WALLAGA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

COLLEGE: NATURAL AND COMPUTATIONAL SCIENCE

DEPARTMENT: MATHEMATICS

MALARIA MATHEMATICAL MODEL WITH AN ISOLATED INFECTED HUMAN POPULATION

MSc RESEARCH PROPOSAL

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JANUARY, 2022

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APPROVAL SHEET FOR SUBMITTING THESIS PROPPOSAL ON

TITLE: MALARIA MATHEMATICAL MODEL WITH AN ISOLATED INFECTED HUMAN POPULATION

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Acknowledgement

First of all I would like to thank the almighty God, who gave me this chance and shephered me a life. Secondly I would like to thank my advisor Dr. Alemu Geleta who helped me to do every activity in every time. My special and heart full gratitude and appreciation for his great assistance, contribution, useful suggestion and constructive idea on this excellence advising and limitless effort in encouraging me in my work, correcting and giving comments by devoting his time. I greatly appreciate him who gave me valuable suggestion and comments during the preparation of this proposal.

Thirdly, I would like to thank my family those tired with me until now and supporting me by financial as well as encouraging me in every day to day.

Finally, I would like to thanks my colleagues who helping me in all ways as well as whom shared different ideas and supporting me by their own material needed to complete this proposal.

Abbreviations and Acronyms

DFE	Disease Free Equilibrium
EE	Endemic Equilibrium
ODE	Ordinary Differential Equation
SIS	Susceptible Infective Susceptible
SI	Susceptible Infective
SIRS	Susceptible Infective Recovered Susceptible
SEIR	Susceptile Exposed Infective Recovered
SEI	Susceptile Exposed Infective

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Summary of the proposal

This proposal plan to develop a malaria mathematical model with an isolated infected human population that describes the impact of isolation on malaria epidemics transmi ssion. We introduce the back ground of the study. The model will be formulated using non-linear differential equations and it will be analyzed for disease free and endemic equilibrium point. We define the reproduction number in terms of parameters. Then the well positivity solution of the mathematical model in sense of epidemiology and mathematics will be studied. Both local and global stability analysis of equilibrium points will be investigated. Sensitivity analysis will be studied based on the model parameters to reveal the crucial steps in the dynamics of the diseases as a result of isolation. The proposed model will also be studied numerically to see the agreements with analytical results. Finally, the established model will be analyzed based on theory for identifying best control strategies with minimum cost and maximum benefit. The study will have a great contribution for health care sectors, public health policy makers, national health authorities, researchers and act as plat form for further studies of related problem.

CHAPTER ONE
INTRODUCTION

1.1 Background of the study

According to the latest world malaria report in December 2020, an estimated 229 million cases occurred and 409000 deaths were reported worldwide and the African Region
accounted for 94% of all cases in 2019:(World Health Organiatioon,2002)(WHO,2002). It is caused by pathogens called protozoan. As a region, Africa is characterized by the greatest infectious disease burden and, overall, the weakest public health infrastructure among all regions in the world. Malaria is caused by Plasmodium parasites and it is transmitted from one individual to another by the bite of infected female anopheles mosquitoes. The malaria parasite enters a human when an infectious mosquito bites a person. After entering a human the parasite transforms through a complicated life-cycle. The parasites multiply in the human liver and bloodstream. Finally, when it has developed into an infectious form, it spreads the disease to a new mosquito that bites the infectious human. After approximately 10 to 15 days the mosquito takes her next blood meal and can infect a new person: (S.Sinha et al,2011). Malaria is a global deadly vector-borne disease, whose vectors are the mosquitoes. It can be transmitted through blood transfusion, sharing needles, or congenital. The infection can lead to serious complications affecting the brain, lungs, kidneys and other organs. Clinical symptoms such as fever, pain, chills and sweats may develop a few days after infected mosquito bites:LS.Luboobi et al,2007).

However, malaria is preventable and curable when treatment and prevention measures are soughtearly.Despite unrelenting constant efforts of researchers though, there is no breakthrough yet for malaria vaccine. Like other infectious diseases malaria may be introduced by infected immigrants into the population:(OD.Makinde&KO. Okosun,2011).The transmission of malaria disease in tropical Africa is sustained by three main vectors which are Anopheles Gambia, Anopheles arabinoses and Anopheles funfests:(RW. Snow & SI.Hay,2006).

1.2 Statement of the Problem

Malaria has for many years been considered as a global issue and major causes of deaths in Ethiopia. Many epidemiologists and other scientists invest their effort in understanding the dynamics of malaria and to control its transmission. From interactions with those scientists, Mathematicians have developed a significant and effective tool, namely mathematical models Of malaria, giving an insight into the interaction between the host and vector population, the dynamics of malaria, how to control malaria transmission. Mathematical modeling of malaria has flourished since the days of Ronald Ross, who received the Nobel Prize in Physiology or medicine in 1902 for his work on the life cycle of the malaria parasite: (M.Marteheva,20115). Ross developed a simple SIS for the human and SI for the vector model. Several models have been developed considering the impact of temperature and rainfall variability on mosquito birth rate and bite rate:(R.Ross,1911;LD.Berkovitz,2013;R.Ouifki et al,2019). Gashaw et al. (2019) proposed SIRS for human population and SI malaria model. This study is investigated the effect of temperature in the biting rate and the effects of both temperature and rainfall in the birth rate and death rate of the vector population.

To best of our knowledge, they did not consider the impact of isolation on malaria epi demics transmition in the populassion.Motivated by the works of:(R.Ross,1911;LD.Berk ovitz,2013;R.Ouifki et al,2019) ,we consider a malaria disease transmission with impact of isolation on malaria epidemics with respect to mosquitoes breeding and malaria infection. Therefore, this study proposes to build up a mathematical model for SII_2RS human population and SI for mosquito population to analyze the impact of isolation on spread and control of malaria epidemic transmission with cost effective analysis.

1.3 Research Questions

1. What are the dynamics of malaria transmission if isolation is added to SIRS?
2. Which parameter plays greater role in the dynamics of malaria transmission in SII_2RS-SI?
3.What are the basic assumptions to develop a mathematical model for the dynamics of m alaria transmission SII_2RS-SI?

4. What are the biological interpretations of the solution of the mathematical model which describes the dynamics malaria transmission?

1.4 Objectives of the Study

1.4.1 General objective

The general objective of this study is to understand the impact of isolation on dynamics of Malaria epidemics and its transmission using mathematical model and propose optimal control strategy with cost effective analysis.

1.4.2 Specific objectives

The specific objectives are to:

- Understand the dynamics of malaria transmission if isolation is added to SIRS.
- Determine which parameter plays greater role in the dynamics of malaria transmission in SII_2RS-SI.
- Determine the basic assumptions to develop a mathematical model for the dynamics of malaria transmission SII_2RS-SI.
- Identify the biological interpretations of the solution of the mathematical model which describes the dynamics malaria transmission.

1.5 Significance of the Study

The study is significant for the following reasons:

- It will help to improve control strategies for the occurrence of malaria diseases outbreak in a community.
- The output of this study, will serve as an input for public health policy makers
- The study will also serve as a reference for further research on optimal control of malaria diseases and form a base for further studies of related problem.
- Develop awareness about the dynamics of malaria and its transmission.
- Suggest the possible intervention mechanisms.
- Improve our understanding of the dynamical properties of malaria and its transmission.
- Help to understand ways to control the spread of malaria by applying the optimal diseases intervention strategies.

1.6 Mathematical Preliminary Concepts

Invariant Region

The model represented by the system (3.1.1) will be analyzed in the feasible region and since we are working with population all state variables and parameters are assumed to be positive. The invariant region can be obtained by the following theorem.

Theorem 1: The solutions of the system (3.1.1) are feasible for all $t > 0$ if they enter the invariant region $\Pi = \Pi_h \times \Pi_m$, where

$$\Pi_h = (S_h\ , I_h\ ,\ I_{2h}, R_h) \in \mathbb{R}^4\ : S_h + I_h + I_{2h} + R_h \leq \frac{\phi_h}{\mu_h},$$

$$\Pi_m = \ (S_m\ , I_m) \in \mathbb{R}^2\ : S_m + I_m \leq \frac{\psi_m}{\mu_m}.$$

Positivity of Solutions

Theorem 2: Let the initial conditions of system (3.1.1) be positive.Then the solutions (S_h (t), I_h (t), R_h (t), S_m (t), I_m (t) of the system is non-negative for all $t \geq 0$.

1.7 Organization of the Proposal

This proposal is organized as follows:

- Chapter one deals on background of study, statement of the problem, research questions, objectives, significance of the study and preliminary concepts.
- Chapter two presents literature views and vector transmitted disease models.
- Chapter three is about sources of information, mathematical procedures, model formulation and expected outcomes.
- Chapter four is work plan and budget.

CHAPTER TWO
LITERATURE REVIEW

2.1. Introduction

Malaria disease becomes a serious problem in Africa and researchers have focused their attention on understanding how this disease is treated and controlled. There were many studies have been conducted to highlight the control of the disease and it's epidemiology. In this chapter, we review some researches that were studied to develop mathematical model of vector transmitted disease dynamics that are directly related to the objectives of this study

2.2. Vector Transmitted Disease Models

A number of studies have been conducted to emphasize the control of the diseases and their dynamic by building different type of Mathematical models. The study on malaria using mathematical modeling began in 1911 with Ronald Ross: (M.Martcheva,2015). From the Ross model, several models have been developed by researchers who extended his model by considering different factors such as latent period of infection in mosquitoes and humans:(Okosun et al, 2010) proposed SEIR for the human population and SEI model for mathematical epidemiology of malaria disease transmission and its optimal control analyses. The authors studied a mathematical model of the dynamics of malaria with three-time dependent control measures. These are personal protection, treatment, and indoor residual spray. The cost effective analysis of the adopted control strategies revealed that the combination of personal protection and indoor residual spray is the most cost-effective intervention strategies to combat the malaria endemic. They concluded that control programs that follow these strategies can effectively reduce the spread of malaria disease in different malaria transmission: (Miliyon Tilahun,2017, Otieno et al,20116), studied a mathematical model of the dynamics of malaria with four-time dependent control measures in Kenya. These are insecticide treated bed nets, treatment, indoor residual spray and intermittent preventive treatment of malaria in pregnancy. They considered constant control parameters and calculated the reproduction number of disease-free and endemic equilibrium, followed by the sensitivity analysis and numerical simulations of the optimal control problem using reasonable parameters. The cost-effectiveness analysis of the adopted control strategies revealed that the combination of prevention and treatment is the most cost-effective intervention strategies to combat the malaria endemic:(Gashaw et al,209) proposed SIRS for human population and SI malaria mode for the climate dependent malaria disease transmission model with optimal control. This study is investigated a model incorporating the effect of temperature in the biting rate and the effects of both temperature and rainfall in the birth rate and death rate of the vector population. The authors study concluded that the biting rate of mosquito is very low in temperature below $20^{o}C$; optimum in $30^{o}C$ and become greater than $36^{o}C$ have negative impact on the life of the mosquito birth rate(Tumwiine et al,2007).

In general, there are plenty mathematical studies that have been undertaken to model of malaria transmission with optimal control, but there are no studies that have been undertaken for modeling the impact of isolation on malaria epidemics with optimal control and cost effective analysis considering logistic growth of isolation in their models.

Motivated by the work of them, to fill this gap, we consider the impact of isolation on ma laria epidemic infection. Due to this, we proposed modeling the impact of isolation on ma laria epidemic with optimal control and costeffective analysis.Thus we are going to devel op a mathematical model SII_2RS for human population and SI for mosquito population. T his study has planned with the following research methodology.

CHAPTER THREE

METHODOLOGY

3.1. Introduction

This chapter is devoted to see about description, model formulation and analysis techniques of the formulated model that will be used in the study.

3.2. Sources of information

The study will involve collecting information input of data and informations are obtained mainly equation from internet based sources, some books that available in libraries and recent research reduced differential transform method for solving exact solution of parabolic and hyperbolic partial differential. All the information obtained will be recording in the project that will be done.

3.3 Mathematical procedure

The study will involve both qualitative and quantitative analysis of the mathematical model. To derive conditions or threshold parameters that characterize the behavior of disease, mathematical methods of analysis of differential equations will be used. We will use next generation method to derive the basic reproduction number. Sensitivity analysis of model parameters for their effects on the outcome of the model results or predictions will be performed.

3.4 Description and Model Formulation

Mathematical models play great role in understanding the dynamics of malaria and its transmission. To understand this using system of ordinary differential equations, the mathematical model of malaria transmission will be formulated. The model divides the host population at a time t into four sub populations according to their disease status.

Susceptible S(t): includes those individuals that are at risk for developing an infection from the disease.

Infected I(t): this class includes all individuals that are showing the symptom of the disease and can transmit the disease.

Isolated I_2(t): this class includes all individuals that are infected and isolated from others not to transmit the disease.

Recovered R(t): includes all individuals that have recovered from the disease and got temporary immunity.

A deterministic transmission model is developed as a framework for understanding the impact of isolation on malaria dynamics. The basic assumptions that will be used to formulate the model are discussed below in detail. The model we introduce consists of two populations: the human population and the mosquito population. The model sub-divides the total human population at time t is denoted by $N_h(t)$ into the following sub-populations of susceptible human $\mathbf{S_h(t)}$; infected humans $\mathbf{I_h(t)}$; and recovered individuals with temporary immunity $\mathbf{R_h(t)}$: So that $\mathbf{N_h(t) = S_h(t)+I_h(t)+R_h(t)}$.

The total mosquito population at time t is denoted by $\mathbf{N_m (t)}$ is sub-divided into susceptible mosquito $\mathbf{S_m(t)}$; infected mosquito $\mathbf{I_m(t)}$: Thus $\mathbf{N_m(t)} = \mathbf{S_m(t)+I_m(t)}$. We use the SIRS type model for humans to describe a disease with temporary immunity on recovery from infection. Mosquitoes are assumed not to recover from the parasites so the mosquito population can be described by the SI model. The assumptions have been used in the formulation of the model are as follows: all parameters in the model being non-negative.

Table 3.1: State variables of malaria model

Symbol	Description
S_h	The number of susceptible human population
I_h	The number of infected human population
I_{2h}	The number of isolated human population
R_h	The number of recovered human population
S_m	The number of susceptible mosquitoes population
I_m	The number of infected mosquitoes population

Table 3.2: Parameters of malaria model

Symbol	Description
Φ	The recruitment rate of humans
μ_h	The natural death rate of humans
σ_h	The contact rate of humans
β	The recovery rate of humans without isolation
θ_h	Disease-induced death rate for humans
ω	The per capita rate of loss of immunity in human
α	The isolation rate of human
φ	The recovery rate of human after isolation
ψ	The recruitment rate of mosquitoes
μ_m	The natural death rate of mosquitoes
σ_m	The mosquito contact rate

The transmission dynamics of malaria is summarized in the compartmental diagra m in Figure (3.1) below.

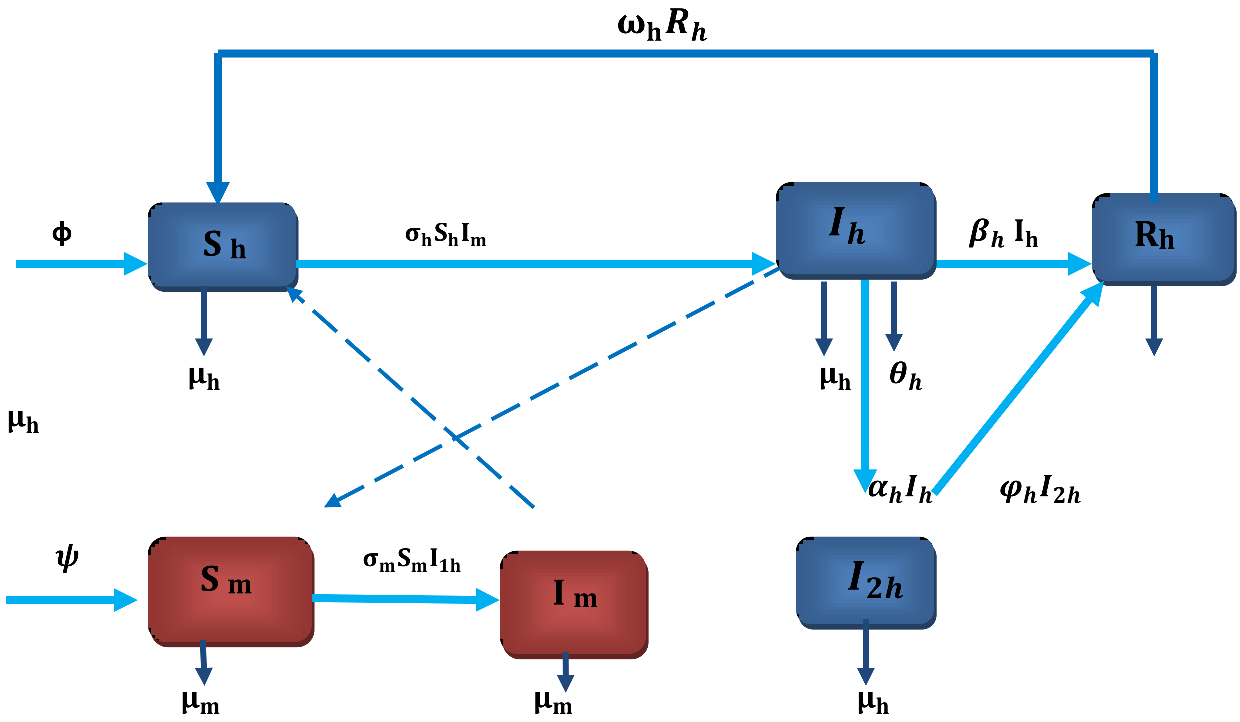

Figure 3.1.1

From the diagram described in Figure (3.1), the model that governs the transmission of the malaria is depicted by the system of ordinary differential equations

$$\begin{cases} \dfrac{dS_h}{dt} = \phi - \sigma_h S_h I_m - \mu_h S_h + \omega_h R_h \\ \dfrac{dI_h}{dt} = \sigma_h S_h I_h - \alpha_h I_h - (\mu_h + \theta_h + \beta_h) I_h \\ \dfrac{dI_{2h}}{dt} = \alpha_h I_h - \mu_h I_{2h} \\ \dfrac{dR_h}{dt} = \beta_h I_h - (\mu_h + \omega_h) R_h + \varphi_h I_{2h} \\ \dfrac{dS_m}{dt} = \psi - \sigma_m S_m I_m - \mu_m S_m \\ \dfrac{dI_m}{dt} = \sigma_m S_m I_m - \mu_m I_m \end{cases} \quad \ldots\ldots\ldots.\ldots\ldots\ldots\ldots \quad 3.1.1$$

3.5 The Basic Reproduction Number

Intuitively from the epidemiological point of view, the basic reproduction number (R_0) is the average number of new cases that one infected case will generate during their entire infectious lifetime. It is very important in determining whether the disease persist in the population or die out. To determine the basic reproduction number from the system (3.1.1), F and V are defined as

$$F = \begin{pmatrix} \delta_h S_h I_h \\ \delta_m S_m I_m \end{pmatrix} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3.1.2) \qquad \text{and}$$

$$V = \begin{pmatrix} \alpha_h I_h - (\mu_h + \theta_h + \beta_h) I_h \\ \mu_m I_m \end{pmatrix} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3.1.3)$$

The disease free equilibrium (DFE) of the model is computed by setting the right hand side of the model (3.1.1) equal to zero with $I_h = 0$ and $I_m = 0$. Then the Jacobian matrix of (3.1.2) at the disease free equilibrium (DFE) $E_0 = (\frac{\psi}{\mu_m}, 0, 0, 0, \frac{\phi}{\mu_h}, 0)$ is given by

$$F = \begin{pmatrix} 0 & \delta_h S_h \\ \delta_m S_m & 0 \end{pmatrix}$$

Similarly, the Jacobian matrix of (3.1.3) at the DFE E_0 is

$$V = \begin{pmatrix} \alpha_h - (\mu_h + \theta_h + \beta_h) & 0 \\ 0 & \mu_m \end{pmatrix}$$

The inverse of V is

$$V^{-1} = \begin{pmatrix} \frac{1}{\alpha_h - (\mu_h + \theta_h + \beta_h} & 0 \\ 0 & \frac{1}{\mu_m} \end{pmatrix}$$

Therefore, our next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\delta_h S_h}{\mu_m} \\ \frac{\delta_m S_m}{\alpha_h - (\mu_h + \theta_h + \beta_h)} & 0 \end{pmatrix}$$

The eigenvalues of the next generation matrix are

$$\lambda_{1,2} = \sqrt{\frac{\delta_m \psi \delta_h \phi}{\mu_m^2 \mu_h (\alpha_h - (\mu_h + \theta_h + \beta_h))}}$$

Since R0 is the biggest non-negative eigenvalue of the next generation matrix, we have

$$R_0 = \sqrt{\frac{\delta_m \psi \delta_h \phi}{\mu_m^2 \mu_h (\alpha_h - (\mu_h + \theta_h + \beta_h))}}$$

Stability of Disease Free Equilibrium Point

The equilibria are obtained by equating the right hand side of the system (3.1.1) to zero. Disease-free equilibrium (DFE) of the model is the steady-state solution of the model in the absence of the disease (malaria). Hence, the DFE of the malaria model (3.1.1) is given by **Theorem 1**: The DFE, E_0 of the system (3.1.1) is locally asymptotically stable if R0 < 1 and unstable if $R_0 > 1$.

Theorem 2: If $R0 < 1$, then the disease free equilibrium point E_o is globally asymptotically stable and the disease dies out, but if $R_0 > 1$, then E_0 is unstable.

Sensitivity Analysis of a Dynamical System

Definition 2: A parameter is called sensitive if small changes in the value of the parameter produce large changes in the solution of the differential equations.

Definition 3: Local sensitivity analysis is a sensitivity analysis that examines the change in the output values that result from change in one input value (parameter).Global sensitivity analysis examines the change in the output values that result from changes in all parameter values over the parameters' ranges.

Local and global stability for disease free equilibrium point (DFE) and endemic equilibrium (EE) will be analyzed using linearization techniques and Lyaponuov function theory respectively. Study of dynamical behavior in terms of threshold parameters and numerical simulations will be done.

In this study, the qualitative optimal control analysis of the developed model and the necessary conditions for optimal control of the impact of control on malaria disease will be performed. Here the control system that is defined as a system of differential equations will be used. The control to the system ordinary differential equations (ODE) will be introduced with the aim of adjusting them in order to maximize or minimize the objective function.

3.6 Expected Outcomes

This study mainly focused on the analysis of mathematical model of the transmission of disease with optimal control. So after the study of this research the expected outcomes are:

- The mathematical model of the transmission of malaria disease with optimal control and cost-effective.
- The sensitivity analysis of each parameter on the spread and control of malaria.
- The best control strategy for the malaria disease control that applicable for public health policy makers.

CHAPTER FOUR

WORK PLAN AND BUDGET

4.1. Work Plan

Table1. Work Time plan

Number	*Work to be done*	**Months In Year**									
		2022							**2023**		
		J	**J**	**A**	**S**	**O**	**N**	**D**	**J**	**F**	**M**
1	Title selection	X									
2	Writing proposal		X								
3	Writing final proposal			X	X						
4	Proposal defense					X					
5	Collecting data						X				
6	Analyzing data							X			
7	Writing report								X	X	
8	Final defense										X

4.2. Budget Schedule

The following table shows the budget break down.

Table2. Estimated budget

Number	Description	Quantity	Unit	U. price	Total
1	Printing paper	2	Ream	200 birr	400 birr
2	Pens	10	Item	45 birr	450birr
3	Typing	80	Pages	8 birr	5640 birr
4	Retyping	40	Pages	6 birr	240 birr
5	Binding	2	Textbook	265 birr	530birr
6	Transportation				2000 birr
7	Mobile card	8		100	800 birr
8	Contingency				10,440 birr
9	Duplicating paper	5	Packets	300	1500
10	Flesh disk	2	Pecks	500	1000
11	Writing final report			500	1500
	Grand total				25,000

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