,9),
'r','LineWidth',2);
xlabel('Time (years)','FontSize',11)
ylabel('Population in patch 1','FontSize',11)
legend('S_1','V_1','E_1','I_1','R_1')
grid on
hold on
figure (2)
```

```
plot(t,y(:,2), 'g',t,y(:,4), 'y',t,y(:,6), 'b',t,y(:,8), 'm',t,y(:,10),
'r','LineWidth',2);
xlabel('Time (years)','FontSize',11)
ylabel('Population in patch 2','FontSize',11)
legend('S_2','V_2','E_2','I_2','R_2')
grid on
hold off
```

APPENDIX 11: Measles prevalence and incidence in metapopulation.

```
function dy=PRE__INC(~,y)
dy= zeros(size(y));
beta1=0.6;beta2=0.3;pi1=250;pi2=245;theta=0.9;mu=0.01;eta=0.024;rho=0.01;delt
a=0.44;sigma=0.52;b1=0.1;b2=0.4;
S1=y(1);
S2=y(2);
V1=y(3);
V2=y(4);
E1=y(5);
E2=y(6);
I1=y(7);
I2=y(8);
R1=y(9);
R2=y(10);
N1=S1+V1+E1+I1+R1;
N2=S2+V2+E2+I2+R2;
dy(1)=pi1-((beta1*S1*I1)./N1)+b2*S2-(mu+theta+b1)*S1;
dy(2)=pi2-((beta2*S2*I2)./N2)+b1*S1-(mu+theta+b2)*S2;
dy(3)=theta*S1+b2*V2-(mu+sigma+b1)*V1;
dy(4)=theta*S2+b1*V1-(mu+sigma+b2)*V2;
dy(5)=((beta1*S1*I1)./N1)+b2*E2-(mu+delta+b1)*E1;
dy(6)=((beta2*S2*I2)./N2)+b1*E1-(mu+delta+b2)*E2;
dy(7)=delta*E1+b2*I2-(mu+rho+eta+b1)*I1;
dy(8)=delta*E2+b1*I1-(mu+rho+eta+b2)*I2;
dy(9)=eta*I1+sigma*V1+b2*R2-(mu+b1)*R1;
dy(10)=eta*I2+sigma*V2+b1*R1-(mu+b2)*R2;
```

APPENDIX 12: Matlab code for plotting measles prevalence and incidence in metapopulation when individual movements between the two pathes are allowed.

```
clear all
tspan=[0 50];
y0=[20000, 14800, 0, 0, 40000, 9000, 30000, 8000, 0, 0];
[t,y]=ode45(@PRE__INC, tspan, y0);
N=y(:,1)+y(:,2)+y(:,3)+y(:,4)+y(:,5)+y(:,6)+y(:,7)+y(:,8)+y(:,9)+y(:,10);
T1=y(:,1)+y(:,3)+y(:,5)+y(:,7)+y(:,9);
T2=y(:,2)+y(:,4)+y(:,6)+y(:,8)+y(:,10);
Prev=(y(:,7)+y(:,8))./N;
Inc=(0.6*(y(:,1).*y(:,7))./T1)+(0.3*(y(:,2).*y(:,8))./T2);
figure(1)
plot(t,Prev,'k','Linewidth',3)
grid on
xlabel('Time[years]','Fontsize',12)
ylabel('Prevalence','Fontsize',12)
legend('theta=0.2','theta=0.5','theta=0.8')
hold on
figure(2)
plot(t,Inc,'y','Linewidth',3)
grid on
xlabel('Time[years]')
ylabel('Incidence')
legend('theta=0.53','theta=0.72','theta=0.9')
hold off
```

APPENDIX 13: Measles prevalence and incidence in metapopulation when there are no movement of individuals between the two patches.

```
function dy=PRE__INC_iso(~,y)
dy= zeros(size(y));
beta1=30;beta2=10;pi1=2950;pi2=2985;theta=0.53;mu=0.0909;eta=0.14;rho=0.02;de
lta=0.064;sigma=0.11;
S1=y(1);
S2=y(2);
V1=y(3);
V2=y(4);
E1=y(5);
E2=y(6);
I1=y(7);
```

```
I2=y(8);
R1=y(9);
R2=y(10);
N1=S1+V1+E1+I1+R1;
N2=S2+V2+E2+I2+R2;
dy(1)=pi1-((beta1*S1*I1)./N1)-(mu+theta)*S1;
dy(2)=pi2-((beta2*S2*I2)./N2)-(mu+theta)*S2;
dy(3)=theta*S1-(mu+sigma)*V1;
dy(4)=theta*S2-(mu+sigma)*V2;
dy(5)=((beta1*S1*I1)./N1)-(mu+delta)*E1;
dy(6)=((beta2*S2*I2)./N2)-(mu+delta)*E2;
dy(7)=delta*E1-(mu+rho+eta)*I1;
dy(8)=delta*E2-(mu+rho+eta)*I2;
dy(9)=eta*I1+sigma*V1-mu*R1;
dy(10)=eta*I2+sigma*V2-mu*R2;
```

APPENDIX 14: Matlab code for plotting measles prevalence and incidence in metapopulation when individual movements between the two patches are not allowed.

```
clear all
tspan=[0 50];
y0=[16000, 12500, 0, 0, 35000, 8000, 20000, 6500, 0, 0];
[t,y]=ode45(@PRE__INC_iso, tspan, y0);
N=y(:,1)+y(:,2)+y(:,3)+y(:,4)+y(:,5)+y(:,6)+y(:,7)+y(:,8)+y(:,9)+y(:,10);
T1=y(:,1)+y(:,3)+y(:,5)+y(:,7)+y(:,9);
T2=y(:,2)+y(:,4)+y(:,6)+y(:,8)+y(:,10);
Prev=(y(:,7)+y(:,8))./N;
Inc=(0.6*(y(:,1).*y(:,7))./T1)+(0.3*(y(:,2).*y(:,8))./T2);
figure(1)
plot(t,Prev,'k','Linewidth',2)
grid on
xlabel('Time[years]','Fontsize',12)
ylabel('Prevalence','Fontsize',12)
legend('theta=0.53','theta=0.72','theta=0.9')
hold on
figure(2)
plot(t,Inc,'y','Linewidth',2)
grid on
```

```
xlabel('Time[years]')
ylabel('Incidence')
legend('theta=0.53','theta=0.72','theta=0.9')
hold off
```