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A Generalized Mathematical Model of Toxoplasmosis with an Intermediate Host and the Definitive Cat Host

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Abstract: In this paper, we construct a generalized epidemiological mathematical model to study toxoplasmosis dynamics, taking into consideration both cat and mouse populations. The model incorporates generalized proportions for the congenital transmission in the mouse and cat populations, along with the oocysts available in the environment. We focus on determining the conditions under which toxoplasmosis can be eradicated. We conduct a stability analysis in order to reveal the dynamics of toxoplasmosis in the cat and mouse populations; moreover, we compute the basic reproduction number \mathcal{R}_0 , which is crucial for the long-term behavior of the toxoplasmosis disease in these populations as well as the steady states related to both populations. We find that vertical transmission in the cat population is essential, and affects the basic reproduction number \mathcal{R}_0 . If full vertical transmission is considered in the mouse population and $\mathcal{R}_0 < 1$, we find that all solutions converge to the limit set comprised by the infinitely many toxoplasmosis-free-cat steady states, meaning that toxoplasmosis would vanish from the cat population regardless of the initial conditions. On the other hand, if $\mathcal{R}_0 > 1$, then there is only one toxoplasmosis-endemic steady state. When full vertical transmission is not considered in the mouse population, then a unique toxoplasmosis-free equilibrium exists and toxoplasmosis can be eradicated for both the cat and mouse populations. This has important public health implications. Numerical simulations are carried out to reinforce our theoretical stability analysis and observe the repercussion of some parameters on the dynamics.

Keywords: mathematical modeling; stability analysis; toxoplasmosis; hosts; oocysts; vaccination**MSC:** 34K05; 34K60; 37N25; 37M05; 92D30

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1. Introduction

Toxoplasma gondii is a parasite that is common in a variety of animals. Cats are the main hosts, and the parasite is transmitted by various paths [1–3]. In cats, the parasite completes its whole life cycle without impacting their life. Cats can eject more than 20 million oocysts [4]. In pregnant cats, *T. gondii* can be transmitted to the fetus [5]. It is important to point out that cats are among the most popular pets in the world [6].

More than 40 million people in the U.S. carry the *Toxoplasma* parasite. However, most of these people do not have infections due to the protection provided by their immune systems [7,8]. *T. gondii* is a parasite that is able to infect many species of warm-blooded animals, including humans [7,8]. *T. gondii* infection is very common in different parts of the world. It has been reported that its seroprevalence in cats and humans can be around 30 to 40 percent [9]. The only known definitive hosts for *T. gondii* are members of the family Felidae, which includes domestic cats. A cat that is infected sheds oocysts in its feces; the oocysts can then contaminate the surroundings, including water and food [7,9–11]. Several types of meat are important sources of infections of *Toxoplasma* [12]. It has been reported that gamma irradiation can kill oocysts that are present in foods [11]. Oocysts are spread by different means, including water and wind. Intermediate hosts can become infected

by consuming oocysts present in the water or in the environment [7,8,13]. In addition, it has been reported that cats can shed oocysts after they have ingested infected mice [13]. Toxoplasma infection can be acquired by humans due to eating cysts that are present in raw/uncooked meat [8,14]. In addition, it has been shown that cats are a major reservoir of this infection [8,9,15–17].

The consequences of toxoplasmosis infection during pregnancy are complicated. In this instance, in approximately 30% of cases the fetus suffers a congenital infection, in which neurological or eye problems may occur. The severity of these problems depend on the gestational age. Preventive protocols can help to reduce the severity of infection [18]. The placenta plays a direct role in *T. gondii* transmission to the fetus. In [19], the authors evaluated congenital transmission via experiments on mice. They were able to determine parasite load and study further vertical transmission. In addition, it has been found that *T. gondii* in pregnant mice can be transmitted through the placenta [18,20]. Due to the similarities of human and rodent placentas, it is common to use mice as an experimental model of congenital toxoplasmosis [21,22]. Congenital transmission in mice has been noted in several consecutive generations [23]. Moreover, it has been suggested that previous infection with a particular *T. gondii* strain does not prevent toxoplasmosis in mice in the case of re-infection with another *T. gondii* strain [22,24]. Thus, the available evidence indicates that congenital transmission is common in populations of mice [25]. It has been suggested that the deer mouse could be a factor in maintaining *T. gondii* due to vertical transmission, despite the lack of feline hosts [23]. Finally, in [26], it was reported that transmission happens in at least 1% of fetal cases. The observed high percentages of vertical transmission in populations of mice, as well as in other populations, suggest that these transmissions are common.

It is possible that mice can help to maintain the propagation of *T. gondii*. In Manchester, UK, it was found that 59% of 200 mice taken from infested properties tested positive for Toxoplasma. It has been shown that vertical transmission from the infected dam to the fetus can occur, which could be another factor in maintaining infection rates in non-rural areas. It is important to take into account these results for the purposes of rodent control [27]; thus, in the present research we include congenital transmission in the mouse population in our mathematical model.

Mathematical models have been implemented to investigate epidemics involving parasites, viruses, and, recently, the COVID-19 pandemic [28–31]. While mathematical models in many fields are simplifications of the real world, they can nonetheless provide important insights into a wide variety of real processes. Mathematical modeling has been used broadly to investigate the dynamics of numerous diseases in various populations [28,31]. The dynamics of *T. gondii* infection have been explored using mathematical models with different approaches [17]. One approach is to focus the models on cat–human transmission [32,33]. These models vary depending on assumptions/hypotheses related to demographic factors and to horizontal and vertical transmission. More complex models include the transmission of *T. gondii* between susceptible and infected hosts at the population level [16,34,35]. In addition, articles have explored and incorporated the vaccination of cats and swine [16,34–37]. The involvement of vaccines in these models allows the outcomes of particular control strategies to be explored [38]. Vaccines can have a variety of effects. If vaccination is included in the model, it is assumed that it provides lifelong immunity [39,40]. Vaccines for cats are justified, as the *T. gondii* parasite has supportive circumstances for survival, especially in cats [15]. In addition, several researchers have proposed within-host models to study the dynamics of *T. gondii* invasion [41]. Recently, researchers have explored the effect of discrete time delay to see how this affects the dynamics of toxoplasmosis disease in the cat population [42,43]. For a detailed review of mathematical models related to toxoplasmosis, interested readers may refer to [17].

In this work, we design a generalized mathematical model to research toxoplasmosis dynamics in cat and mouse populations. The model incorporates congenital transmission in both the mouse and cat populations. The generalized model considers a much broader

spectrum of possibilities than in our previous work, where partial congenital transmission was not considered [44]. In this study, the model includes infinitely many proportions of vertical transmissions for the mouse and cat populations. The model takes into account the possibility of transmission between oocysts and mice, and considers the option of vaccinating the cat population. In the model, cats can have three disease statuses, namely, infected, susceptible, and recovered/vaccinated, while mice can be either susceptible $S_m(t)$ or infected $I_m(t)$. In addition, the model encompasses *T. gondii* oocysts. We examine the stability of the equilibrium points of the system, and design suitable Lyapunov functions that let us demonstrate the global stability of the equilibrium points. Lyapunov functions have been used extensively to study the global stability of equilibrium points of epidemic models [45–48]. We compute the basic reproductive number \mathcal{R}_0 that is crucial for the dynamics of toxoplasmosis. We execute simulations in order to obtain useful insights into the dynamics of toxoplasmosis and to support our theoretical results; such simulations can additionally be used to explore the effect of public health strategies to control toxoplasmosis.

The rest of this manuscript is organized as follows. In Section 2 we design the toxoplasmosis mathematical model with intermediate and definitive hosts. Section 3 is devoted to the stability analysis of the equilibrium points and to computing the basic reproduction number \mathcal{R}_0 . In addition, we build suitable Lyapunov functions that let us to demonstrate the global stability of the toxoplasmosis-free equilibrium point. Section 4 incorporates simulations of various scenarios, and finally in Section 5 conclusions are given.

2. Mathematical Model

Here, we modify and extend a mathematical model that has previously been used to examine the transmission of toxoplasmosis in cat populations [34]. A constant immunization program is included for the population of cats [16,34–37]. The model includes the oocyst population as a state variable due to oocysts being the primary reason for the persistence of *T. gondii* in the environment [9]. The cat is the only vector known to excrete *T. gondii* oocysts [7,9]. The proposed model contemplates encounters between the *T. gondii* oocysts and both cats and mice. The model considers the probability of infection to be related to the amount of sporulated oocysts in the environment [36].

The generalized mathematical model is comprised of ordinary differential equations. Among the parameters of the model are those describing the birth, death, and vaccination rates. Other parameters are related to the lifespan of oocysts and their production by each infected cat. After infection or vaccination, it is assumed that cats have lifelong immunity [8]. A generalized proportion of vertical transmission is assumed in the definitive and intermediate hosts [23,24,49]. The model assumes that sporulated oocysts decay exponentially [17,34,35].

The developed model includes the following assumptions/hypotheses:

- Cats can be susceptible (S), infected (I), or recovered/vaccinated (V_R).
- The mouse population N_m is divided into two classes, namely, susceptible (S_m) and infectious (I_m).
- Oocysts (O) denotes the amount of *T. gondii* oocysts.
- The mouse and cat populations are assumed to be constant.
- A susceptible mouse or cat moves to the infectious class after contact with *T. gondii* oocysts (at rates β_m and β , respectively).
- A susceptible cat flows to the recovered/vaccinated class V_R at a rate γ . An infectious cat flows to the vaccinated/recovered subpopulation $V_R(t)$ at a rate α .
- *T. gondii* oocysts $O(t)$ are generated by infectious cats $I(t)$.
- μ_0 is the degradation/removal rate of *T. gondii* oocysts in the environment.
- μ represents the birth and death rate for cats.
- μ_c represents the birth and death rate of mice.
- A proportion q of vertical transmission is assumed in the cat population.
- A proportion p of vertical transmission is assumed in the mouse population.

The constructed generalized mathematical model assuming vertical transmission for the mouse and cat populations is provided by the following system:

$$\begin{aligned}
 \dot{S}(t) &= \mu N - q\mu I(t) - \beta S(t)O(t) - (\gamma + \mu)S(t), \\
 \dot{I}(t) &= \beta S(t)O(t) - \alpha I(t) - \mu I(t) + q\mu I(t), \\
 \dot{V}_R(t) &= \alpha I(t) + \gamma S(t) - \mu V_R(t), \\
 \dot{O}(t) &= k I(t) - \mu_0 O(t), \\
 \dot{S}_m(t) &= \mu_m S_m + \mu_m (1 - p) I_m - \beta_m S_m(t) O(t) - \mu_m S_m, \\
 \dot{I}_m(t) &= \beta_m S_m(t) O(t) + \mu_m p I_m - \mu_m I_m.
 \end{aligned}
 \tag{1}$$

The parameter $k > 0$ is the production rate of oocysts per infectious cat. The term $q\mu I(t)$ represents newborn cats that are born with toxoplasmosis due to congenital transmission. Note that there is no vertical transmission in the cat population if $q = 0$. Analogously, the term $p\mu I_m(t)$ represents newborn mice born with toxoplasmosis due to congenital transmission; if $p = 0$, there is no vertical transmission in the mouse population. We denote the population of cats by $N(t)$ and the mouse population by $N_m(t)$. In order to work with proportions, we scale both the mouse and cat populations. After changing the variables and using a number of simplifications, we obtain the following reduced system:

$$\begin{aligned}
 \dot{S}(t) &= \mu - q\mu I(t) - \beta S(t)O(t) - (\gamma + \mu)S(t), \\
 \dot{I}(t) &= \beta S(t)O(t) - \alpha I(t) - \mu I(t) + q\mu I(t), \\
 \dot{O}(t) &= k I(t) - \mu_0 O(t), \\
 \dot{S}_m(t) &= \mu_m (1 - p) (1 - S_m) - \beta_m S_m(t) O(t).
 \end{aligned}
 \tag{2}$$

where $V_R = 1 - S - I$ and $I_m = 1 - S_m$. The initial conditions of the subpopulations are as follows:

$$S_m(0) \geq 0, O(0) \geq 0, S(0) > 0, I(0) \geq 0.
 \tag{3}$$

The designed model is depicted in Figure 1.

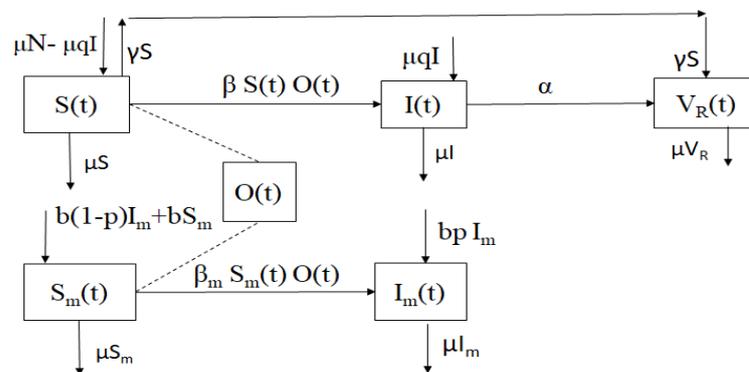


Figure 1. Chart of the mathematical model of generalized toxoplasmosis transmission (1) for mouse and cat populations taking into account generalized vertical transmission.

3. Stability Analysis

Here, we qualitatively analyze the mathematical model (2) and obtain the proof of the uniqueness of the solution.

First, we want to demonstrate that the solutions of system (2) are bounded and positive ($\forall t \geq 0$).

Theorem 1. When the initial values satisfy (3) and the positivity of the parameters inherent in the system (2) is satisfied, then the solution curves of (2) remain positive and are bounded for $t \geq 0$.

Proof. Replacing the inequality $I(t) \leq 1$ in the third equation of (2), it follows that

$$\dot{O}(t) \leq k - \mu_0 O(t).$$

Thus, if $O(0) \leq \frac{k}{\mu_0}$, then $O(t) \leq \frac{k}{\mu_0}$. For the case $O(0) > \frac{k}{\mu_0}$, we have $O(t) < O(0)$.

Taking $B_M = \max\left\{O(0), \frac{k}{\mu_0}\right\}$, it is then the case that $O(t) \leq B_O$ for all $t \leq 0$. In addition, we have

$$\dot{S}(t) > -\beta S(t)B_O - (\mu + \gamma)S(t),$$

which implies that

$$S(t) \geq S(0) \exp(-B_0 t) > 0,$$

i.e., $S(t) > 0$ for all $t \geq 0$ and $B_0 = \beta B_O + \mu + \gamma$. Now, if $t_0 > 0$ exists such that $I(t_0) = 0$, $\dot{I}(t_0) \leq 0$, and $I(t) > 0$ for all $t \in [0, t_0)$, we have $0 \geq \beta S(t_0)O(t_0)$. However, from the equation related to the the variation of $O(t)$ in model (2), we obtain

$$\dot{O}(t) > -\mu_0 O(t), \quad \forall t \in [0, t_0),$$

and

$$O(t_0) \geq O(0) e^{-\mu_0 t_0} > 0,$$

leading to a contradiction. Then, $I(t) > 0, \forall t > 0$. For the rest of state variables, it is sufficient to verify that they are non-negative for $t \geq 0$. From the first equation of model (2), by applying a comparison theorem [50] it can be seen that

$$S(t) \leq S(0) e^{-(\mu+\gamma)t} + \frac{\mu}{\mu + \gamma} (1 - e^{-(\mu+\gamma)t}).$$

Thus, if $S(0) \leq \frac{\mu}{\mu+\gamma}$, then $S(t) \leq \frac{\mu}{\mu+\gamma}$. In addition, the second equation of system (2) shows that

$$\dot{I}(t) \leq \frac{\beta\mu k}{(\mu + \gamma)\mu_0} - (\alpha + \mu(1 - q)) I(t),$$

and again, we have

$$I(t) \leq \frac{\beta\mu k}{(\mu + \gamma)\mu_0(\alpha + \mu(1 - q))}$$

for $I(0) \leq \frac{\beta\mu k}{(\mu+\gamma)\mu_0(\alpha+\mu(1-q))}$. Thus, we investigate model (2) in the next region, as follows:

$$\Omega_r = \left\{ (S, I, O, S_m) \in \mathbb{R}_+^4 / 0 < S \leq \frac{\mu}{\mu+\gamma}, 0 \leq I \leq \frac{\beta\mu k}{(\mu+\gamma)\mu_0(\alpha+\mu(1-q))}, \right. \\ \left. 0 < S + I < 1, 0 \leq O \leq \frac{k}{\mu_0}, 0 \leq S_m + I_m \leq 1 \right\}. \tag{4}$$

Thus, Ω_r is positively invariant. Note that if $S(0) > \frac{\mu}{\mu+\gamma}$ the solutions enter Ω_r or $S(t)$, approaching asymptotically to $\frac{\mu}{\mu+\gamma}$. The same is the case for the rest of the variables. Therefore, the region Ω_r attracts all solutions in \mathbb{R}_+^4 . \square

Thus, we can study model (2) in Ω_r , and model (2) is mathematically well-posed in Ω_r .

4. Mathematical Model with Full Vertical Transmission in the Mouse Population

We separate the cases of full vertical transmission ($p = 1$) and without vertical transmission ($p \neq 1$) for the mouse population, as their mathematical analyses vary and the public health consequences are different. For the sake of clarity, we present system (2) with $p = 1$, which translates to full vertical transmission in the mouse population. Then, we have

$$\begin{aligned} \dot{S}(t) &= \mu - q\mu I(t) - \beta S(t)O(t) - (\gamma + \mu)S(t), \\ \dot{I}(t) &= \beta S(t)O(t) - \alpha I(t) - \mu I(t) + q\mu I(t), \\ \dot{O}(t) &= kI(t) - \mu_0 O(t), \\ \dot{S}_m(t) &= -\beta_m S_m(t)O(t). \end{aligned} \tag{5}$$

We begin by studying the stability of the toxoplasmosis-free steady states, assuming full vertical transmission in the mouse population. We then proceed to find the equilibrium points and study their stability.

4.1. Toxoplasmosis-Free Steady State Considering Full Vertical Transmission in Mice

The steady states of epidemiological models are crucial for studying disease dynamics. Such models might have multiple equilibria and periodic solutions. From the generalized mathematical model (5), we can clearly see that infinite steady states are attained when $I = 0$ and $O = 0$. These steady states are part of a subset of Ω_r . Now, we define the following set:

$$J = \left\{ (S, I, O, S_m) : \left(\frac{\mu}{\mu + \gamma}, 0, 0, S_m^* \right) \in \Omega_r \right\}. \tag{6}$$

We name this set the toxoplasmosis-free set. LaSalle’s invariance principle can be used to rule the stability of this set J [50]. As a matter of fact, we can build a Lyapunov function in order to show that all the solutions of the model (5) are attracted to set J when $\mathcal{R}_0 < 1$.

Remark 1. *The set J that includes all toxoplasmosis-free equilibrium points considers the possibility of toxoplasmosis disease in the mouse population. However, because mice are not able to spread the disease to cats in system (5) with $p = 1$, we consider the set J as a toxoplasmosis-free situation.*

Remark 2. *From system 5, we can take the subsystem of the equations where the compartments into which new infectious agents enter are located. Thus, we can compute the matrices V and F that represent the Jacobian matrices of the compartments with new infections evaluated at points $I = 0$ and $O = 0$. In this way, we have*

$$F = \begin{bmatrix} 0 & \frac{\mu\beta}{\gamma+\mu} \\ k & 0 \end{bmatrix} \quad V = \begin{bmatrix} \alpha + \mu - q\mu & 0 \\ 0 & \mu_0 \end{bmatrix}.$$

We define the basic reproduction number

$$\mathcal{R}_0 = \sqrt{\frac{\mu k\beta}{\mu_0 (\gamma + \mu)(\alpha + \mu - q\mu)}}, \tag{7}$$

which is obtained by calculating the maximum eigenvalue of the product FV^{-1} provided by

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\mu\beta}{(\gamma+\mu)\mu_0} \\ \frac{k}{\alpha+\mu-q\mu} & 0 \end{bmatrix}.$$

4.2. Global Stability of Toxoplasmosis-Free Equilibrium Points

First, we show that the set J is the largest invariant set if $\mathcal{R}_0 < 1$ and that for any initial conditions the solutions are attracted to the set J .

Theorem 2. When $\mathcal{R}_0 \leq 1$, the convergence of the solution curves of the model (5) occurs on set J .

Proof. We now propose the next function \mathfrak{S} ,

$$\mathfrak{S}(\mathcal{X}(t)) = \frac{kI(t)}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} + \frac{O(t)}{\mu_0}, \tag{8}$$

where $\mathcal{X}(t) = (S(t), I(t), O(t), S_m(t))$ and $F^* \in J$. Here, \mathfrak{S} is a function such that:

$$\begin{aligned} \mathfrak{S}(F^*) &= 0 \text{ for all } F^* \in J; \\ \mathfrak{S}(\mathcal{X}(t)) &> 0 \text{ for all } \mathcal{X}(t) \neq F^*; \\ \mathfrak{S}(\mathcal{X}(t)) &\rightarrow \infty, \text{ as } \|\mathcal{X}\| \rightarrow \infty. \end{aligned} \tag{9}$$

Thus, $\mathfrak{S}(\mathcal{X}(t))$ is radially unbounded.

Computing the time derivative of $\mathfrak{S}(\mathcal{X}(t))$ along the trajectories of model (5), from Ω_r it follows that

$$\begin{aligned} \frac{d\mathfrak{S}(\mathcal{X}(t))}{dt} &= \frac{k\dot{I}(t)}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} + \frac{\dot{O}(t)}{\mu_0} = \frac{k(\beta S(t)O(t) - (\alpha + \mu - q\mu)I(t))}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} + \frac{kI(t) - \mu_0 O(t)}{\mu_0} \\ &= \frac{k\beta S(t)O(t) - kI(t)(\alpha + \mu - q\mu) + kI(t)\mathcal{R}_0^2(\alpha + \mu - q\mu) - O(t)\mu_0\mathcal{R}_0^2(\alpha + \mu - q\mu)}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} \\ &= \frac{kI(t)(\alpha + \mu - q\mu)(\mathcal{R}_0^2 - 1) + O(t)(k\beta S(t) - \mathcal{R}_0^2\mu_0(\alpha + \mu - q\mu))}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} \\ &\leq \frac{kI(t)(\alpha + \mu - q\mu)(\mathcal{R}_0^2 - 1) + O(t)\left(\frac{k\beta\mu}{\mu + \gamma} - \mathcal{R}_0^2\mu_0(\alpha + \mu - q\mu)\right)}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0} \\ &= \frac{kI(t)(\alpha + \mu - q\mu)(\mathcal{R}_0^2 - 1)}{\mathcal{R}_0^2(\alpha + \mu - q\mu)\mu_0}. \end{aligned}$$

Thus, when $\mathcal{R}_0 \leq 1$, it is the case that $\frac{d\mathfrak{S}(\mathcal{X}(t))}{dt} \leq 0$ and $\frac{d\mathfrak{S}(\mathcal{X}(t))}{dt} = 0$ iff $I(t) = 0$ and $O(t) = 0$. Therefore, the set

$$\mathfrak{S}_{F^*} = \left\{ \mathcal{X}(t) \in \Omega_r : \frac{d\mathfrak{S}(\mathcal{X}(t))}{dt} = 0 \right\}$$

is simply the set J . Per LaSalle’s invariance principle, we find that the limit set of all solutions belongs to the largest time-invariant set $J \in \Omega_r$ whenever $\mathcal{R}_0 \leq 1$. \square

4.3. Toxoplasmosis-Endemic Steady State

The biological toxoplasmosis-endemic steady states can be obtained by solving the algebraic system

$$\begin{aligned} 0 &= \mu - q\mu I^* - \beta S^* O^* - (\gamma + \mu)S^*, \\ 0 &= \beta S^* O^* - \alpha I^* - \mu I^* + q\mu I^*, \\ 0 &= kI^* - \mu_0 O^*, \\ 0 &= -\beta_m S_m^* O^*. \end{aligned} \tag{10}$$

We denote the toxoplasmosis-endemic point by

$$E_0^* = (S^*, I^*, O^*, S_m^*). \tag{11}$$

Then, from (10), we find that $S_m^* = 0$, as $O^* \neq 0$. Therefore, the components of the toxoplasmosis-endemic steady state are

$$\begin{aligned} S^* &= \frac{\mu_0 (\alpha + \mu - q \mu)}{\beta k}, \\ I^* &= \frac{\mu \beta k - (\gamma + \mu) \mu_0 (\alpha + \mu - q \mu)}{\beta k (\mu q + \alpha + \mu - q \mu)}, \\ O^* &= \frac{\mu \beta k - (\gamma + \mu) \mu_0 (\alpha + \mu - q \mu)}{\beta (\mu q + \alpha + \mu - q \mu) \mu_0}, \\ S_m^* &= 0. \end{aligned} \tag{12}$$

Using \mathcal{R}_0 , we find that the endemic point E_0^* is provided as follows:

$$\begin{aligned} S^* &= \frac{\mu}{\mathcal{R}_0^2 (\mu + \gamma)}, \\ I^* &= \frac{\mu_0 (\gamma + \mu) (\alpha + \mu - q \mu) (\mathcal{R}_0^2 - 1)}{\beta k (\mu q + \alpha + \mu - q \mu)}, \\ O^* &= \frac{(\gamma + \mu) (\alpha + \mu - q \mu) (\mathcal{R}_0^2 - 1)}{\beta k (\mu q + \alpha + \mu - q \mu)}, \\ S_m^* &= 0. \end{aligned} \tag{13}$$

The endemic steady state E_0^* is biologically appropriate if $\mu \beta k - \mu_0 (\gamma + \mu) (\alpha + \mu - q \mu) > 0$. If $\mathcal{R}_0 = 1$, this endemic equilibrium becomes part of the set J composed by the toxoplasmosis-free steady states. As a matter of fact, the endemic and disease-free equilibrium points collide when $\mathcal{R}_0 = 1$. The characteristic polynomial is provided by

$$P(\lambda) = \begin{vmatrix} -\beta O^* - \mu - \gamma - \lambda & -q \mu & -\beta S^* & 0 \\ \beta O^* & -\alpha - \mu + q \mu - \lambda & \beta S^* & 0 \\ 0 & k & -\mu_0 - \lambda & 0 \\ 0 & 0 & -\beta_m S_m^* & -\beta_m O^* - \lambda \end{vmatrix}$$

Then, the eigenvalue $\lambda = -\beta_m O^*$ is clearly negative. To compute the further eigenvalues, we simply need to compute the roots of

$$\begin{aligned} &\lambda^3 + (\beta O^* + \alpha + \gamma + \mu_0 + \mu (2 - q)) \lambda^2 \\ &+ (O^* \alpha \beta + O^* \beta \mu_0 + O^* \beta \mu_c - k \beta S^* - \gamma \mu q - \mu_0 \mu q - \mu^2 q + \alpha \gamma + \alpha \mu_0 + \mu \alpha + \gamma \mu_0 + \gamma \mu + 2 \mu_0 \mu + \mu^2) \lambda \\ &+ O^* \alpha \beta \mu_0 + O^* \beta \mu_0 \mu - S^* \beta k (\gamma + \mu) - \gamma \mu_0 \mu q - \mu_0 \mu^2 q + \alpha \gamma \mu_0 + \alpha \mu_0 \mu + \gamma \mu_0 \mu + \mu_0 \mu^2 = 0. \end{aligned} \tag{14}$$

We can rewrite this characteristic equation as

$$\lambda^3 + A \lambda^2 + B \lambda + C = 0 \tag{15}$$

where

$$\begin{aligned}
 A &= O^* \beta + \alpha + \gamma + \mu_0 + \mu (2 - q) = \frac{\mathcal{R}}{\alpha + \mu} + \alpha + \gamma + \mu_0 + \mu (2 - q), \\
 B &= \frac{\mathcal{R} \mu_0}{\alpha + \mu} + \mathcal{R} + \mu_0 \mu + \alpha \gamma + \mu \alpha + \gamma \mu_0 + \gamma \mu (1 - q) + (1 - q) \mu^2, \\
 C &= \mu_0 \beta O^* (\mu + \alpha) = \mu_0 \mathcal{R}.
 \end{aligned}$$

Here, $\mathcal{R} = (\mu + \gamma) (\alpha + \mu - \mu q) (\mathcal{R}_0^2 - 1) > 0$, because $\mathcal{R}_0 > 1$. Per the Routh–Hurwitz theorem [51], we can conclude that all the eigenvalues have negative real parts if $AB > C$ and A, C are positive; note that $A, B, C > 0$. As such, we can obtain

$$\begin{aligned}
 AB - C &= \left(\frac{\mathcal{R}}{\alpha + \mu} + \alpha + \gamma + \mu_0 + \mu (2 - q) \right) \left(\frac{\mathcal{R} \mu_0}{\alpha + \mu} + \mathcal{R} + \mu_0 \mu + \alpha \gamma + \mu \alpha + \gamma \mu_0 \right. \\
 &\quad \left. + \gamma \mu (1 - q) + (1 - q) \mu^2 \right) - \mu_0 \mathcal{R} \\
 &= \left(\frac{\mathcal{R}}{\alpha + \mu} + \alpha + \gamma + \mu_0 + \mu (2 - q) \right) \left(\frac{\mathcal{R} \mu_0}{\alpha + \mu} + \mu_0 \mu + \alpha \gamma + \mu \alpha + \gamma \mu_0 \right. \\
 &\quad \left. + \gamma \mu (1 - q) + (1 - q) \mu^2 \right) + \left(\frac{\mathcal{R}}{\alpha + \mu_c} + \alpha + \gamma + \mu_0 + \mu (2 - q) \right) \mathcal{R} - \mathcal{R} \mu_0 > 0
 \end{aligned}$$

when $\mathcal{R}_0 > 1$. Thus, all the eigenvalues are located in the left-half plane. Accordingly, the theorem below is proven.

Theorem 3. For $\mathcal{R}_0 > 1$, the stationary toxoplasmosis endemic point E_0^* is locally asymptotically stable in $\Omega_r \setminus J$.

4.4. Global Stability of the Toxoplasmosis-Endemic Equilibrium Point

First, let us examine the global stability of the toxoplasmosis-endemic point E_0^* . We propose the following theorem:

Theorem 4. The toxoplasmosis-endemic steady state E_0^* of model (5) is global asymptotically stable in $\Omega_r \setminus J$ whenever $\mathcal{R}_0 > 1$.

Proof. We define the function \mathcal{L} as

$$\mathcal{L}(\mathcal{X}(t)) = S_m(t), \tag{16}$$

which complies with (9). Then,

$$\frac{d\mathcal{L}(\mathcal{X}(t))}{dt} = -\beta_m S_m(t) O(t).$$

Therefore, $\frac{d\mathcal{L}(\mathcal{X}(t))}{dt} \leq 0$ and $\frac{d\mathcal{L}(\mathcal{X}(t))}{dt} = 0$ if and only if $S_m(t) = 0$ or $O(t) = 0$. Following LaSalle’s invariance principle, the toxoplasmosis endemic equilibrium E_0^* is globally asymptotically stable with respect to $\Omega_0 \setminus J$ if $\mathcal{R}_0 > 1$. \square

This stability result implies that system (5) approaches the toxoplasmosis endemic equilibrium point E_0^* for $\mathcal{R}_0 > 1$ and for any initial conditions.

5. Mathematical Model Without Full Vertical Transmission in the Mouse Population

In this section, we consider the mathematical model (2) without full vertical transmission in the mouse population, i.e., $0 \leq p < 1$. From the previous section, we know

that toxoplasmosis cannot be eradicated from the mouse population due to full vertical transmission. Now, we consider the case without full vertical transmission in the mouse population ($0 \leq p < 1$). The reason for considering this separate case is that, as will be seen, it is possible to eradicate toxoplasmosis from both the cat and mouse populations if there is not full vertical transmission. Moreover, there are only two steady states here instead of infinitely many. Proceeding with the analysis of the mathematical model without full vertical transmission in the mouse population, the model under investigation here is provided by system (2) with $0 < p < 1$.

5.1. Stability Analysis of the Toxoplasmosis-Free Equilibrium Point

We denote the total toxoplasmosis-free equilibrium point of model (2) as

$$F_0^* = (S^*, I^*, O^*, S_m^*) = \left(\frac{\mu}{\mu + \gamma}, 0, 0, 1 \right).$$

Note that the whole population of mice is susceptible. There are no oocysts and no infected cats. We call this steady state a total toxoplasmosis-free state, as none of the subpopulations are infected. This case is different from the one in which there is full vertical transmission in the mouse population. Next, we proceed to study the local stability of the total toxoplasmosis-free equilibrium point F_0^* . The local stability of F_0^* can be examined by analyzing the eigenvalues of $J(F_0^*)$. Evaluating the Jacobian of Equation (2) at F_0^* , we have

$$J(F_0^*) = \begin{pmatrix} -\mu - \gamma & -q\mu & -\frac{\beta\mu}{\mu + \gamma} & 0 \\ 0 & q\mu - \mu - \alpha & \frac{\beta\mu}{\mu + \gamma} & 0 \\ 0 & k & -\mu_0 & 0 \\ 0 & 0 & -\beta_m & -\mu_m(1 - p) \end{pmatrix}.$$

By calculating the eigenvalues of the matrix $J(F_0^*)$, we obtain the characteristic equation, which can be factored as

$$\frac{(\mu_m p - \lambda - \mu_m)(\gamma + \lambda + \mu)}{\gamma + \mu} * \left((\gamma + \mu)\lambda^2 + (\mu + \gamma)\left((1 - q)\mu + \alpha + \mu_0\right)\lambda + (\mu + \gamma)\mu_0\left((1 - q)\mu + \alpha\right) - \mu k\beta \right) = 0.$$

We can obtain two eigenvalues, $\lambda_1 = -\mu - \gamma$ and $\lambda_2 = -\mu_m(1 - p)$. To compute further eigenvalues, we can find the roots of

$$p(\lambda) = \lambda^2 + (\alpha + \mu_0 + \mu(1 - q))\lambda + \mu_0(\alpha + \mu(1 - q))(1 - \mathcal{R}_0), \tag{17}$$

where $\mathcal{R}_0 = \frac{\mu\beta k}{\mu_0(\gamma + \mu)(\alpha + \mu - q\mu)}$. The polynomial in Equation (17) can be rewritten as

$$p(\lambda) = \lambda^2 + a_1\lambda + a_0, \tag{18}$$

where $a_1 = \alpha + \mu_0 + \mu(1 - q) > 0$ and $a_0 = \mu(1 - q)(1 - \mathcal{R}_0) > 0$. Then, according to the Routh–Hurwitz criterion, all the roots of the polynomial $p(\lambda)$ have a negative real part. Hence, the total toxoplasmosis-free steady state F_0^* is locally asymptotically stable. Now, we proceed to examine the global stability of the toxoplasmosis-free steady state F_0^* . Using the same reproduction number \mathcal{R}_0 and the same Lyapunov function provided in Equation (16), we can prove the global stability of the toxoplasmosis-free steady state F_0^* . Note that in this case the largest time invariant set is reduced to $F_0^* \in \Omega_r$ if $\mathcal{R}_0 \leq 1$.

5.2. Stability Analysis of the Toxoplasmosis Endemic Equilibrium Point

Using Equation (17), we can see that the steady state F_0^* is unstable when $\mathcal{R}_0 > 1$. Thus, the solutions of model (2) might converge to endemic equilibrium points when

$\mathcal{R}_0 > 1$. Examining the stability of the endemic steady state, we can find the endemic state by solving the following system:

$$\begin{aligned} 0 &= \mu - q\mu I^* - \beta S^* O^* - (\gamma + \mu)S^*, \\ 0 &= \beta S^* O^* - \alpha I^* - \mu I^* + q\mu I^*, \\ 0 &= kI^* - \mu_0 O^*, \\ 0 &= -\beta_m S_m^* O^* + \mu_m (1 - p) (1 - S_m^*). \end{aligned} \tag{19}$$

The biologically realistic endemic point is the positive solution of system (19), and is denoted by

$$E_1^* = (S^*, I^*, O^*, S_m^*), \tag{20}$$

where

$$\begin{aligned} S^* &= \frac{\mu_0 (\alpha + \mu - q\mu)}{\beta k}, \\ I^* &= \frac{\mu\beta k - \mu_0 (\gamma + \mu) (\alpha + \mu - q\mu)}{\beta k (\mu + \alpha)}, \\ O^* &= \frac{\mu\beta k - \mu_0 (\gamma + \mu) (\alpha + \mu - q\mu)}{\beta \mu_0 (\mu + \alpha)}, \\ S_m^* &= \frac{\mu_m \beta \mu_0 (1 - p) (\mu + \alpha)}{\mu_m \beta \mu_0 (1 - p) (\mu + \alpha) - \beta_m \mu_0 (\alpha + \mu (1 - q)) (\mu + \gamma) + \beta \beta_m k \mu}. \end{aligned} \tag{21}$$

Now, using \mathcal{R}_0 , the unique endemic equilibrium point E_1^* can be rewritten as follows:

$$\begin{aligned} S^* &= \frac{\mu}{\mathcal{R}_0^2 (\mu + \gamma)}, \\ I^* &= \frac{\mu_0 (\gamma + \mu) (\alpha + \mu - q\mu) (\mathcal{R}_0^2 - 1)}{\beta k (\mu + \alpha)}, \\ O^* &= \frac{(\gamma + \mu) (\alpha + \mu - q\mu) (\mathcal{R}_0^2 - 1)}{\beta (\mu + \alpha)}, \\ S_m^* &= \frac{\mu_m \beta \mu_0 (1 - p) (\mu + \alpha)}{\mu_m \beta \mu_0 (1 - p) (\mu + \alpha) + \beta_m \mu_0 (\alpha + \mu (1 - q)) (\mu + \gamma)} (\mathcal{R}_0^2 - 1). \end{aligned} \tag{22}$$

It can be observed that we obtain a practical endemic equilibrium E_1^* if $\mu\beta k - \mu_0 (\gamma + \mu) (\alpha + \mu - q\mu) > 0$. Note that this previous condition is equivalent to having $\mathcal{R}_0 > 1$. Further, note that the endemic equilibrium point E_1 depends on the respective generalized proportions of vertical transmission in the cat and mouse populations. Calculating the Jacobian at E_1^* , we obtain

$$P(\lambda) = \begin{vmatrix} -\beta O^* - \mu - \gamma - \lambda & -q\mu & -\beta S^* & 0 \\ \beta O^* & -\alpha - \mu + q\mu - \lambda & \beta S^* & 0 \\ 0 & k & -\mu_0 - \lambda & 0 \\ 0 & 0 & -\beta_m S_m^* & -\beta_m O^* - (1 - p) \mu_m - \lambda \end{vmatrix}$$

Clearly, $\lambda = -\beta_m O^* - (1 - p) \mu_m$ is a negative eigenvalue. The other eigenvalues are the zeros in Equation (14). Thus, using the Routh–Hurwitz theorem, we can find that the zeros in Equation (14) are all located on the left half of the complex plane. Therefore, we obtain the following theorem.

Theorem 5. *The stationary endemic point E_1^* is locally asymptotically stable when the value of the parameter \mathcal{R}_0 is greater than 1.*

Note that the toxoplasmosis endemic equilibrium points of systems (2) and (5) are different. A larger value of the proportion p allows system (5) to reach an endemic steady state with more infected mice. The effect of the proportion q is similar for systems (2) and (5). A larger value of q indicates larger infected populations of cats and mice. Thus, the proportion of q related to vertical transmission in cats is more crucial for the prevalence of toxoplasmosis. This has important consequences from a public health viewpoint.

6. Numerical Simulations of Different Scenarios

In this section, we present a variety of numerical simulations using mathematical model (2). We vary the values of the parameters in order to provide different scenarios. We consider simulations with $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$ in order to corroborate the theoretical stability analysis presented in the previous section. We vary the initial conditions of the subpopulations in order to take into account conditions both near to and far from the steady states. We mostly rely on the baseline parameter values shown in Table 1.

Table 1. Baseline values for the parameters and subpopulations.

Parameter	Description	Value
μ	Death and birth rates (cats)	1/260 (1/weeks) [52]
α	Shedding period	1/2 (1/weeks) [4]
μ_0	Clearance rate	1/26 (1/day) [4,36]
k	Oocysts per day (cat)	20×10^6 (1/day) [53]
β	Transmission rate	varying
β_m	Transmission rate	0.1×10^{-8}
γ	Vaccination rate	varying
Subpopulations	Description	Initial values
S	Susceptible cats	0.45 [36,54,55]
I	Infected cats	1/130 [36,54,55]
V_R	Vaccinated/Recovered	$1 - S(0) - V(0)$
O	Oocysts	5.92×10^6
S_m	Susceptible mice (proportion)	0.9
I_m	Infected mice (proportion)	0.1

6.1. Toxoplasmosis-Free Scenario ($\mathcal{R}_0 < 1$)

Initially, we consider the case such that $\mathcal{R}_0 < 1$ with initial conditions close to and far from set J . Figure 2 shows the dynamics of the different classes. On the left side, it can be observed that the subpopulation of infectious cats approaches zero when the subpopulations begin near the total toxoplasmosis-free equilibrium point. On the right-hand side, the initial amount of oocysts is a very large number (i.e., far from set J); nevertheless, the system approaches one of the toxoplasmosis-free steady states contained in set J . Note that the oocysts and infected cat populations become extinct here, as $\mathcal{R}_0 < 1$. This simulation result supports the theoretical stability analysis results. Additional simulations were performed, though the results are not shown here. In Figure 3, the main difference is that all the components of the initial conditions are far from the toxoplasmosis-free situation. We considered two vaccination cases, namely, with and without vaccination. On the right-hand side, the case with no vaccination is considered, together with a larger death/clearance rate μ_0 . Note that in the latter case there is a larger population of susceptible mice due to a smaller amount of oocysts at the steady state. Thus, it can be seen that it is feasible for the disease to disappear despite a low vaccination rate. Again, the numerical simulations support the theoretical stability analysis in the previous section.

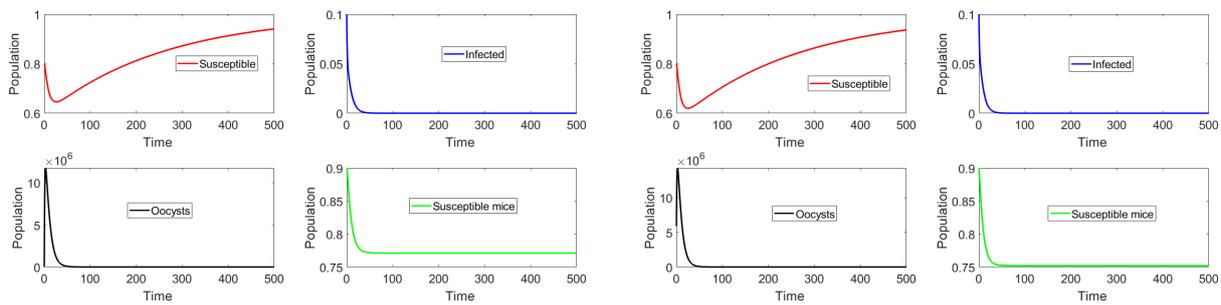


Figure 2. Trajectories of the subpopulations with no vaccination and $\mathcal{R}_0 = 0.98$. The initial subpopulations are near the toxoplasmosis-free point F^* . On the right-hand side, the initial amount of oocysts $O(0)$ is very large.

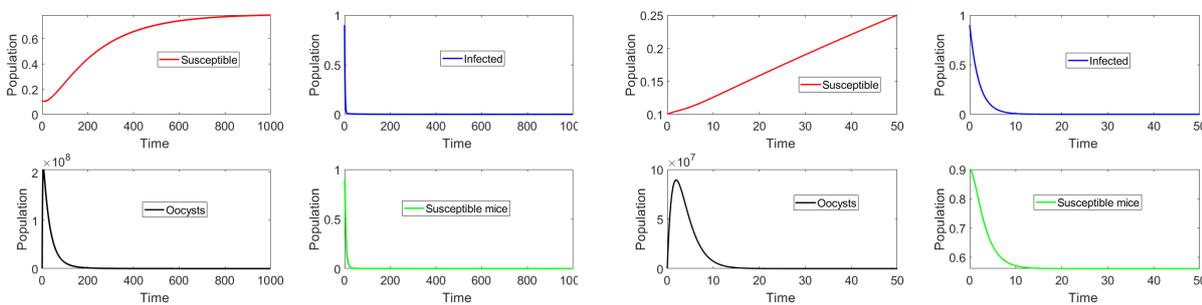


Figure 3. Trajectories of the subpopulations when $\mathcal{R}_0 = 0.98$. The initial subpopulations are distant from the toxoplasmosis-free steady state F^* . The left-hand side shows the case in which vaccination is implemented, while the right-hand side shows the case with no vaccination and a larger death/clearance rate μ_0 .

6.2. Toxoplasmosis Endemic Scenario ($\mathcal{R}_0 > 1$)

In this section we present the results of in silico simulations, where the parameter values are such that the basic reproduction number $\mathcal{R}_0 > 1$. Figure 4 shows that toxoplasmosis becomes endemic and the subpopulations approach the toxoplasmosis endemic point E_0^* . The full transient behavior of system (2) can be observed. The system reaches an endemic steady state where I_m and $O(t)$ do not vanish. Thus, the long term behavior ($t \rightarrow \infty$) is the endemic steady state. The number of infected cats is low due to the fact that $\mathcal{R}_0 = 1.04$, i.e., barely above one. If we increase \mathcal{R}_0 , then the infectious population of cats increases. Moreover, the population of susceptible mice $S_m(t)$ vanishes, due to the oocysts always being present in the environment and to the fact that vertical transmission ($p \neq 0$) is considered in the mouse population.

Finally, an additional numerical simulation with a larger basic reproduction number can be used to examine its effects on the different populations. In particular, we consider no vaccination ($\gamma = 0$) and set the parameter β such that $\mathcal{R}_0 \approx 13$. In addition, the initial subpopulations are set to be distant from the toxoplasmosis-free equilibria. Figure 5 shows that the number of infectious cats increases when the basic reproduction number increases. Analogously, the same happens with respect to the quantity of oocysts at the toxoplasmosis endemic equilibrium point. It is apparent that all of these simulation results support our theoretical stability analysis.

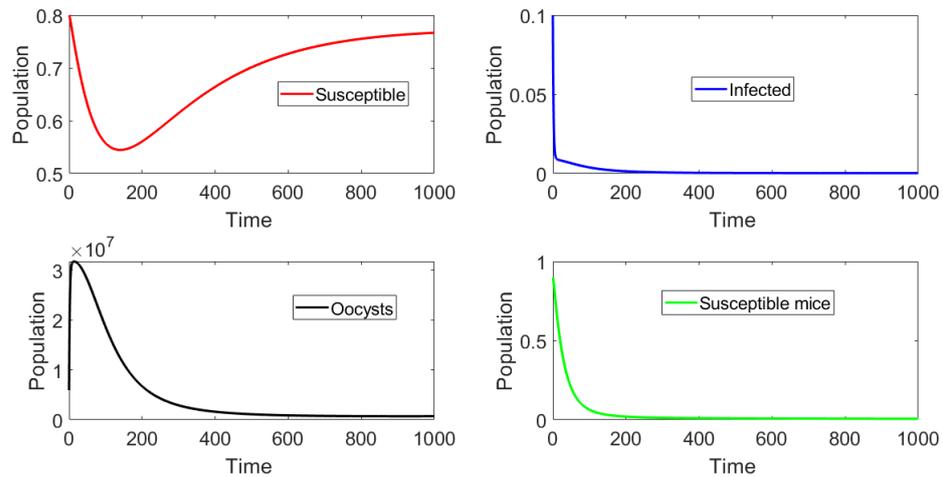


Figure 4. Dynamics of the different classes when $\mathcal{R}_0 = 1.04$ and the initial subpopulations are distant from the endemic equilibrium E_0^* . Note that the oocyst and infected cat populations never become extinct, as $\mathcal{R}_0 > 1$.

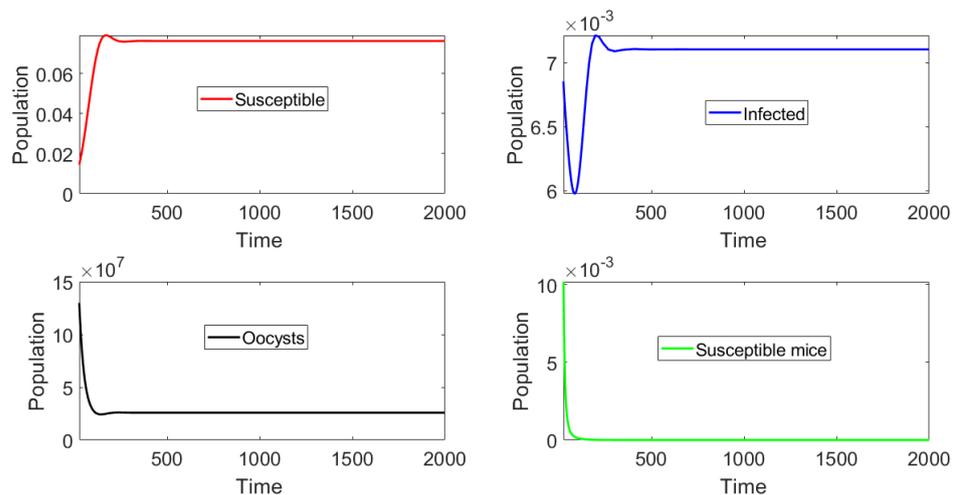


Figure 5. Dynamics of the different classes with no vaccination and $\mathcal{R}_0 \approx 13$.

7. Conclusions

We created a generalized epidemiological mathematical model to examine and investigate toxoplasmosis disease dynamics. The model incorporates the mouse as an intermediate host for *T. gondii* and the cat as the primary host. We considered generalized proportions for the vertical transmission in both the cat and mouse populations. We focused on finding the circumstances under which toxoplasmosis can be eradicated. We performed a stability analysis in order to reveal the evolution of toxoplasmosis disease in the cat and mouse populations. We calculated the basic reproduction number \mathcal{R}_0 , and found that it is a crucial secondary parameter that dictates the evolution of toxoplasmosis. Furthermore, this parameter \mathcal{R}_0 impacts the steady state related to the populations and the disease status. We found that vertical transmission in cats affects the basic reproduction number \mathcal{R}_0 and that this aspect is crucial for the evolution of toxoplasmosis. The toxoplasmosis-free steady state is globally stable when $\mathcal{R}_0 < 1$ and there is no full vertical transmission, meaning that toxoplasmosis is eradicated regardless of the initial population conditions. However, if we consider the very particular scenario in which there is full vertical transmission in the mouse subpopulation, then the population of infected mice $I_m(t)$ does not vanish, while both the level of infection in the cat population and the quantity of oocysts in the

environment approaches zero. On the other hand, we have proven the uniqueness of the only biologically realistic toxoplasmosis endemic steady state when $\mathcal{R}_0 > 1$ and demonstrated that this endemic state is stable whenever $\mathcal{R}_0 > 1$. Moreover, the population of susceptible mice $S_m(t)$ vanishes, as the oocysts are always present and continue to infect cats. In summary, we were able to determine the conditions in which the single-celled parasite *T. gondii* can disappear from the environment. We found that the intermediate host (the mouse population) does not affect the likelihood of achieving the toxoplasmosis-free steady state. Based on the constructed model, the crucial population for eradication of the *T. gondii* parasite is the definitive host, that is, the cat population.

We performed several numerical simulations that supported the theoretical stability analysis obtained in this research. We used a number of parameter values that involved a degree of uncertainty. We varied a few of these parameters (such as the transmission rate) in order to determine dynamic aspects that were predicted from the theoretical results. This research is useful for health institutions, as it can assist in understanding the main factors that affect the dynamics of toxoplasmosis.

Finally, we need to mention several limitations of this research. A number of of these are common to mathematical modeling studies of epidemics. First, accurate estimations of certain parameter values are not yet available. Another important limitation is that the model does not incorporate all intermediate hosts. For instance, it has been documented that birds and sheep can act as intermediate hosts. Including more intermediate hosts would, of course, make the theoretical analysis more difficult. We expect to include these other hosts in future work. Additional limitations include the fact that cat and mouse populations were assumed to be constant. This could be unrealistic in many places around the world. Furthermore, we did not include the prey–predator relationship between the populations, which could be a factor in the eradication of toxoplasmosis. All these limitations are natural in epidemiological models, and are more relevant for multiple hosts. Nevertheless, this research provides deeper insight and understanding of toxoplasmosis dynamics. For instance, based on the analytical form of the basic reproduction number \mathcal{R}_0 , it can be deduced that the prevalence of toxoplasmosis can be reduced by implementing vaccination programs for cats and/or designing a process to reduce the amount of oocysts in the environment.

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