Mathematical Modeling of CRYPTOSPORIDIOSIS Disease

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DEPARTMENT OF MATHEMATICS

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A Thesis submitted to the department of mathematics Addis Ababa University in partial of the requirements for the degree of Master of Science in mathematics.

August 2016 EC

AAU, Ethiopi

Permission

This is to certify that the project prepared by Endalkachew Tazeze Wondim entitled generalized Mathematical modeling on Cryptosporidiosis Disease and submitted in partial fulfillment for the requirement of the degree of master of science in mathematics(Differential) complies with the regulation of the university and meets the accepted standards with respect to originally and quality.

Signed by the Examining Committee

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Examiner 1: Signature Date

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Manalebish Debalike (PHD) …… …….

Advisor Signature Date

Acknowledgements

I would first like to express my gratefulness to God for awarding me access to this program, as well as to my advisor Manalebish Debalike(PHD), my wife Agerie Zeleke, my three children, Solomon, Ermias, and Saron Endalkachew, as well as my parents, Tazeze Wondim, Acham Tina, and my best sister .

Table of Contents

Abstract

The mathematical consequence of the disease-free equilibrium being locally asymptotically stable with the related epidemic fundamental reproduction of cryptosporidiosis is studied in the mathematical model for cryptosporidium infection. The infection model from the sensitivity analysis 0 is more sensitive to δ and crypto parameters when Rcr0>1. For the cryptosporidiosis reproductive number (Rcr0) >1 is less sensitive. this is explanation of cryptospridiosis. Cryptosporidium is organized with water born transmission implement through dejection –oral path in many recreational water facilities. The homotopy decomposition method (HDM), a recently discovered analytical technique, is used to get the approximation or estimate solution by the numerical result. The etiological agent of cryptosporidiosis, an intestinal disease marked by frequent watery diarrhea, is Cryptosporidium, a protozoan parasite belonging to the species Ape complex. There are more than 30 known species of Cryptosporidium. The species most often linked to human infection include Cryptosporidium parvum and Cryptosporidium hominidi.Contact with diseased animals has been linked to the zoonotic transmission of cryptosporidiosis in humans in several cases, while a cryptosporidium infection by itself is not deadly, cryptosporidiosis which can lead to periodic epidemic disease—remains a significant worldwide cause of morbidity and mortality if an immune system is weakened.

Glossary

DFE disease free equilibrium

SIR Susptible infected recovered

SIRS susptible infected recovered susptible

EEP endemic equilibrium point

HDM homotopy decomposition method

INTRODUCTION

Microsporidium, a parasitic disease that causes cryptosporidiosis in the intestines of mammals, is the source of this diarrheal illness. Clarke and Tyzzer [16] originally described this condition in 1976, and records were kept up to 1982. Cryptosporidiosis is one of the most common waterborne illnesses, especially in the US. The parasite is not destroyed by hand sanitizers or alcohol either. Chlorine is used in most swimming pools to kill germs, but crypto is not killed by this. The incidence is typically linked to water use for drinking and relaxation. In addition to being re-infected, it can spread through contact with an infected individual [20, 21]. The most common ways for the disease to spread are usually through consuming of the microorganisms found in food and water, or through physical contact with an infected person. Cryptosporidiosis can live in the intestines of both humans and animals and spread through their waste. Common names for the parasite and the illness include "Crypto." The parasite is shielded from chorine-based cleaners by an exterior shell that permits it to remain outside the body for extended periods of time. Infected humans or animals can discharge millions of Crypto germs in a single movement and the soil-found Cryptosporidium. While blood contact is not the way that crypto currency is transferred. While a cryptosporidiosis infection in and of itself is not fatal.It is possible to prevent Cryptosporidium infection by leading a healthy lifestyle and abstaining from swimming in pools, lakes, recreational water parks, and streams. As a result, cryptosporidiosis, which can occasionally cause epidemic disease, continues to be a significant global source of morbidity and mortality. In the past, after Ernest Edward Tizzies described Cryptosporidium in mice [16]. After widespread research, it has been determined that the genus Cryptosporidium includes a wide variety of species and genotypes that are adapted to parasitic existence in practically all vertebrate groups. However, it took another 70 years to fully understand the importance of this protozoan in medicine and veterinary medicine in1976; it was identified as a possible cause of illness. The protozoa were more habitually implicated in human disease as techniques for analyzing stool samples were developed [9].Additionally, it has been observed that 155 animal species, primarily mammals, are infected with Cryptosporidium partum, also referred to as C. parvum [42]. It has been claimed that humans can contract Cryptosporidium from any of the 15 identified species, which are infective to non-human vertebrate hosts, including C. Baileyi, C. felis, C. homoinis, C. meleagridis, C. Marie, and C. parvum. With the exception of C. parvum, which is most commonly known to be present in non-human hosts and is the predominant host for C. hominids, humans are the primary hosts for this species.

1. The disease's biological background of cryptosporidiosis

1.1 Cryptosporidiosis's past

along with Human The protozoan parasite known as Cryptosporidium causes cryptosporidiosis, which is linked to several abdominal illnesses typically associated with recreational water. Severe watery diarrhea is the hallmark of cryptosporidiosis, which is spread via contact with infected food surfaces and water. The simplest way to contract the illness is by recreational swimming, where water can enter the mouth and enter the stomach. The condition of Cryptosporidium is good associated with recreational water facilities' waterborne transmission routes. Nevertheless, asymptomatic infective develop and spread to several recreational water facilities. It is known that the infection rate with cryptosporidiosis is quite low. For instance, in a healthy adult, its low infectious dosage is thought to be between 10 and 30 [7–10]. In many recreational water facilities, the disease can resist the dejection-oral route, which is a well-known method of water-borne transmission.The recommended amounts of halogen disinfection for treating water recreational facilities include cryptosporidiosis [11]. Anyone with a cryptosporidiosis diagnosis is probably immune system compromised. One of the species' unicellular parasite protozoa is called Cryptosporidium. Almost thirty species of Cryptosporidium have been identified to date; some are more promiscuous in terms of host infectivity, while others are host specific. Additionally, while infections with certain Cryptosporidium species are typically linked with little or no symptoms, others are extremely toxic and can cause serious symptoms, potentially leading to death. The most typical clinical manifestation of cryptosporidiosis is diarrhea, which typically appears as a gastrointestinal illness. Generally speaking, Earnest Edward Tyzzer made the initial discovery and description of the parasite cryptosporidium, popularly known as "Crypto," in 1907.Additionally, the asexual and sexual stages are the two primary phases of the cryptosporidium life cycle. The intestinal tracts of sick humans or animals are home to Cryptosporidium. The mostly oral and fecal, but frequently indirect transfer by a food or water carrier (see Figure 1)

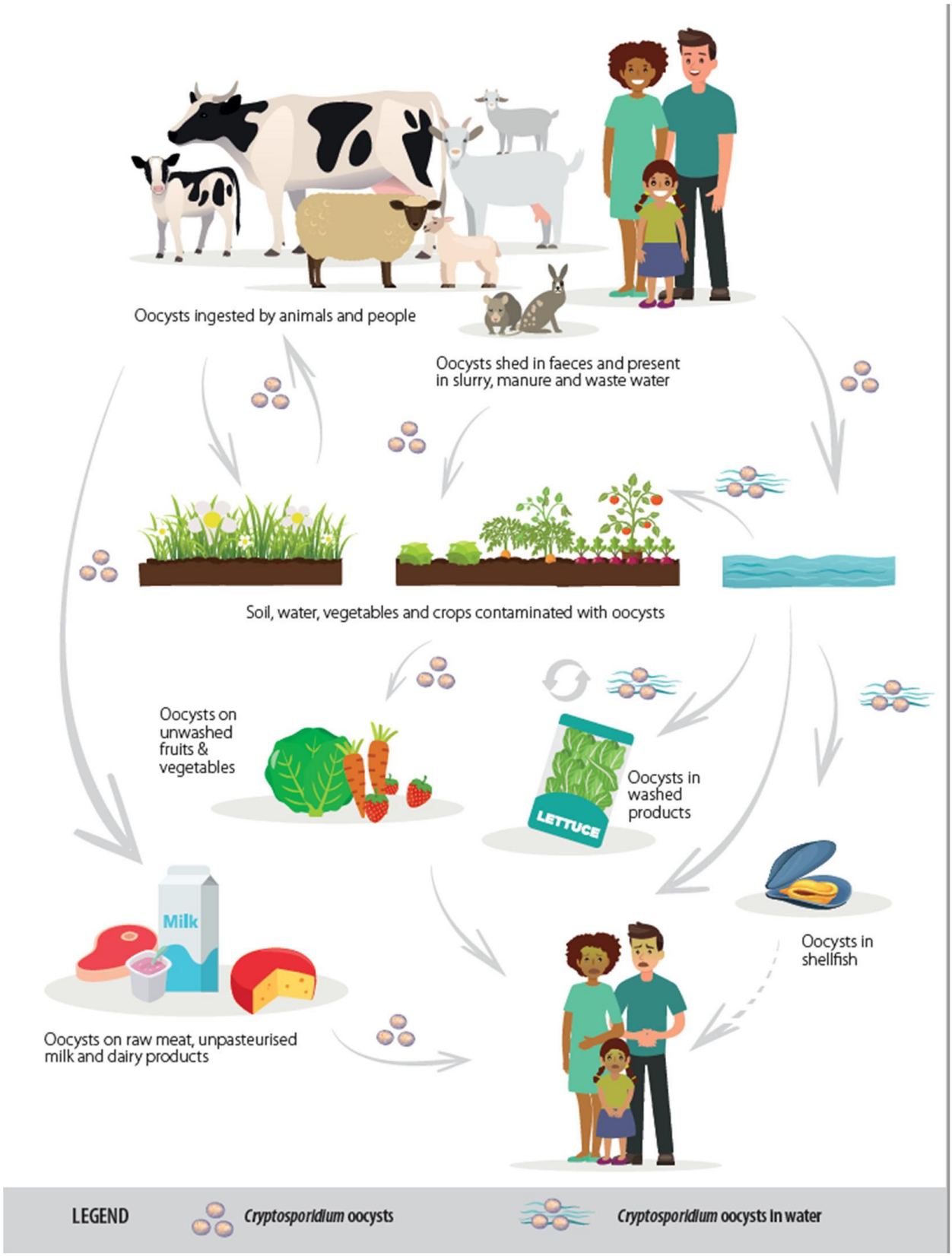


Figure 1; Transmission routs of cryptosporidium Sap,

1.2. Life Cycle, Spread, Symptoms and Prevention

The life cycles of cryptosporidiosis are the eggs are swallowed in contaminated water, food and devise inside the body. The parasites change forms several times by multiple asexually and develop in to male or female .Symptoms include; Stomach cramps, Dehydration, Vomiting, Fever and weight loss. Generally, Symptoms of Cryptosporidiosis begin within 2 or 10 (average 7 days) and The treatment diarrhea can be managed by drinking plenty of fluids to treatment cryptosporidiosis of dehydration .cryptosporidium has a complex duplicate life cycle.

1.3, Goals of the study

.To increases a mathematical model that expresses the dynamic of cryptosporidiosis
. To express the numerical role of the mathematical model
. To know the dynamics of cryptosporidiosis and its transmission
.To express the biological conclusions of the analysis.
.To express the biological of the solutions

1.4. Important of the research

To acknowledge the capacity of cryptosporidiosis

To provide potential tools for involvement

To deepen our understanding of the characteristics of cryptosporidiosis and how it spreads

1.5, Review of the Literature

It is obvious that the invasion of new ecosystems by humans and animals, environmental degeneration, global warming, and shifts in economic patterns will result in the emergence of new infective illnesses. As a result of these extensive studies, epidemiologists in particular have worked to find solutions for the transmission, developing a mathematical model and making predictions about it based on the data they collected. Hethcote [HetOO] states that Daniel Bernoulli developed and solved a smallpox model in 1760.In an effort to completely understand the measles epidemic's recurrence, Hamer developed and examined a discrete time model in 1906 [Wo6]. Additionally, Okosun K.O. [OMT 13] conducted research on the effects of optimal control on the management of infectious disease transmission, including the disease cryptosporidiosis.But not much work has been done in the mathematics

2, Background Information for Mathematical Modeling

2.1Overview

The protozoan cryptosporidium is the cause of human cryptosporidiosis a common abdominal illness that is typically linked to recreational water consumption, as is the case in Australia [1, 2]. It is typified by deadly watery diarrhea, but an asymptomatic illness can sometimes develop and become the infection's source [1].Interaction with polluted surfaces, food, and water can spread cryptosporidiosis. The simplest way to spread the illness is by recreational swimming, where water can enter the stomach through the mouth. Crypto is extremely transmissible; if it is not treated, a person may contract it again and perhaps spread it to others. Several recreational water facilities have been linked to the waterborne transmission of Cryptosporidium through the dejection-oral pathway. One type of sickness in humans is thought to be caused by a single species. Additionally, children with self-limited diarrheal illnesses are the principal victims.

2.2, Ordinary differential equations' deep recommendability

Lyapunuv originally established the stability of ODE solutions on a solid mathematical foundation in the setting of linear homogeneous (LH) systems about 1890:

$$x^{'} = A(t)\,x$$

Where A: R $\rightarrow\leftarrow$ $F^{n\times n}$.We began by providing a precise definition for these ideas .A point $x_{e\,\in F^n}$ is said to be an equilibrium point for (LH) for the IVP:

$x_{'} = A(t)\,x$, $x(t_0) = x_{\in}$ is the unique solution $X(t) \equiv x_{\in}$ $\forall t \geq t_0$

Theorem (Existence and uniqueness) ; Let f(x, y) and $\frac{df}{dy}$(x ,y) both are continuous in a rectangular region

R= {(x, y): $x_0 - \delta < x < x_0 + \delta, y_0 - \in < y < y_0 + \epsilon$},where

δ *and* ϵ *are positive. then there exists a number* $\delta_i >$ 0 *such that there is one and only one solution to the following first order ODE*:

$$\begin{cases} \frac{dy}{dx} = f(x,y) \\ y(x_0) = y_0 \end{cases} \quad , \quad \text{for} \quad x_0 - \delta_1 < x < x_0 + \delta_1.$$

Theorem (continuity) : Let p and q are continuous functions on an interval I = (a ,b) contains the point t = t_0, and there exists a unique function y = $\varphi(t)$ satisfies the differential equation:

y' + P (t) y= q (t) for each t ∈ [a, b], and that also satisfies the initial condition Y(t_0) = y_0

Where y_0 is an arbitrary initial value

2.3, Ordinary Differential Equations Stability

The local stability of the disease-free equilibrium of the ordinary differential equations (ODE) can be certained by applying the following definition to the system.

2.3.1 Definition: The projected number of secondary cases generated is known as the basic reproductive number (R_0), which is used to determine the disease's capacity for reproduction. An infected individual may eventually die ifR_0<1. On average, an infected individual produced less than one new infected individual. However, if R_0 >1, then the sickness will gradually spread across the population as each afflicted person often produces multiple new infections.

2.3.2 Definition: The overall approach to obtaining R_0 that involves one or more infectious classes is known as the "next generation method." Assume that there are q non-disease compartments and p disease compartments, and that the sizes of these compartments are sϵR^q and r$\in R^p$. It indicates that the i^{th} disease compartments have an increase in the rate of secondary infection byF_i. Nonetheless,V_i, which represents the rate at which the disease advances, mortality, and recovery diminishes the i^{th} compartmental model, may be expressed as follows:

$$\frac{dr_i}{dt} = F_i\,(r, s) - V_i(r, s), \qquad i = 1,\ldots,n \qquad (2.3.2)$$

$$\frac{ds_i}{dt} = V_J\,(r, s), \qquad j = 1,\ldots...,m$$

The basic reproduction number is found based on the linearization of the ODE model evaluated at disease-free equilibrium and the following assumptions are used for the existence and deep-recommend of a model.

a) Imagine $F_i(0,y) = 0$ and $V_i = (0,y), \forall_y \geq 0$ and i = 1, …..,n. All the new infections were secondary infections arise from the infected hosts.
b) If $F_i(0,y) \geq 0$ for all non-negative r and s for i = 1,……,n ,then F is a function represents new infection.
c) $V_i(0,y) \leq 0$ when $r_i = 0$,for i = 1,……,n the components v_i represents a net outflow from compartments must be negative

2.4, Routh-Hurwitz Criteria

The Routh Hurwitz method, also known as the Routh array, is based on the order of coefficients of the characteristic polynomial and offers a quick and simple way to determine stability without having to break down the characteristic equation. Now take a look at the characteristic equation below.

$$Q(s) = a_0 s^n + a_1 s^{n-1} + \ldots + a_{n-1} s + a_n = 0 \qquad (2.4.1)$$

Where a_i is real constants, i= 1,2,…,n defines the n Hurwitz matrices. Now we can determine n eigenvalues S of a real n $\times n$ matrix A, then the eigenvalues S will all have negative real parts.

2.5, Lyapunov function and stability

2.5.1, Definition (Lyapunov function). A f unction V: $F^N \rightarrow R$ is a positive definite function if:

1) V(x) $\geq 0, \forall_x \in R^n$
2) V(x) = 0, if x=0 , and
3) For all $\alpha \epsilon R$ *the set* $\{ x \epsilon F^n$: V(x)$\leq \alpha\}$ is compact

2.6, Compartmental Modeling

Modeling the outbreak and circulate of an epidemic consisting of different individuals of various classes. These subdivisions of the population are known as Compartments (partitions). In some classes usually considerations are:

1) Susceptible class(S)-it is a set of individuals who are not infected but a risk of being infect by the disease.

2) Exposed class (E) –it is a set of individuals who are infected but cannot infect others with the disease. 3) Infected class (I) - This class consists of pe0ple who are infected.

4) Recovered class (R) - This class contains individuals who are to get back from the disease either temporary or permanent.

For more accurate model to be constructed, we may add classes to the model in particular the population size of classes at a time t are denoted by S(t), E(t), I(t), R(t) respectively and. N (t) represents the total size of the population which is:

$$N(t) = S(t) + E(t) + I(t) + R(t)$$

2.7, Basic SIR Model

The simplest compartmental models used for the description of the transmission of infection diseases are proposed by:

SIR denotes susceptible $\rightarrow$ *Infected* $\rightarrow$ Re cov*ered* .or

S $\xrightarrow{\beta} I \xrightarrow{\alpha} R$ this is called basic SIR model.

And the corresponding differentials equation to this effect is given as:

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \alpha I \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(2.7.1)}$$

$$\frac{dR}{dt} = \alpha I$$

From the above model (2.7.1) we can solve for R if I is known such that S and I compartment alone,

Implies that: $\frac{dI}{dS} = \frac{(\beta S - \alpha)I}{-\beta SI} = -1 + \frac{\alpha}{\beta S}$ And we get for I by integrating both sides, we have I = -S + $\frac{\alpha}{\beta}$ ln$S$ + C, where C is constant of integration

2.8, other complex SIR models

By modification the Basic SIR model may be made such as Vaccine administration. In this case Susceptible individuals who are Vaccinated go directly into the Recovered class which is they get permanent immunity. Number of vaccination given to individuals is like to be prescribed number of dose at a given period of time.

S $\overset{k}{\rightarrow}$ R $\overset{\alpha}{\leftarrow}$ I $\overset{\beta}{\leftarrow}$ S this called other complex SIR model with vaccination parameter formation and the corresponding differentials equation to this effect is given as:

$$\frac{dS}{dt} = -\beta SI - k$$

$$\frac{dI}{dt} = \beta SI - \alpha I \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(2.81)}$$

$$\frac{dR}{dt} = \alpha I + k$$

3 MODEL DESCRIPTION AND ANALYSIS

3.1 Model Formulation

In order to formulate the SIR model (1), we analyze a model (1) for the disease cryptosporidiosis. The model divides the entire human population, represented by N, into subpopulations of susceptible individuals (S), individuals with cryptosporidiosis (I), and recovered individuals from cryptosporidiosis (R). Consequently, N = S + I + R, and En represented the contaminated environment. Assume that there are only a few contacts between the host and the environment, that the environmental contamination is caused by a mass action type of infection, and that the host transmission is caused by a standard form of infection. As a result, the following is the Crypto disease transmission model:

$$\begin{cases} \frac{dS}{dt} = A + \delta R - \mu S - {\beta_m}^* S \\ \frac{dI}{dt} = {\beta_m}^* S - (\alpha + \mu + \varphi) I \\ \frac{dR}{dt} = \alpha I - (\mu + \delta) R \\ \frac{dE_n}{dt} = \theta I - v E_n \end{cases} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

And $\beta_m^* = \frac{\lambda\, \epsilon I}{S+I+R+A}\, \rho E_n$ ……………………………………………………(2)

Where $\epsilon = contact\ rate, \lambda$ = transmission probability, $\varphi = the\ parameter\ of\ cryptosporidiosis\ related\ with\ death$

$\theta = the\ averagecontribution\ of\ cryptosporidiosis\ infected\ individual\ to\ the\ env't$

V = the rate at which crypto leaves the environment , $\alpha = the\ recovery\ rate$ $\delta = immunity\ waning\ rate$

A = human recruitment rate , $\mu = the\ human\ mortality\ rate$ $E_n = environmental\ contamination$ $\rho = the\ modification\ parameter\ due\ to\ environmental\ treatment$

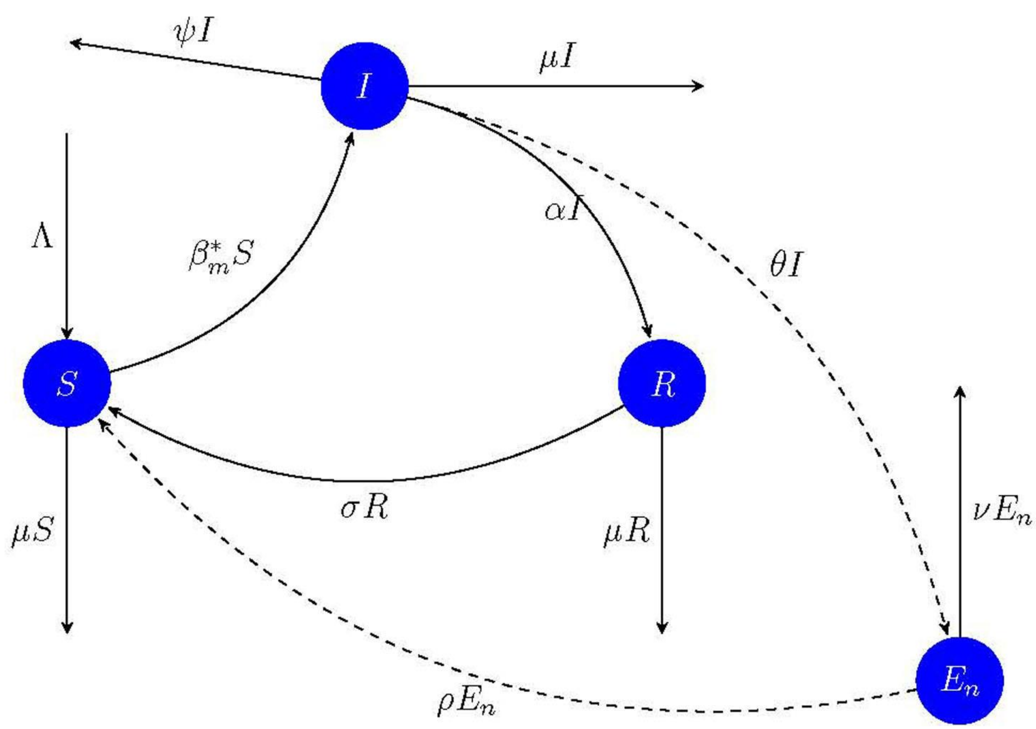


Figure 3.1 Diagram showing the model Formation

3.2, Characters of the Basic Model

3.2.1, Positiveness of Analysis

Lemma 3.2.1: the closed set

$$D = \begin{cases} (S, I, R, A)\varepsilon\, R_+^{\,4} : N \le \frac{A}{\mu} \\ E_n\ \varepsilon R_+ : E_n \le \frac{A(\theta+\delta)}{\mu v} \end{cases} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

is the model does not forecast negative values for the state variables at any some day. In taking human population only in to consideration, the vector field in the right hand of the system (2) points to the direction of the boundary of $R_+^{\,4}|\{0\}$.

.

3.2.2, Sectors of Invariable

The state of variables continue positive all the time and disease free equilibrium (DFE) of the model is:

$$\frac{dS}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = \frac{E_n}{dt} = 0$$

Lemma 3.2.2, *D* is a compact set (i.e. the *compact attracting set is* limit set of a sector starting in R_+^3 lies in *D*).

Proof: By the positivity of the model state of variables when obtained in Lemma 3.2.1 we have:

$$\frac{dN}{dt} = A - \mu N - \varphi I \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

For initial conditions in R_+^3 and $t \ge 0, we\ have$:

$$\frac{dN}{dt} \le A - \mu N$$

$$\Rightarrow \frac{d}{dt}(N\, e^{\mu t}) \le A e^{\mu t} \quad , \quad \int_0^t dN e^{\mu t} \le \int_0^t A e^{\mu t}\, dt$$

$$N(t)\, e^{\mu t} - N(0) \le \frac{A}{\mu}[\, e^{\mu t} - 1]$$

$$\le \frac{A}{\mu} e^{\mu t}$$

$$\Rightarrow \quad N(t) \le N(0)e^{-\mu t} + \frac{A}{\mu} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Such that all $t \ge 0$, from equation (8) ,we get

$$N(t) \le N(0)e^{-\mu t} + \frac{A}{\mu} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

If $S^* + I^* + R^*$ is explained as a D Limit point of a sector in R_t^3 , then there is a sub-sequence denoted by

$$t_i \to \infty \quad such\ that$$

$$\lim_{i \to \infty} \big(S(ti), I(ti), \ R(ti)\big) = (S^*, I^*, R^*).$$

Hence, $\lim_{i \to \infty}\big(N(ti)\big) = N^* = S^* + I^* + R^*$ From equation (6), evaluate for $t = ti$ and entering to the limit $i \to \infty$, we get that $N \leq \frac{A}{\mu}$ *and hence* $(S^*, I^*, R^*) \in D$, By lemma3.2.1, for any initial point, $(S0, I0, R0) \in R^3_+$, the direction lies in D. Thus, in D the basic model (1) is both mathematically and epidemiologically deep recommend. Hence, it is sufficient to study the dynamics of the model in D

3.3, Basic Reproduction Number

Because this quantity can indicate whether a disease will continue in a community or eventually die out, epidemiologists have always been interested in determining the fundamental reproduction number of an originating disease represented by R_0. The most significant number in the epidemiology of infectious diseases is this parameter. The average number of new cases (infectives) caused by a single infective is its definition.
In this instance, the lack of sick people joining the population determines both the stability of the DFE and the existence of the endemic equilibrium of the model. We possess:

$$(S, I, R, E_n = \frac{A}{\mu}, 0, 0, 0)$$

$$Hence, the\ disease\ free\ equilibrium\ (DFE)\ of\ the\ model(1) is\ given\ by$$
$$\in_{0=} (S^*, I^*, R^*, E_n^*) =$$
$\left(\frac{A}{\mu}, 0, 0, 0\right)$. *we now compute the basic reproduction number* R_0 *of the model*(1) *and* by the Van den Driessche and Watmough [40], the basic reproduction number $R0$ of the model is computby using the Next Generation Matrix Method. we derived R0 :

$$R_0 = \frac{\in \mu v \lambda + \theta A \rho}{\mu v(\alpha + \mu + \varphi)} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (7)$$

Each infectious agent will create fewer than one if $R_0 < 1$, and the disease will eventually die out when the DFE is stable. Since the DFE is unstable, the sickness will persist if $R_0 > 1$ since each infectious will, on average, produce several new infectious agents. Stated differently, there is going to be a pandemic. If R_0 can be found, it will be simple to identify the transmission parameters that will cause R_0 to be more than or less than 1, and control measures can be created with effectiveness.

3.4 Analysis of Steady States

3.4.1 Disease-Free Equilibrium (DFE): The stability analysis of a model (1) is very important, that allows to form the behavior of the model and the disease-free equilibrium is obtained by putting the system to be equal to Zero and solving. The disease free equilibrium (DFE) of the model (1) is given by:

$$\varepsilon_0 = (S^*, I^*, R^*, E_n{}^*) = \left(\frac{A}{\mu}, 0,0,0\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

The linear stability of ε_0 is determined by applying the next-generation operator technique [26] on the system and the reproduction number is obtained as follows:

$$R_0 = \frac{VA\sqrt{\mu b}}{2k\mu\sqrt{\mu b(\mu+\alpha+\varphi}} + \frac{\sqrt{v^2A^2\mu b + 4k^2\pi\mu^2\rho(\mu+\alpha+\varphi)}}{2k\mu\sqrt{\mu b(\mu+\alpha+\varphi)}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (9)$$

Theorem 1 *The disease free equilibrium of the model* 1, *given by* R0 , *is locally asymptotically Stable if* R0 < 1, *and unstable if* R0 > 1.

Proof: By Jacobin matrix of the model evaluated at the disease-free equilibrium given by: Now it is enough to find the eigen values of the Matrix $J\left(\frac{A}{\mu}, 0,0,0\right)$. Let r_i , i = 1, 2, 3, 4 be the eigen values. We have:

$$\mathbf{D}\text{et}\left(J\left(\frac{A}{\mu}, 0,0,0\right) - r_i\right)$$

$$= det\begin{pmatrix} -\mu - r & -\varepsilon\lambda & \delta & \frac{-\rho A}{\mu} \\ 0 & -(\alpha+\mu+\varphi) - \varepsilon\lambda - r & 0 & \frac{\rho A}{\mu} \\ 0 & \alpha & -\mu-\delta-r & 0 \\ 0 & \theta & 0 & -v-r \end{pmatrix} = 0 \ldots\ldots (10)$$

The Characteristic equation of the matrix (10) is:

$$r^4 + k_1 r^3 + k_2 r^2 + k_3 r + k_4 = 0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (11)$$

Where $k_1 = \alpha - \varepsilon\lambda + 3\mu + v + \delta + \varphi$, $k_2 = v(\alpha+\mu+\varphi)(P - R_0)$

$$k_3 = v(2\mu+\delta)(\alpha+\mu+\varphi)(Q - R_0) \text{ , } k_4 = \mu v(\mu+\delta)(\alpha+\mu+\varphi)(1 - R_0)$$

With $P = \frac{3\mu(\mu+v)+\delta(2\mu+v)-\varepsilon\lambda(2\mu+\delta)+(\alpha+\varphi)(2\mu+v+\delta)}{v(\alpha+\mu+\varphi)}$

$$Q = \frac{2(\mu+\delta)(\alpha\mu(\mu+2v)+\alpha\delta(\mu+v)+\mu(\mu^2+3\mu v+\mu\delta+2v\delta-\varepsilon\lambda(\mu+\delta))+G_g}{v(\alpha+\mu+\varphi)}$$

$$G_g = (\mu(\mu+2v) + (\mu+v)\delta)\varphi) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (12)$$

Thus, when *R*0 < 1 provide that *R*0 < *P* and *R*0 < *Q*, the disease-free equilibrium is locally and asymptotically stable, otherwise it is unstable. The requirement of the real and positive Eigen values stability is clearly satisfied by *r*. Now, for the roots of the characteristic equation 10 by which the eigenvalues are obtained, using the Routh-Hurwitz stability criterion and We have :
• all the coefficients *K*1, *K2*,K3, *K4* > 0, that is, are positive.

• for the eigen values to have real negative parts,k_1k_2-k_3, $k_3k_2 - k_1k_4$ *and* $k_1k_2k_3 - {k_3}^2 - {k_1}^2k_4$
are be positive. Therefore, by the Routh-Hurwitz criterion for stability, we conclude that the disease free equilibrium is locally asymptotically stable whenever $R0 < 1$.

Theorem 2 *For* K = 0, *the system has no endemic equilibrium and* for model *exhibits two conditions: a transcritical bifurcation if Rp* ≥ 1 *and a backward bifurcation If* Rp < 1.

.

3.5. Sensitivity Analysis of Cryptosporidiosis Model

For investigate the model (1) robustness, due to uncertainties associated with the estimation of certain parameter values, it is important and useful to carry out a sensitivity analysis to investigate how sensitive the basic reproduction number is with respect to these parameters [29].To see this analysis, we compute the normalized forward sensitivity index of the reproduction number 10 with respect to these parameters [26, 36]. The normalized forward sensitivity index of a variable f, that depends differentially on a parameter *n* is defined as:

$$r^f = \frac{df}{dn} \times \frac{n}{f} \qquad \text{.. (13)}$$

3.5.1. Indices Sensitivity of *R*0

We can derive the sensitivity of *R*0 (10) based on the following parameters:

$${r_A}^f := \frac{dR_O}{dA} \times \frac{A}{R_o} = \frac{\theta A_\rho}{\epsilon\, \lambda\, \mu v + \theta A_\rho} = {r_\theta}^f = {r_\rho}^f,$$

$${r_\epsilon}^f := \frac{\epsilon \mu v\, \lambda}{\epsilon\, \lambda\, \mu v + \theta A \rho} = {r_l}^f\, \lambda, \quad {r_\alpha}^f := \frac{\alpha}{\alpha+\mu+\varphi}, \qquad {r_\varphi}^f := \frac{\varphi}{\alpha+\mu+\varphi},$$

$${r_v}^f := -\frac{\theta A_\rho}{\epsilon\, \lambda\, \mu v + \theta A_\rho}, \qquad \text{.. (14)}$$

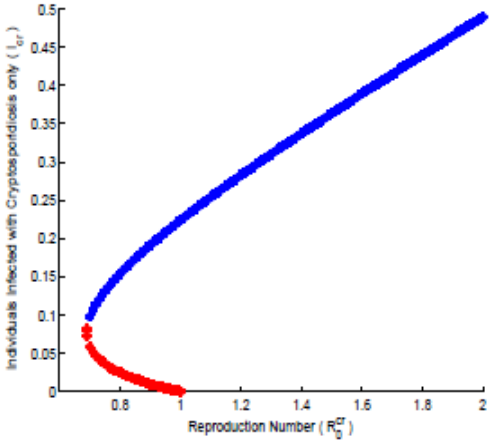
$${r_\mu}^f := \frac{\theta A \mu \rho}{\epsilon v\, \lambda\, \mu^2 + \theta A \mu \rho} - \frac{\mu}{\alpha+\mu+\varphi}$$

Sensitivity analysis of ***R*****0**

Parameters	Descriptions	Sensitivity
μ	Natural of death rate	−1.8061
v	Rate of Crypto leaves the environment	−0.9999

A	Human Recruitment	0.9996
θ	Average contribution of Crypto infected people to the env't	0.9996
ρ	Modification parameter due to environmental treatment	0.9996
α	Recovery rate from the disease	−0.1660
ψ	Crypto related death	−0.0277
$\in$	Human contact rate	0.0001
Λ	Transmission Probability	0.0001

Using parameter values from the above parameters are chosen for illustrative purpose only, and may not necessarily be realistic in terms of epidemiological interpretations, we calculate the sensitivity indices of $R0$ based on the following parameters μ, A, θ, ρ, v, $\in$, λ, α,*and* ψ, Since it is not epidemiologically reasonable to increase the mortality rate as a means of controlling the disease [29, 26].the most sensitive to least. The most sensitive parameter is proportion of the natural death rate $r_{\mu}{}^{f} = -1.8061$. While the least of the sensitivity parameters is the Transmission probability $r_{\lambda}{}^{f} = -0.0001$. An increase (or decrease) in the natural death rate of Humans μ by 10% decreases (or increases) the $R0$ by 18.06%. Similarly increasing (or decreasing) the rate at which Crypto leaves the environment v by 10% decreases (or increases) the $R0$ by 9.999%. In the other words, increasing (or decreasing) the Human Recruitment rate A, Average contribution of each Crypto infected individuals into the environment θ and the modification parameter due to environmental treatment ρ by 10% each would increase (or decrease) $R0$ by 9.996%.From the sensitivity analysis, it is clear that control efforts should be targeted towards the rate at which Crypto leaves the environment *(v)* through treatment of water e.g, water, plants and environment. Since it is not epidemiologically reasonable to increase the mortality rate as a means of controlling the disease [29, 26].we can show the above data by using graphs which simulation of model (1) showing the bifurcation phenomena of Cryptosporidiosis.



4, MODIFIED Cryptosporidiosis model

In this section, we modified the Cryptosporidiosis model (1) to include Susceptible individuals with weakened immune system in order to investigate the effect of such individuals in the disease dynamics, we sub-divide the total human population at time t , denoted by N, into the following sub-populations of two susceptible individuals; susceptible individuals with strong immunity $S1$, susceptible individuals with weakened immunity $S2$, infected strong immune individuals $I1$, infected weakened immune individuals $I2$, those who are treated T, the recovered R and together with the environmental contamination En. We chose a mass action form of infection here in order to reduce the model analysis complexity. So we have,
$N = S1 + S2 + I1 + I2 + T + R$, and we have the following corresponding system of differential equations:

$$\frac{dS_1}{dt} = A(1-a) + \delta kR - b\beta_m{}^* S_1 - \mu S_1$$

$$\frac{dS_2}{dt} = aA + (1-k)\delta R - \beta_m{}^* S_2 - \mu S_2$$

$$\frac{dI_1}{dt} = b\beta_m{}^* S_1 - (\alpha + \mu + \varphi) I_1$$

$$\frac{dI_2}{dt} = \beta_m{}^* S_2 - (\delta + \mu + \varphi) I_2 \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (15)$$

$$\frac{dT}{dt} = \delta I_2 - (\eta + \mu) T$$

$$\frac{dR}{dt} = \alpha I_1 + \eta \mathrm{T} - (\delta + \mu) R$$

$$\frac{dE_n}{dt} = (I_1 + I_2)\theta - vE_n$$

Where $\beta_m{}^* = \lambda\varepsilon(I_1 + I_2) + \rho E_n$ …….. (16)

4.1, BASIC Properties of the Cryptosporidiosis Modified model

4.1.1 Positivity Analysis

From the above system of differential equations (15) $\lim_{t\to\infty} N(t) \leq \frac{A}{\mu}$ or

. By the dynamics explanation in equation (15) the region $\emptyset$ defined by:

$\emptyset = \{(S_1, S_2, I_1, I_2, T, R)\varepsilon R_+{}^6 \mid S_1 + S_2 + I_1 + I_2 + T + R \leq \frac{A}{\mu}\}$ …….. (17)

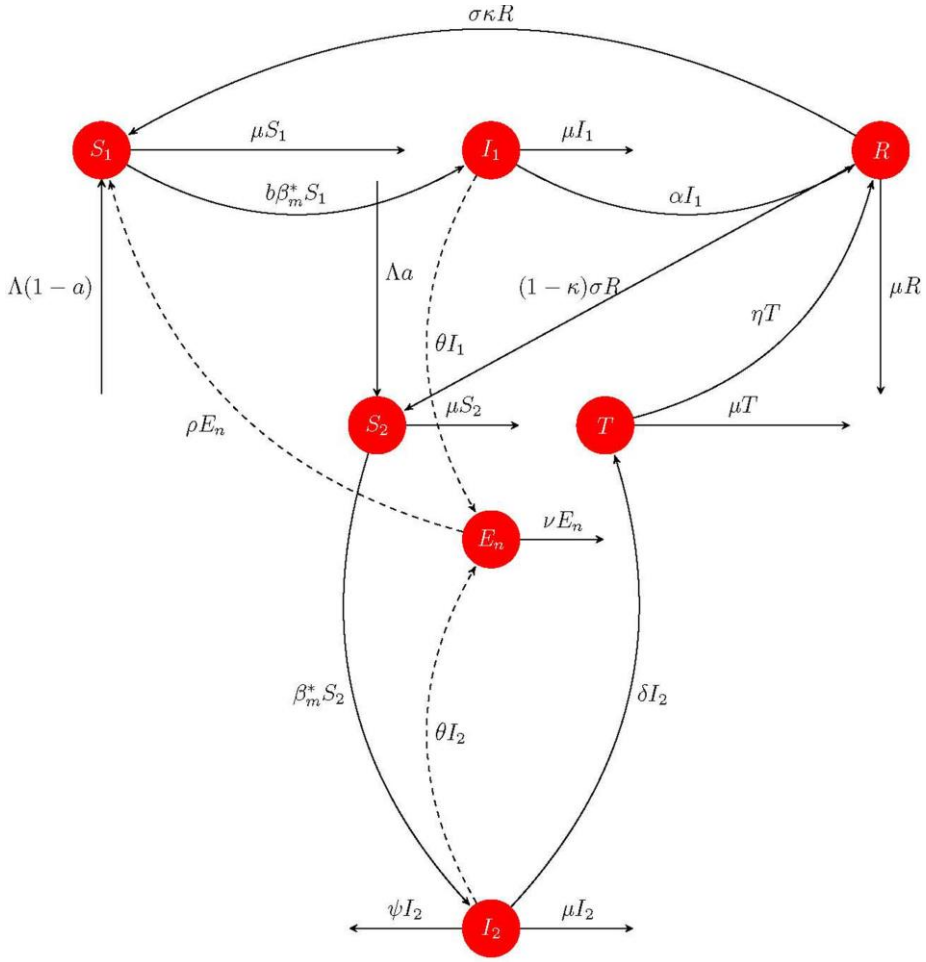


Figure 2 showing the modified Cryptosporidiosis model

By lemmas (3.2.1) and (3.2.2), we conclude that the model (15) is positively invariant and for any initial starting point, *(S*10, *S*20, *I*10, *I*20, *T*0, *R0)* $\in R_t^*$, the trajectory lies in $\emptyset$ the basic model (16) is both mathematically and epidemiologically well posed. Hence, it is sufficient to study the dynamics of the model in $\emptyset$.By the Van den Driessche and Watmough [40], the basic reproduction number *R*0 of the modified Cryptosporidiosis model is given by:

$$R_0 = \frac{A\left(\epsilon V\,\lambda + \rho\theta\right)(b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi)-b(\delta+\mu+\varphi))}{\mu v(\alpha+\mu+\varphi)(\delta+\mu+\varphi)} \quad \ldots\ldots\ldots\ldots\ldots\ldots (18)$$

Modified Cryptosporidiosis Model Notations

Parameters	**Definition**	**Dimension**
*S*1	number of susceptible individuals with strong immunity……	*Humans*
*S*2	number of susceptible individuals with weakened immune system. .	*Humans*

$I1$ number of infected strong immune individuals……………………. *Humans*

$I2$ number of infected individuals with weakened immune system …. *Humans*

T number of treated infected individuals with weakened immune system… *Humans*

R number of Recovered individuals. …………………………………….. *Humans*

En Environmental contamination class…………………………………… *Cont*

N total number of human population…………………………………… *Humans*

K rate of ingestion of Cryptosporidiosis disease………………………… $time^{-1}$

a proportion of the Humans with weakened immunity………………… *Humans'*

b modification parameter of the infection rate………………………… $time^{-1}$

A Human recruitment rate………………………………………………. *Humans'* $\times\ time$

$\in$ Human contact rate…………………………………………………. $(Humans \times time)^{-\frac{1}{2}}$

$\beta_m{}^*$ infection of force………………………………………………. $time^{-1}$

Λ transmission probability…………………………………… $(Humans \times time)^{-\frac{1}{2}}$

α recovery rate from the disease……………………………… $time^{-1}$

δ treatment rate of the infected individuals with weakened immune system……….. $time^{-1}$

η recovery rate of the treated individuals with weakened immune system from the disease….. $time^{-1}$

θ Average contribution of each cryptosporidiosis infected individual to the environment……. $time^{-1}$

σ Immunity waning rate………………………………………. $time^{-1}$

ρ modification parameter due to environmental treatment…………….. $(time \times cont)^{-1}$

μ Human mortality rate. ………………………………………………………. $time^{-1}$

ψ Cryptosporidiosis related death……………………………………. $time^{-1}$

v rate at which crypto's leaves the environment… …. $time^{-1}$

4.2, Analysis of Steady States of the Modified Model

4.2.1, Disease-Free Equilibrium of stability

Disease-free equilibrium modified model (15) is given by:

$$\varepsilon_1 = (S_1{}^0, S_2{}^0, I_1{}^0, I_2{}^0, T^0, R^0, E_N{}^0)$$

$$= \left(\frac{A(1-a)}{\mu}, \frac{aA}{\mu}, 0,0,0,0,0\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{(19)}$$

4.2.2, Local Stability of the Diseases-Free Equilibrium

Theorem 4.1. Disease-free equilibrium point ε_0, is locally asymptotically stable for $R0 < 1$ and unstable for $R0 > 1$.

Proof. Assuming Jacobian matrix of modified cryptosporidiosis model at the DFE we have that:

Let a Jacobian be defined by:

$$J = \begin{pmatrix} J_{11}J_{12}J_{13}J_{14}J_{15}J_{16}J_{17} \\ J_{21}J_{22}J_{23}J_{24}J_{25}J_{26}J_{27} \\ J_{31}J_{32}J_{33}J_{34}J_{35}J_{36}J_{37} \\ J_{41}J_{42}J_{43}J_{44}J_{45}J_{46}J_{47} \\ J_{51}J_{52}J_{53}J_{54}J_{55}J_{56}J_{57} \\ J_{61}J_{62}J_{63}J_{64}J_{65}J_{66}J_{67} \\ J_{71}J_{72}J_{73}J_{74}J_{75}J_{76}J_{77} \end{pmatrix}$$

Thus, the Jacobian matrix of the model (15) evaluated at DFE is given as:

$$J_{\varepsilon_0} = \begin{pmatrix} J_{11} & 0 & J_{13} & J_{14} & 0 & J_{16} & J_{17} \\ 0 & J_{22} & J_{23} & J_{24} & 0 & J_{26} & J_{27} \\ 0 & 0 & J_{33} & J_{34} & 0 & 0 & J_{37} \\ 0 & 0 & J_{43} & J_{44} & 0 & 0 & J_{47} \\ 0 & 0 & 0 & J_{54} & J_{55} & 0 & 0 \\ 0 & 0 & J_{63} & 0 & J_{65} & J_{66} & 0 \\ 0 & 0 & J_{73} & J_{74} & 0 & 0 & J_{77} \end{pmatrix} \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{(20)}$$

.

Where, $J_{11} = -\mu$, $J_{13} = -(1-a)b\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{14} = -(1-a)b\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{16} = \delta k$, $J_{17} = -(1-a)b\rho\frac{A}{\mu}$, $J_{22} = -\mu$, $J_{23} = -a\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{24} = -a\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{26} = (1-k)\delta$, $J_{27} = -a\rho\frac{A}{\mu}$, $J_{33} = -(\alpha+\mu+\varphi)+(1-a)b\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{34} = (1-a)b\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{37} = (1-a)b\rho\frac{A}{\mu}$, $J_{43} = a\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{44} = -(\delta+\mu+$

$\varphi)a\,\lambda\,\epsilon\frac{A}{\mu}$, $J_{47}=a\rho\frac{A}{\mu}$, $J_{54}=\rho$, $J_{55}=-(\eta+\mu)$, $J_{63}=\alpha$, $J_{65}=\eta$, $J_{66}=-(\mu+\delta)$, $J_{73=}\theta$, $J_{74}=\theta$, $J_{77}=-v$

…… .(21)

From the above Jacobian matrix we see the first and the second columns contain only the diagonal terms which form the two negative eigen values (*J*11 and *J*22). To obtain the other eigen values, the above matrix can be reduced to a sub-matrix (21). $J_{\varepsilon_{00}}$ is formed by deleting the first and the second rows and columns of the matrix .

4.3. Sensitivity Analysis of the Modified Model

From model (1) we also check for the robustness of model (15), due to uncertainties associated with the estimation of certain parameter values that are included in the model modification.

4.3.1. Indices Sensitivity of *R*0

We derive the sensitivity of *R*0 above corresponding to the following parameters:

$$r_A{}^f := \frac{dR_0}{dA}\times\frac{A}{R_0}=1, \qquad r_\theta{}^f := \frac{dR_0}{d\theta}\times\frac{\theta}{R_0}=\frac{\rho\theta}{\epsilon\,\lambda\,v+\rho\theta}$$

$$r_\epsilon{}^f := \frac{dR_0}{d\epsilon}\times\frac{\epsilon}{R_0}=\frac{\epsilon v\,\lambda}{\epsilon v\,\lambda+\rho\theta}, \quad r_v{}^f := \frac{dR_0}{dv}\times\frac{v}{R_0}=\frac{-\rho\theta}{\epsilon v\,\lambda+\rho\theta},$$

$$r_\lambda{}^f := \frac{dR_0}{d\lambda}\times\frac{\lambda}{R_0}=\frac{\epsilon v\,\lambda}{\epsilon v\,\lambda+\rho\theta}, \qquad r_\rho{}^f := \frac{dR_0}{d\rho}\times\frac{\rho}{R_0}=\frac{\rho\theta}{\epsilon v\,\lambda+\rho\theta},$$

$$r_a{}^f := \frac{dR_0}{da}\times\frac{a}{R_0}=\frac{a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi))}{b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi))},$$

$$r_b{}^f := \frac{dR_0}{db}\times\frac{b}{R_0}=\frac{b(\delta+\mu+\varphi-a(\delta+\mu+\varphi))}{b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi))},$$

$$r_b{}^f := \frac{dR_0}{db}\times\frac{b}{R_0}=\frac{b(\delta+\mu+\varphi-a(\delta+\mu+\varphi))}{b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi))},$$

$$r_\alpha{}^f := \frac{dR_0}{d\alpha}\times\frac{\alpha}{R_0}=\frac{\alpha(a-1)b(\delta+\mu+\varphi)}{(\alpha+\mu+\varphi)b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi))}, \quad , \quad r_\delta{}^f := \frac{dR_0}{d\delta}\times\frac{\delta}{R_0}=\frac{a\delta(\alpha+\mu+\varphi)}{(\delta+\mu+\varphi)b(\delta+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi)))},$$

$$r_\varphi{}^f := \frac{dR_0}{d\varphi}\times\frac{\varphi}{R_0}=\frac{-(b(\delta+\mu+\varphi)^2+a(\alpha^2+2\alpha(\mu+\varphi)+(\mu+\varphi)^2-b(\delta+\mu+\varphi)^2))\varphi}{(\alpha+\mu+\varphi)(\delta+\mu+\varphi)(b(\delta+\mu+\varphi-b(\delta+\mu+\varphi)))},$$

$$r_\mu{}^f := \frac{-\mu}{\alpha+\mu+\varphi} + \frac{-\mu}{n} - \frac{a\mu(b-1)-b}{b(\alpha+\mu+\varphi)+a(\alpha+\mu+\varphi-b(\delta+\mu+\varphi)} - 1,$$

$$r_{\varphi_0}{}^f = r_\eta{}^f = r_k{}^f = 0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (22)$$

We have some values of parameters below and calculated the sensitivity of $R0$ with respect to such parameters are arranged in the order of the most sensitive to the least. The most sensitive parameter here is the natural death rate $r_\mu{}^f = -1.8650$. Increasing (or decreasing) the natural death rate of Humans μ by 10% decreases (or increases) the $R0$ by 18.65%. Similarly increasing (or decreasing) the rate at which Crypto leaves the environment v by 10% decreases (or increases) the $R0$ by 9.901%. In the same case, increasing (or decreasing) the Human Recruitment rate A .Average contribution of each Crypto infected individuals into the environment θ and the modification parameter due to environmental treatment ρ by 10% each would increase (or decrease) $R0$ by 9.9%. Also, increasing (decreasing) 0f the Infection rate modification parameter b and Proportion of Humans with weakened immunity a by 10% each would increase (or decrease) the $R0$ by 5.467% and 2.189% respectively.

Sensitivity analysis of $R0$

Parameters	**Descriptions**	**Sensitivity**
μ	Natural death rate ……..	−1.8650
A	Human Recruitment ……..	1.0000
v	Rate of Crypto leaves the environment……	−0.9901
θ	Average contribution of Crypto infected …..... persons to the environment	0.9900
ρ	Modification parameter due to environmental treatment ..	0.9900
b	Infection rate modification parameter ……	0.5467
a	Proportion of Humans with weakened immunity ……	0.2189
α	Recovery rate from the disease ……	−0.0908
ψ	Crypto related death …….	−0.0297
δ	Treatment rate of infected persons with ……. weakened immunity	−0.0146
ϵ	Human contact rate ……..	0.0099
λ	Transmission Probability …… leaves	0.0099

5. Analysis of optimal control

In this section, we apply optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the disease. We incorporate time dependent controls into the model (15) to determine the optimal strategy for controlling the disease. Hence we have,

$$\begin{cases} \frac{dS_1}{dt} = A(1-a)U_1 + \delta kR - (1-U_2)b\beta_m{}^* S_1 - \mu S_1 \\ \frac{dS_2}{dt} = aU_1 A + (1-k)\delta R - (1-U_2)\beta_m{}^* S_2 - \mu S_2 \\ \frac{dI_1}{dt} = (1-U_2)b\beta_m{}^* S_1 - (U_3 m\alpha + \mu + \varphi)I_1 \\ \frac{dI_2}{dt} = (1-U_2)\beta_m{}^* S_2 - (U_3\delta + \mu + \varphi)I_2 \\ \frac{dT}{dt} = \delta I_2 - (\eta + \mu)T \\ \frac{dR}{dt} = U_3 m\alpha I_1 + \eta T - (\delta + \mu)R \\ \frac{dE_n}{dt} = (1-U_2)(I_1 - I_2)\theta - vE_n \end{cases} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (23)$$

For this, we consider the objective functional:

$$\mathrm{H}(U_1, U_2, U_3) = \int_0^{t_f} (h_1 I_1 + h_2 I_2 + h_3 E_n + \beta_1 {U_1}^2 + \beta_2 {U_2}^2 + \beta_3 {U_3}^2) dA \ldots\ldots\ldots\ldots\ldots (24)$$

The control functions, $U_1(t)$, $U_2(t) and U_3(t)$ are bounded, Lebesgue integrable functions.we choice the control functions $U_1(t)$ and $U_2(t)$represents the efforts on preventing infection. The control efforts on treatment of infected individuals $U_3(t)$ satisfies $0 \leq U_3 \leq g_2$, where g_2 is the drug efficacy use for treatment of infected individuals. Where t_f*the final time and the coefficients of the objective function is* $h_1, h_2, h_3, \beta_1, \beta_2 and \beta_3$ are the balancing cost factors due to scales and We seek to find an optimal control, ${U_1}^*, {U_2}^* and {U_3}^*, such\ that$

$$\mathrm{H}({U_1}^*, {U_2}^*, {U_3}^*) = \min\{J(U_1, U_2, U_3): U_1, U_2, U_3 \epsilon U_0 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (25)$$

Where $U_0 = \{(U_1, U_2, U_3 : U_1, U_2, U_3\ are\ measurable\ with : 0 \leq U_1 \leq 1, 0 \leq U_2 \leq 1\ and\ 0 \leq U_3 \leq g_2\ for\ t\epsilon[0, t_f]\}$ is the control set.

The necessary conditions of an optimal solution must satisfy come from the Pontryaginet al. [24] Maximum Principle. This principle converts (24)–(26) into a problem of minimizing point wise a Hamiltonian

H_a, with respect to $U_1, U_2, U_3, U_4\ and\ U_5$.

$$\begin{aligned} H_a = {} & h_1 I_1 + h_2 I_2 + h_3 E_n + \beta_1 {u_1}^2 + \beta_2 {U_2}^2 + \beta_3 {U_3}^2 \\ & + \mathrm{N}S_1\{A(1-a)U_1 + \delta kR - (1-U_2)b\beta_m{}^* S_1 - \mu S_1\} \\ & + \mathrm{N}S_2\{aU_1 A + (1-k)\delta R - (1-U_2)\beta_m{}^* S_2 - \mu S_2\} \\ & + \mathrm{N}I_1\{(1-U_2)b\beta_m{}^* S_1 - (U_3 m\alpha + \mu + \varphi)I_1\} \\ & + \mathrm{N}I_2\{(1-U_2)\beta_m{}^* S_2 - (U_3\delta + \mu + \varphi)I_2\} \\ & + \mathrm{NT}\{\delta I_2 - (\eta + \mu)T\} \end{aligned} \quad (26)$$

+ NR $\{U_3 m\alpha I_1 + \eta$ T-$(\delta + \mu)R\}$

+ NE_n $\{(1 - U_2)(I_1 + I_2)\theta - vE_n\}$

Where

N$S_1, NS_2, NI_1, NI_2, NT, NR$ *and* NE_n *ar*e the adjoint variables and the system of equations are found by taking the appropriate partial derivatives of the Hamiltonian (26) with respect to the associated adjoint variable.

Theorem. Given optimal control $U_1^*, U_2^*, U_3^*$and solutions $S_1, S_2, I_1, I_2 T, R, E_n$ *of corresponding* state system (23)-(24) that minimize J (u_1, U_2, U_3) *over* U. *then there exists adjoint variables*, then there exists adjoint variables N$S_1, NS_2, NI_1, NI_2, NT, NR$ *and* NE_n satisfying:

$$\frac{-dN_i}{dt} = \frac{dH_a}{di} \quad \text{..... (27)}$$

Where

i = $S_1, S_2, I_1, I_2, T, R, E_n$ *and with transversality conditions*

$$NS_1(t_f) = NS_2(t_f) = NI_1(t_f) = NI_2(t_f) = NT(t_f) = \text{NR}\,(t_f) = NE_n(t_f) = 0$$

And

$$U_1^* = \min\{1, \max(0, \frac{aANS_2 - (1-a)ANS_1}{2\beta_1})\}$$

$$U_2^* = \min\{1, \max(0, \frac{(NI_1 - NS_1)b\beta_m^* S_1 + (NI_2 - NS_2)\beta_m^* S_2 + \theta NE_n(I_1 + I_2)}{2\beta_2})\} \text{.....(28)}$$

$$U_3^* = \min\{1, \max(0, \frac{\alpha n(NI_1 - NR)I_1 + \delta(NI_2 - NT)}{2\beta_3})\}$$

The existence of an optimal control due to the convexity of the integrand of *J* with respect to U_1, U_2 and $U_3 are$ given Rishel [17] and boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function, evaluated at the optimal control.

By standard control arguments involving the bounds on the controls, we conclude

$$U_i^* = \begin{cases} 0, if\ \exists_i \leq 0 \\ \exists_i, if\ 0 < \exists_i < 1 \\ 1, if\ \exists_i \geq 1 \end{cases}$$

Where i ε 1,2,3 *and* $\exists_1 = \frac{aANS_2 - (1-a)ANS_1}{2\beta_1}$

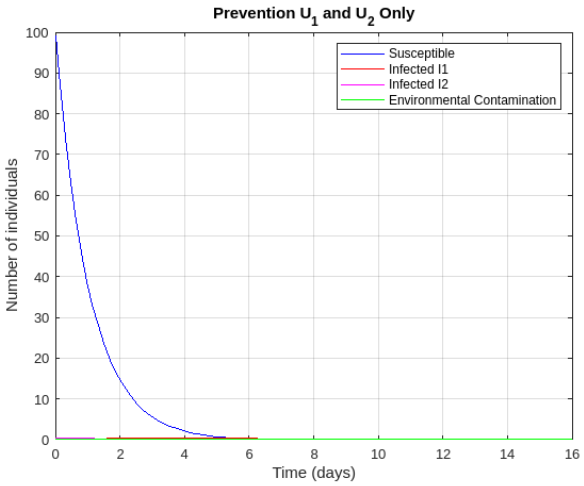
$$\exists_2 = \frac{(NI_1 - NI_2)b\beta_m{}^* S_1 + (NI_2 - NS_2)\beta_m{}^* S_2 + \theta N E_n(I_1 + I_2)}{2\beta_2} \quad , \quad \exists_3 = \frac{\alpha m(NI_1 - NR)I_1 + \delta(NI_2 - NT)I_2}{2\beta_3}$$

5.1. Numerical results and discussions

In this section, we investigate numerically the result of the optimal control strategies listed below on the spread of cryptosporidiosis infection in a population. The optimal control solution is obtained by solving the optimality system, which consists of the adjoint system. An iterative scheme is used for solving the optimality system. We start by solving the state equations with a guess for the controls over the simulated time using the fourth order Runge-Kutta scheme. Because of the transversality conditions (27), the adjoint equations are solved by the backward fourth order Runge-Kutta scheme using the current iterations solutions of the state equations. This process is repeated and the iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iteration.

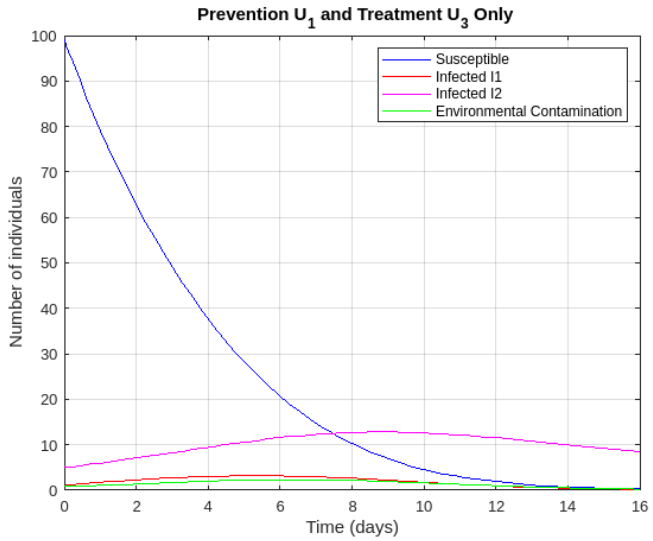
5.1.1. Prevention U_1 and U_2 only

The prevention controls U_1 and U_2 are used to optimize the objective function H while setting the other interventions (U_3) to zero. We observed in Figure below that due to the control strategies, the number of infected individuals I_1 and infected individuals with weak immunity I_2 decreases significantly and while the environmental contamination *En* show significant decrease too.



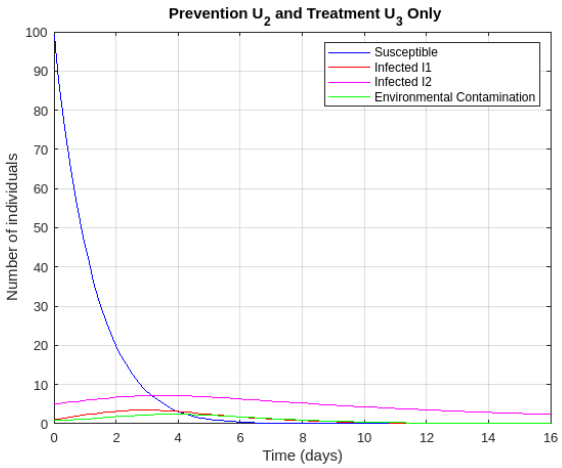
5.1.2. Prevention U_1 and treatment U_3 only

The prevention control U_1 and treatment control U_3 are used to optimize the objective function H while setting the other interventions (U_2) to zero. We observed in Figure belowthat due to the control strategies, the number of infected individuals I_1 and infected individuals with weak immunity I_2 shows no significant difference between cases with control and cases without control



5.1.3. Prevention U_2 and U_3 only

The prevention control U_2 and treatment control U_3 are used to optimize the objective function H while setting the other interventions (U_1) to zero. We observed in Figure below that due to the control strategies, the number of infected individuals I_1 and infected individuals with weak immunity I_2 decreases significantly and while the environmental contamination En show signifcant decrease too..
;

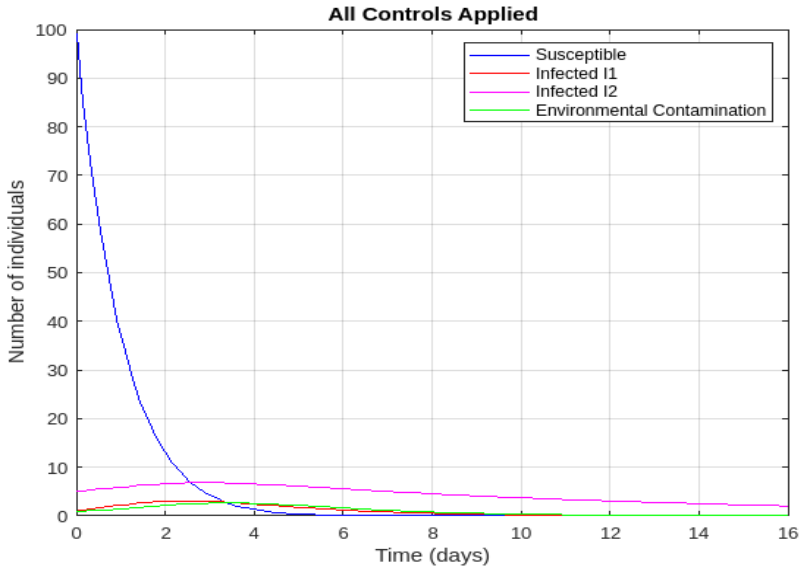


5.1.4. Preventions with treatment (U_1, U_2, U_3)

All control mechanism (U_1, U_2, U_3) are used to optimize the objective function H. We observed in Figure below that due to the control strategies, the number of infected individuals I_1 and

infected individuals with weak immunity I_2 decreases significantly .

.



5.2. Discussion

Having the study of behavior of the mathematical model for the transmission and spread of cryptosporidiosis disease in the long-run through numerical simulations, it was shown the most influential, sensitive and epidemiologically reasonable parameters in controlling the crypto disease spread are the rate at which crypto leaves the environment, the modification parameter due to environmental treatment and the average contribution of crypto infected persons to the environment which confirmed that of the sensitivity analysis.

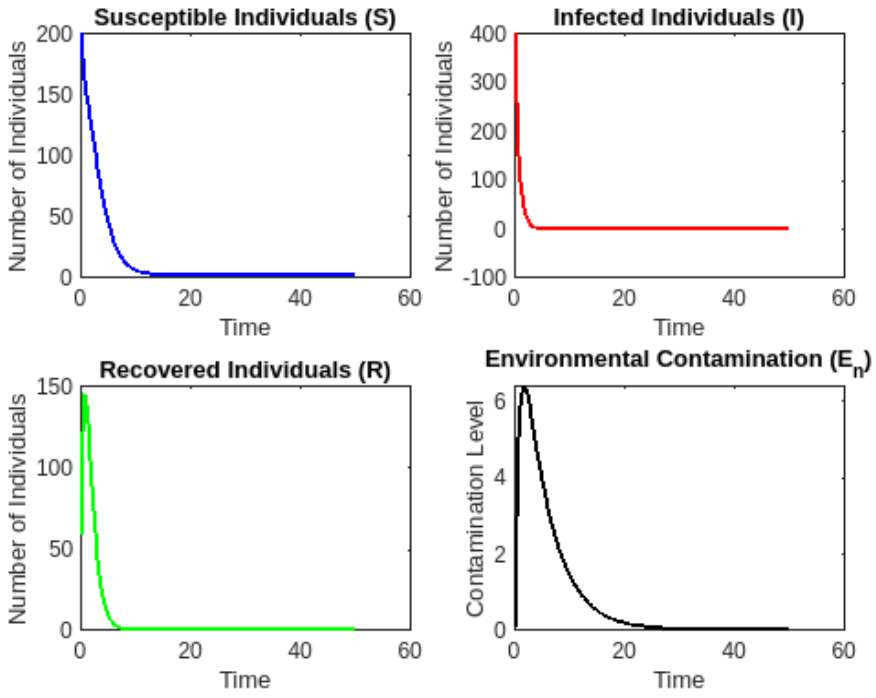
From above figures it is shown that, increase the rate of crypto which leaves the environment [v] and the recovery rate of humans [α] respectively, decreases the rate at which individuals get infected with time and as a result of decreasesR_o.And others shows a decrease in the infected class as a result of decrease in the modification parameter due to environmental treatment [ρ] and reduction in the average contribution of crypto infected persons to the environment [θ] respectively, which also led to a reduction in R_o. also the varying initial values of the state parameters of the infected humans with normal and weakened immunity respectively. As a results of these R_o decreases. Simulations of the cryptosporidiosis model showing the effect of crypto prevention and treatment only on transmission.

6. Conclusion

6.1. Conclusions

We derived and analyzed a deterministic model (1) together with its modified version (15) that includes Susceptible and Infected individuals with weakened immune system and Treatment for the infected persons with weakened immune system for the transmission of Cryptosporidiosis disease. We analyzed the two models for the existence of diseases-free and endemic equilibrium points. We also carried out the sensitivity analysis for the reproduction

numbers ($R0$) and$R0$ for the models (1) and (15) respectively. Analyzing the models so as to gain insights into the qualitative dynamics, the following results listed below were obtained.



Graph Analysis

1. **Susceptible (S)**: This plot shows the number of susceptible individuals over time. Look for how the population of susceptible individuals decreases as more people get infected and eventually recover.
2. **Infected (I)**: This plot shows the number of infected individuals. Observe the peak of infections and how it evolves over time, which can indicate the spread dynamics of the disease.
3. **Recovered (R)**: This plot indicates the number of recovered individuals. It is expected to increase as infected individuals recover, and should eventually approach a stable value.
4. **Environmental Contamination (E_n)**: This plot shows the level of contamination in the environment. It is affected by the rate at which infected individuals contribute to the environment and the rate at which contamination is removed.

Initial Conditions and Parameters

You can experiment with different initial conditions and parameters to see how they affect the dynamics of the model. For instance, varying the contact rate ϵ, recovery rate α, or environmental parameters can provide insights into how these factors influence disease spread and control strategies.

OR

Step-by-Step Graph Analysis

1. **Susceptible Individuals (S)**:
    - **Expected Behavior**: Should decline over time as individuals become infected or recovered. If the recruitment rate is high, this decline might be slower.
    - **Graph Analysis**: Observe the trend and note the rate of decline.
2. **Infected Individuals (I)**:
    - **Expected Behavior**: Typically shows an initial rise, reaching a peak, and then a decline. The peak represents the outbreak.
    - **Graph Analysis**: Look for the peak point and how quickly the infection declines after the peak.
3. **Recovered Individuals (R)**:
    - **Expected Behavior**: Should increase over time as infected individuals recover. The increase rate should correlate with the recovery rate.
    - **Graph Analysis**: Analyze how this number grows and relates to the infected individuals.
4. **Environmental Contamination (En)**:
    - **Expected Behavior**: Depends on the contribution from infected individuals and the removal rate. It may rise and then stabilize.

Graph Analysis: Check how it changes over time and its relationship with the number of infected individual

6.2. Future Work

In the future work we can consider the following factors that may provide a better understanding of the disease transmission and control.

(a) **Stochastic Approach:** By reviewing all the analysis and compare the results obtained with the stochastic modeling approach will give us understanding of the analysis the choice of the control of the transmission and spread of the crypto disease.
(b) **Co-infection:** By this project we can see future work of include the modeling of cryptosporidiosis and HIV disease to further gain the impact of this opportunistic infection in HIV transmission dynamics.
(c) **Optimal control:** the crypto disease model transmission include use of water purifying material to treat water plants, awareness ,distribution of clean and treated water to the rural areas via water container and a possible treatment of infective people.
(d) **Susceptible class:** By described as a set of individuals who are not infecting but have risk of being infected by the disease.

6.3. Challenges

The challenges during the project are the followings:
(a) No work done on the mathematical modeling of Cryptosporidiosis disease transmission.

(b) Non-availability of parameter values to measurable.

6.4 Reference

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Appendix

MATH LAB CODE

```
functiondYdt = control_U1_U2(t, Y, params)
% Unpack parameters
beta = params.beta;
gamma = params.gamma;
   U1 = params.U1;
   U2 = params.U2;

% Unpack state variables
   S = Y(1);
   I1 = Y(2); % Infected individuals
   I2 = Y(3); % Infected individuals with weak immunity
E_n = Y(4); % Environmental contamination

% Total population
   N = S + I1 + I2;
```

```
% Define the differential equations with controls
dSdt = -beta * (S * I1 + S * I2) / N - U1 * S - U2 * S;
    dI1dt = beta * (S * I1 + S * I2) / N - gamma * I1 - U1 * I1;
    dI2dt = beta * (S * I2) / N - gamma * I2 - U2 * I2;
dE_ndt = U2 * I1 - E_n; % Example of how environmental control affects contamination

% Return the derivatives
dYdt = [dSdt; dI1dt; dI2dt; dE_ndt];
end

% Parameters
params = struct('beta', 0.3, 'gamma', 0.1, 'U1', 0.2, 'U2', 0.75);

% Initial conditions
S0 = 99;
I1_0 = 1;
I2_0 = 5;
E_n0 = 1;
Y0 = [S0; I1_0; I2_0; E_n0];

% Time span for the simulation
tspan = [0 16];

% Solve the differential equations
[t, Y] = ode45(@(t, Y) control_U1_U2(t, Y, params), tspan, Y0);

% Plot the results
figure;
plot(t, Y(:,1), 'b', 'DisplayName', 'Susceptible');
holdon;
plot(t, Y(:,2), 'r', 'DisplayName', 'Infected I1');
plot(t, Y(:,3), 'm', 'DisplayName', 'Infected I2');
plot(t, Y(:,4), 'g', 'DisplayName', 'Environmental Contamination');
xlabel('Time (days)');
ylabel('Number of individuals');
title('Prevention U_1 and U_2 Only');
legend;
gridon;


functiondYdt = control_U1_U3(t, Y, params)
% Unpack parameters
beta = params.beta;
gamma = params.gamma;
    U1 = params.U1;
```

```
    U3 = params.U3;

% Unpack state variables
    S = Y(1);
    I1 = Y(2);
    I2 = Y(3);
E_n = Y(4);

% Total population
    N = S + I1 + I2;

% Define the differential equations with controls
dSdt = -beta * (S * I1 + S * I2) / N - U1 * S;
    dI1dt = beta * (S * I1 + S * I2) / N - gamma * I1 - U3 * I1;
    dI2dt = beta * (S * I2) / N - gamma * I2;
dE_ndt = U3 * I1 - E_n; % Example of how treatment control affects environmental
contamination

% Return the derivatives
dYdt = [dSdt; dI1dt; dI2dt; dE_ndt];
end

% Parameters
params = struct('beta', 0.3, 'gamma', 0.1, 'U1', 0.2, 'U3', 0.75);

% Initial conditions
S0 = 99;
I1_0 = 1;
I2_0 = 5;
E_n0 = 1;
Y0 = [S0; I1_0; I2_0; E_n0];

% Time span for the simulation
tspan = [0 16];

% Solve the differential equations
[t, Y] = ode45(@(t, Y) control_U1_U3(t, Y, params), tspan, Y0);

% Plot the results
figure;
plot(t, Y(:,1), 'b', 'DisplayName', 'Susceptible');
holdon;
plot(t, Y(:,2), 'r', 'DisplayName', 'Infected I1');
plot(t, Y(:,3), 'm', 'DisplayName', 'Infected I2');
plot(t, Y(:,4), 'g', 'DisplayName', 'Environmental Contamination');
xlabel('Time (days)');
```

```
ylabel('Number of individuals');
title(' Prevention U_1 and Treatment U_3 Only');
legend;
gridon;


      functiondYdt = control_U2_U3(t, Y, params)
% Unpack parameters
beta = params.beta;
gamma = params.gamma;
   U2 = params.U2;
   U3 = params.U3;

% Unpack state variables
   S = Y(1);
   I1 = Y(2);
   I2 = Y(3);
E_n = Y(4);

% Total population
   N = S + I1 + I2;

% Define the differential equations with controls
dSdt = -beta * (S * I1 + S * I2) / N - U2 * S;
   dI1dt = beta * (S * I1 + S * I2) / N - gamma * I1 - U3 * I1;
   dI2dt = beta * (S * I2) / N - gamma * I2;
dE_ndt = U2 * I1 - E_n; % Example of how environmental control affects contamination

% Return the derivatives
dYdt = [dSdt; dI1dt; dI2dt; dE_ndt];
end

% Parameters
params = struct('beta', 0.3, 'gamma', 0.1, 'U2', 0.75, 'U3', 0.32);

% Initial conditions
S0 = 99;
I1_0 = 1;
I2_0 = 5;
E_n0 = 1;
Y0 = [S0; I1_0; I2_0; E_n0];

% Time span for the simulation
tspan = [0 16];

% Solve the differential equations
```

```
[t, Y] = ode45(@(t, Y) control_U2_U3(t, Y, params), tspan, Y0);

% Plot the results
figure;
plot(t, Y(:,1), 'b', 'DisplayName', 'Susceptible');
holdon;
plot(t, Y(:,2), 'r', 'DisplayName', 'Infected I1');
plot(t, Y(:,3), 'm', 'DisplayName', 'Infected I2');
plot(t, Y(:,4), 'g', 'DisplayName', 'Environmental Contamination');
xlabel('Time (days)');
ylabel('Number of individuals');
title(' Prevention U_2 and Treatment U_3 Only');
legend;
gridon;



functiondYdt = control_all(t, Y, params)
% Unpack parameters
beta = params.beta;
gamma = params.gamma;
    U1 = params.U1;
    U2 = params.U2;
    U3 = params.U3;

% Unpack state variables
    S = Y(1);
    I1 = Y(2);
    I2 = Y(3);
E_n = Y(4);

% Total population
    N = S + I1 + I2;

% Define the differential equations with controls
dSdt = -beta * (S * I1 + S * I2) / N - U1 * S - U2 * S;
    dI1dt = beta * (S * I1 + S * I2) / N - gamma * I1 - U3 * I1;
    dI2dt = beta * (S * I2) / N - gamma * I2;
dE_ndt = U1 * I1 + U2 * I1 - E_n; % Example of combined effect on environmental
contamination

% Return the derivatives
dYdt = [dSdt; dI1dt; dI2dt; dE_ndt];
end

% Parameters
```

```
params = struct('beta', 0.3, 'gamma', 0.1, 'U1', 0.2, 'U2', 0.75, 'U3', 0.32);

% Initial conditions
S0 = 990;
I1_0 = 10;
I2_0 = 5;
E_n0 = 10;
Y0 = [S0; I1_0; I2_0; E_n0];

% Time span for the simulation
tspan = [0 16];

% Solve the differential equations
[t, Y] = ode45(@(t, Y) control_all(t, Y, params), tspan, Y0);

% Plot the results
figure;
plot(t, Y(:,1), 'b', 'DisplayName', 'Susceptible');
holdon;
plot(t, Y(:,2), 'r', 'DisplayName', 'Infected I1');
plot(t, Y(:,3), 'm', 'DisplayName', 'Infected I2');
plot(t, Y(:,4), 'g', 'DisplayName', 'Environmental Contamination');
xlabel('Time (days)');
ylabel('Number of individuals');
title('All Controls Applied');
legend;
gridon;


functioncryptosporidiosis_model
% Parameters
mu = 0.5;     % Natural death rate
phi = 0.04;   % Disease-related death rate
delta = 0.4;  % Immunity waning rate
   v = 0.2;      % Rate at which disease leaves the environment
alpha = 0.9;  % Recovery rate
epsilon = 0.06; % Contact rate
theta = 0.03; % Contribution to the environment
   A = 1;        % Recruitment rate
rho = 1;      % Environmental modification parameter

% Initial conditions
   S0 = 200;     % Initial susceptible population
   I0 = 400;     % Initial infected population
   R0 = 60;      % Initial recovered population
   En0 = 0.1;    % Initial environmental contamination
```

```
init_conditions = [S0, I0, R0, En0];

% Time span
tspan = [0 50];

% Solve ODE
    [t, y] = ode45(@(t, y) odes(t, y, mu, phi, delta, v, alpha, epsilon, theta, A, rho), tspan,
init_conditions);

% Plot results
figure;
subplot(2,2,1);
plot(t, y(:,1), 'b', 'LineWidth', 1.5);
title('Susceptible Individuals (S)');
xlabel('Time');
ylabel('Number of Individuals');

subplot(2,2,2);
plot(t, y(:,2), 'r', 'LineWidth', 1.5);
title('Infected Individuals (I)');
xlabel('Time');
ylabel('Number of Individuals');

subplot(2,2,3);
plot(t, y(:,3), 'g', 'LineWidth', 1.5);
title('Recovered Individuals (R)');
xlabel('Time');
ylabel('Number of Individuals');

subplot(2,2,4);
plot(t, y(:,4), 'k', 'LineWidth', 1.5);
title('Environmental Contamination (E_n)');
xlabel('Time');
ylabel('Contamination Level');

end

functiondydt = odes(t, y, mu, phi, delta, v, alpha, epsilon, theta, A, rho)
    S = y(1);
    I = y(2);
    R = y(3);
E_n = y(4);

% Compute beta_m*
beta_m_star = (epsilon * I / (S + I + R + A)) * rho * E_n;
```

```
% ODE equations
dSdt = A + delta * R - mu * S - beta_m_star * S;
dIdt = beta_m_star * S - (alpha + mu + phi) * I;
dRdt = alpha * I - (mu + delta) * R;
dEn_dt = theta * I - v * E_n;

dydt = [dSdt; dIdt; dRdt; dEn_dt];
end
```