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Mathematical Model of In-host Dynamics of Snakebite Envenoming

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Abstract

In this paper, we develop an in-host mathematical model of snakebite envenoming that includes tissue, red blood and platelet cells of humans as specific targets of different kinds of toxins in the snake venom. The model is use to study some harmful effects of cytotoxic and hemotoxic snake venom on their target cells under the influence of snake antivenom. The model has two equilibrium points, namely, trivial and venom free. It has been shown that both the equilibrium points are globally asymptotically stable and numerical simulations illustrate the global asymptotic stability of the venom free equilibrium point. Furthermore, simulations reveal the importance of administering antivenom to avert the possible damage from venom toxins on the target cells. It is also shown through simulation that administering the required dose of antivenom can lead to the elimination of venom toxins within one week. Therefore, we recommend the administration of an adequate dose of antivenom therapy as it helps in deactivating venom toxins faster and consequently enhances the recovery time.

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1. Introduction

Snakebite envenoming is one of the most devastating neglected tropical diseases. It continues to impose a major public health and socio-economic burden in low and middle income countries around the world [1, 2, 3, 4, 5]. This neglected tropical disease, which is considered a serious public health issue in tropical and subtropical countries worldwide, is caused by venomous snake bites [6, 7, 8]. Globally, more than five million people are bitten by snakes every year [3, 4, 9]. It has been estimated that 1.8 - 2.7 million envenomations and 81 000 - 138 000 deaths occur annually, with an additional 400 000 amputations and other severe health consequences, such as infection, tetanus, scarring, contractures, and psychological sequelae [3, 4, 6, 7, 8, 10, 11]. The majority of snakebites occur in Africa and Southeast Asia. Snakebites are most common among people living in rural, resource-poor settings. Furthermore, agricultural workers, women, and children are the groups most at risk of being bitten by snakes [6, 7, 8, 9, 12, 13]. According to the World Health Organization (WHO) [14], there are more than 3000 species of snakes in the world, of which 600 are venomous and more than 200 are medically important. Venomous snakes cause substantial morbidity and mortality in humans. When a venomous snake strikes, it may likely inject venom into its vic-

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tim, as some bites may be dry, which is a bite that will not lead to the release of venom into its target [15]. These venomous snakes administer bites either as a method of hunting their prey, or as a means of protection against their predators [3]. According to Young and Zahn in [16] the rate of venom discharge and total volume of venom ejected by venomous snakes is much greater during defensive strikes than during predatory strikes. A defensive strike can have 10 times as much venom volume expelled at 8.5 times the flow rate. Snake species accountable for the majority of envenoming in the human population are categorized within the families of Elapidae (cobra, king cobra, krait, etc.) and Viperidae (Saw-scaled viper, pit viper, Russell's viper). Further, species belonging to the families Atractaspididae and Colubridae can also induce significant envenomation [17, 18, 19, 20, 21, 22, 23]. Snake venom is the poisonous, naturally yellow fluid stored in the adapted salivary glands of venomous snakes. Snake venom is mainly categorized into three namely: cytotoxins, neurotoxins and hemotoxins, which target body cells, nervous system and cardiovascular system respectively [14, 24]. According to León et al. in [25] when a snake bites and injects venom into its victim, two concurrent processes occur within the organism: (a) the development of toxic effects and (b) stimulation of immune responses in order to neutralize venom proteins. If the capability of snake venom to cause local and systemic mutilation surpasses the ability of the animal to assimilate and respond to the violence, an envenomation is established. According to some studies, the majority of snakebites occur on the hands, arms, or legs [26, 27]. Some signs and symptoms of snakebite may include: redness, swelling, and severe pain at the bite site, which may take up to an hour to appear. Further, vomiting, blurred vision, tingling of the limbs, and sweating may likely occur [26, 28]. The severity of snakebite depends on some factors, such as the kind of snake, the part of the body bitten, the quantity of venom injected, and the general health of the person bitten. The severity of snakebite is higher in children than in adults, due to their smaller size [9, 13, 29]. Snakebites can be avoided by wearing protective footwear, avoiding snake-infested areas, and not handling snakes [7, 13, 28, 30]. The use of snake antivenom remains the most effective method of averting death from bites. Nevertheless, antivenoms often have side effects [9, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48]. Some researches on snake venom focused on the use of venom toxins to control infections such as protozoal infections, cancers, and so on (see for instance [49, 50, 51, 52, 53] and references therein). Numerous population-based mathematical models have been developed to study the transmission dynamics and control of neglected tropical diseases and other diseases (see, for instance, [54, 55, 56, 57, 58, 59, 60] and references therein). Also, several in-host mathematical models for diseases such as HIV, HBV, HCV, Chagas disease, etc. have been successfully developed and were used to study the transmission dynamics and possible control of the pathogens inside the victim's body (for instance, see [61, 62, 63, 64, 65, 66] and references therein). However, the literature on the use of mathematical modeling techniques to gain an in-depth understanding of the dynamics of snake venom inside an envenomed person is scarce. Although not a mathematical model, Kini and Evans in [67] proposed a hypothetical model and explained how venom phospholipase A_2 enzymes exhibit specific pharmacological effects such as presynaptic neurotoxicity, cardiotoxicity, myotoxicity, anticoagulant and platelet effects. The research revealed how toxins and enzymes contained within the venom are drawn to specific tissues or cells due to their affinity for specific proteins. In 1994, Stagg [68] developed a mathematical model and studied the effect of cobra venom and its anti-venom inside the envenomed body (in-vivo). The work primarily described the neurotoxic type of snake venom and the cell that it targets. Furthermore, Tanos et al. [69] developed a semi-mechanistic model of the clotting cascade to describe the effect of procoagulant toxin from taipan venom and the effect of anti-venom in controlling venom-induced consumptive coagulapathy. Their work focuses on how the hemotoxic venom affects or disrupts blood clotting factors. We are motivated by the fact that in June 2017, WHO added snakebite envenoming to its priority list of neglected tropical diseases and has set a target to reduce its mortality and disability by 50% before the year 2030 [70]. Also, to the best of our knowledge, not much work has been done in terms of mathematical modeling to gain more insight into the dynamics and control of toxic effects of snake venom inside the host body. Thus, the aim of this study is to develop a novel in-host mathematical model that will describe the dynamics and control of cytotoxic snake venom that was not considered by the aforementioned studies. Moreover, the study will also investigate the impact and control of hemotoxic snake venom on red blood cells and platelets. Additionally, it is important to note that providing effective control of snakebite envenoming in a population may depend on a comprehensive understanding of the effects and dynamics of various kinds of toxins inside snake venom on their target cells (in-vivo). Therefore, this paper is committed to study the effects of interactions between snake venom (cytotoxic and hemotoxic) and their associated target cells with and without antivenom therapy. The paper is organized as follows: the model is formulated in section 2, analyzed in section 3. Results and discussion are reported in section 4 and conclusion is provided in section 5.

2. Model Formulation

A mathematical model that consists of nine in-host compartments is proposed in order to investigate the effects of snake venom and its target cells inside the human victim at a given time. The in-host compartments are: quantity of healthy tissue cells denoted by $T(t)$, quantity of healthy red blood cells represented by $R(t)$, quantity of healthy platelets denoted by $P(t)$, quantity of snake venom with cytotoxic and hemotoxic components expressed as $V(t)$, quantity of antivenom to be administered denoted by $A(t)$. We assumed that the quantity of antivenom to be administered is sufficient to neutralize the circulating venom within the victim's bloodstream. We also included damaged tissue cells (necrotic cells) caused by the cytotoxic component of venom toxins (necrotoxins), denoted by $N(t)$, damaged red blood cells (hemolyzed cells) caused by the hemotoxic component of venom toxins, denoted by $H(t)$, damaged

platelets caused by the hemotoxic component of venom toxins (platelets toxins), denoted by $D(t)$, and venom-antivenom complexes expressed as $C(t)$. The quantity of healthy tissue cells is replenished at a logistic growth rate given by $\gamma_T T\left(1-\frac{T}{K_T}\right)$ with $T \leq K_T$. It is decreased as it undergoes necrosis by direct action of the venom's cytotoxic components (necrotoxin) that begin at the bite site at a constant destruction rate that follows the law of mass action given by $(\beta_1 TV)$. The damaged cells caused by venom-induced necrosis are known as necrotic cells. The healthy tissue cells further decreased due to the elimination of the dead cells at a rate μ_T. Thus, the equation governing the dynamics of healthy tissue cells is given by

$$\frac{dT}{dt} = \gamma_T T\left(1-\frac{T}{K_T}\right) - \beta_1 TV - \mu_T T. \tag{1}$$

The quantity of healthy red blood cells is replenished at a logistic growth rate denoted by $\gamma_R R\left(1-\frac{R}{K_R}\right)(R \leq K_R)$. After 120 days it is reduced by natural elimination from the host body at a rate μ_R. It further decreased because of the damage it undergoes as a result of the deleterious effects of the hemotoxic component of the venom as it circulates in the victim's blood stream. The action of the hemotoxic component of the venom also follows the law of mass action given by $(\beta_2 RV)$. The damaged red blood cells due to venom-induced hemolysis are termed hemolyzed cells. Thus, we have

$$\frac{dR}{dt} = \gamma_R R\left(1-\frac{R}{K_R}\right) - \beta_2 RV - \mu_R R. \tag{2}$$

The quantity of healthy platelets is replenished at a logistic growth rate of $\gamma_P P\left(1-\frac{P}{K_P}\right)(P \leq K_P)$. It is reduced by natural elimination of the dead platelet cells at a rate of μ_P. It decreases further because the hemotoxic component of the venom (platelet toxins) activates and damages platelets at a rate of β_3. This effect may cause serious internal bleeding. Thus, the following equation is obtained

$$\frac{dP}{dt} = \gamma_P P\left(1-\frac{P}{K_P}\right) - \beta_3 PV - \mu_P P. \tag{3}$$

It is assumed that an initial quantity of venom injected by an offending snake is in circulation in the host body. Therefore, the quantity of venom decreases because of its reaction with the various target cells, i.e. tissue, red blood, and platelet cells at the rates β_1, β_2 and β_3 respectively. It further diminishes due to its neutralization by antivenom that is describe by the law of mass action $(\beta_4 AV)$. This reaction produces venom-antivenom complexes that are not harmful to the body. The amount of venom is also eliminated at a rate μ_V. Therefor, the following equation is formed

$$\frac{dV}{dt} = -\beta_1 TV - \beta_2 RV - \beta_3 PV - \beta_4 AV - \mu_V V. \tag{4}$$

When the required dose of snake antivenom is administered, its action is to neutralize the circulating venom toxins inside the victim's body. The quantity of antivenom inside the host body is decreased because of the reaction between venom and antivenom that follows the law of mass action given by $(\beta_4 AV)$. The unused antivenom is then removed at a rate of μ_A. Thus, we have

$$\frac{dA}{dt} = -\beta_4 AV - \mu_A A. \tag{5}$$

The quantity of necrotic cells is formed because of the reaction between the cytotoxic component of the venom (necrotoxin) and the tissue cells at the rate β_1 and is eliminated at a rate μ_N. Therefore, we obtain

$$\frac{dN}{dt} = \beta_1 TV - \mu_N N. \tag{6}$$

The quantity of hemolyzed cells is formed due to the reaction between the hemotoxic component of the venom and the red blood cells at the rate β_2 and is eliminated at a rate μ_H. Thus, we have

$$\frac{dH}{dt} = \beta_2 RV - \mu_H H. \tag{7}$$

The formation of the quantity of damaged platelets occurs as a result of reaction between the platelet toxins and the healthy platelet cells at the rate β_3. It decays at a rate of μ_D. Therefore, we have

$$\frac{dD}{dt} = \beta_3 PV - \mu_D D. \tag{8}$$

The quantity of venom-antivenom complexes is produced because of the neutralization of venom by antivenom and is eliminated from the body at a rate μ_C. So that

$$\frac{dC}{dt} = \beta_4 AV - \mu_C C. \tag{9}$$

Based on the aforementioned description of the model, the in-host dynamics of interaction between cytotoxic and hemotoxic venom, their target cells, and antivenom is described by the following system of first order nonlinear ordinary differential equations. The schematic diagram is depicted in Figure 1, and the corresponding variables and parameters are tabulated in Tables 1 and 2, respectively:

$$\begin{aligned}
\frac{dT}{dt} &= \gamma_T T\left(1-\frac{T}{K_T}\right) - \beta_1 TV - \mu_T T,\\
\frac{dR}{dt} &= \gamma_R R\left(1-\frac{R}{K_R}\right) - \beta_2 RV - \mu_R R,\\
\frac{dP}{dt} &= \gamma_P P\left(1-\frac{P}{K_P}\right) - \beta_3 PV - \mu_P P,\\
\frac{dV}{dt} &= -\beta_1 TV - \beta_2 RV - \beta_3 PV - \beta_4 AV - \mu_V V,\\
\frac{dA}{dt} &= -\beta_4 AV - \mu_A A,\\
\frac{dN}{dt} &= \beta_1 TV - \mu_N N,\\
\frac{dH}{dt} &= \beta_2 RV - \mu_H H,\\
\frac{dD}{dt} &= \beta_3 PV - \mu_D D,\\
\frac{dC}{dt} &= \beta_4 AV - \mu_C C,
\end{aligned} \tag{10}$$

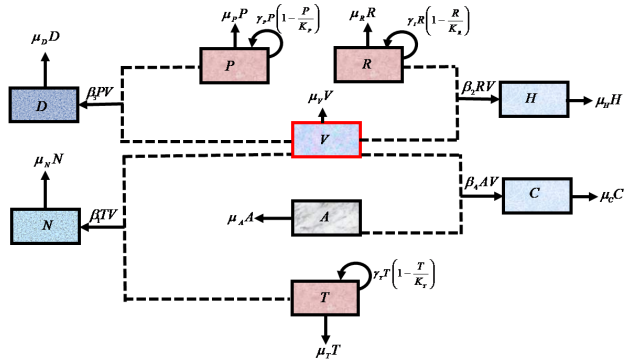


Figure 1. Schematic diagram of the model.
Note that, in the schematic diagram of the model, the dotted lines indicate the reactions between venom toxins and their target cells (which produce damaged cells) and the neutralization of venom toxins by antivenom (which leads to the formation of venom-antivenom complexes). The solid arrows represent the self-replenishment of the healthy cells, the formation of damaged cells and venom-antivenom complexes. It also indicates the natural elimination of damaged or dead cells from the host body.

Table 1. Description of State Variables of the Model.

Variables	Description
T(t)	Quantity of healthy tissue cells at time t
R(t)	Quantity of healthy red blood cells at time t
P(t)	Quantity of healthy platelets at time t
V(t)	Quantity of venom in the victim blood stream at time t
A(t)	Quantity of antivenom in the victim blood stream at time t
N(t)	Quantity of damaged tissue (necrotic cells) at time t
H(t)	Quantity of damaged red blood cells (hemolyzed cells) at time t
D(t)	Quantity of damaged platelets at time t
C(t)	Quantity of venom-antivenom complexes at time t

with the initial conditions

$$T(0) > 0, \quad R(0) > 0, \quad P(0) > 0,$$
$$V(0) = V_0 \geq 0, A(0) = A_0 \geq 0, \quad N(0) \geq 0,$$
$$H(0) \geq 0, \quad D(0) \geq 0, \quad C(0) \geq 0. \quad (11)$$

3. Model Analysis

3.1. Basic properties of the model

This section presents some essential properties of the in-host model. It is vital to show that the state variables of the model

Table 2. Description of Parameter of the Model.

Parameter	Description
$\gamma_i (i = T, R, P)$	Replenishment rates of tissue cells, red blood cells and platelets respectively
$K_i (i = T, R, P)$	Maximum quantities of tissue cells, red blood cells and platelets respectively
$\mu_i (i = T, R, P)$	Elimination rates of tissue, red blood, platelet cells respectively
$\mu_i (i = N, H, D)$	Elimination rates of damaged tissue, red blood, and platelet cells respectively
$\mu_i (i = V, A, C)$	Elimination rates of venom, antivenom and venom-antivenom complexes respectively
β_1	Rates at which cytotoxic component of the venom (necrotoxins) destroys tissue cells
β_2	Rate at which hemotoxic component of the venom (hemotoxins) destroys red blood cells
β_3	Rate at which hemotoxic component of the venom (platelet toxins) damages platelets
β_4	Naturalization rate of venom by antivenom

are non-negative for all $t > 0$. If this result is established, then it is sufficient to say that the model (10) is mathematically and biologically reasonable. It is crucial to assume that the model parameters given in Table 2 are positive. For mathematical convenience let $\mu_1 = min\{\mu_T, \mu_N\}$, $\mu_2 = min\{\mu_R, \mu_H\}$ and $\mu_3 = min\{\mu_P, \mu_D\}$. Further, let V_0 denotes the amount of venom that the offending snake injected into its victim at the initial time. Thus, we assume that quantity of venom inside the host at any given time is presented as

$$V(t) \leq V_0. \quad (12)$$

Similarly, let A_0 be the initial dose of antivenom administered into the victim's bloodstream, which we assumed was sufficient to neutralize the circulating venom for simplicity. Thus, it is assumed that the quantity of antivenom inside the host at any given time is given

$$A(t) \leq A_0. \quad (13)$$

Theorem 3.1. *Let the initial data of the model (10) be non-negative, then the model solutions given by* $(T, R, P, V, A, N, H, D, C)$ *are all non-negative for every* $t > 0$.

Proof. Let $t^1 = sup\{t > 0 : T > 0, R > 0, P > 0, V > 0, A > 0, N > 0, H > 0, D > 0, C > 0, \}$.
Thus, $t^1 > 0$. Taking the first equation of the model (10) we have,

$$\frac{dT}{dt} = \gamma_T T\left(1 - \frac{T}{K_T}\right) - \beta_1 TV - \mu_T T. \quad (14)$$

Since, $T \leq K_T$ we have

$$\frac{dT}{dt} \geq -(\beta_1 TV + \mu_T T). \quad (15)$$

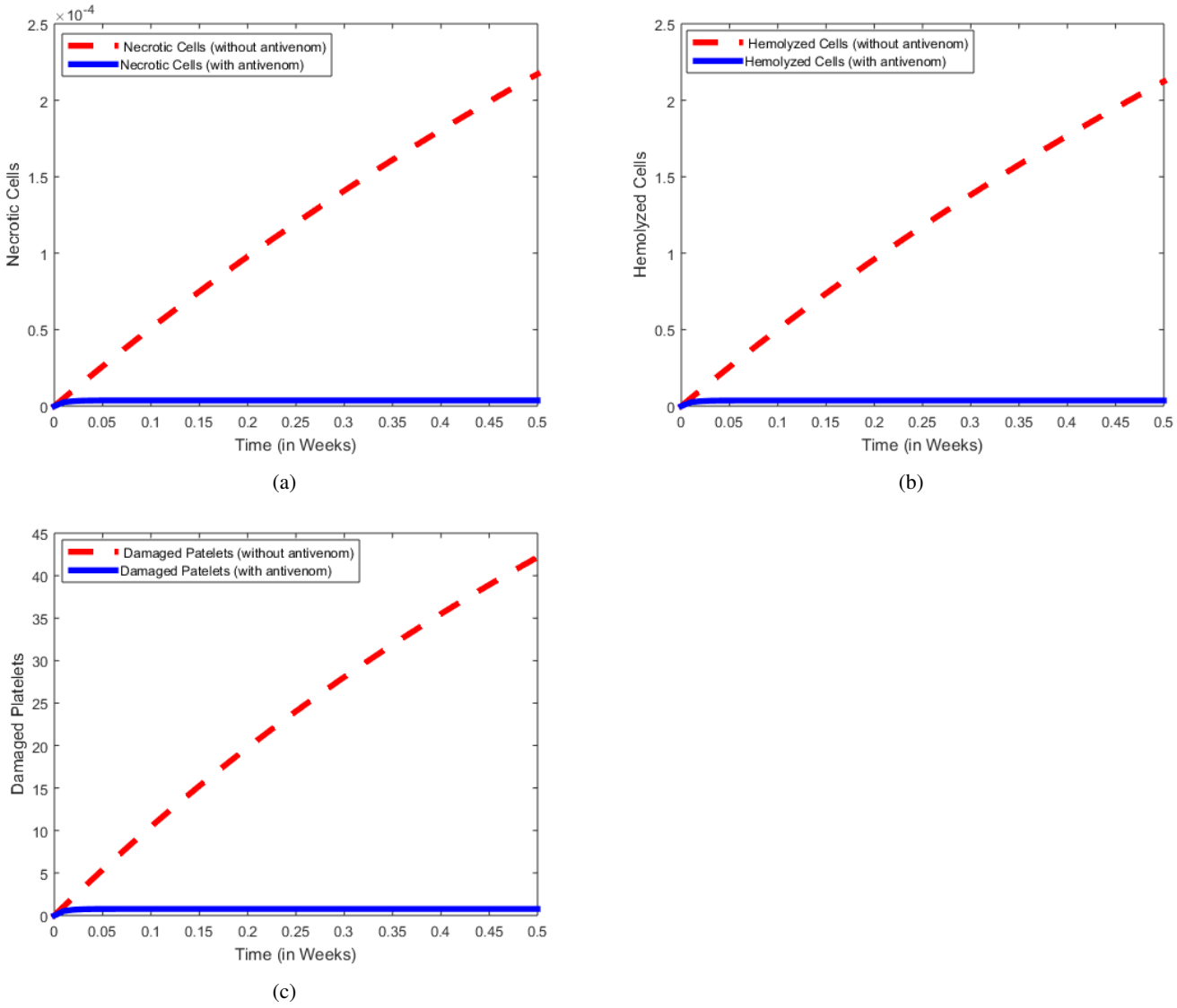


Figure 2. Graph showing the lethal effects of Russell's Viper venom with and without antivenom on **(a)** tissue cells **(b)** red blood cells **(c)** Platelets. In Figures (a), (b) and (c), the red dotted lines indicate the quantities of damaged tissue cells, red blood cells and platelets without the influence of antivenom. While the blue solid lines represent quantities of damaged tissue cells, red blood cells and platelets under the influence of antivenom.

Now integrating both sides from t=0 to $t = t^1$ we obtain,

$$\int_0^{t^1} \left(\frac{1}{T}\right) dT \geq -\left[\int_0^{t^1} (\mu)\, dt + \int_0^{t^1} (\beta_1 V(\tau))\, d\tau\right]$$

$$T(t) \geq T(0) \exp\left[-\left(\mu t^1 + \int_0^{t^1} \beta_1 V(\tau) d\tau\right)\right] > 0.$$

Thus, $T\left(t^1\right) > 0$ for all $t^1 > 0$, hence, $T(t) > 0$ for $t > 0$. Following similar technique, it can be established that the remaining eight variables R, P, V, A, N, H, D, C are all positive for $t > 0$. Consequently , the solutions of the system (10) remain positive for all $t > 0$. □

Lemma 3.1. *The closed set*
$\Omega = \{(T, R, P, V, A, N, H, D, C) \in \mathbb{R}^9_+ : P_1 \leq \frac{\gamma_T K_T}{\mu_T}, P_2 \leq \frac{\gamma_R K_R}{\mu_R}, P_3 \leq \frac{\gamma_P K_P}{\mu_P}, C \leq \frac{\beta_4 A_0 V_0}{\mu_C}\}$, *is positively invariant.*

Proof. Let P_1 represents the total quantity of healthy and damaged tissue cells (necrotic). Thus, $P_1 = T + N$ and $\frac{dP_1}{dt} = \frac{dT}{dt} + \frac{dN}{dt}$. Now, adding the first and sixth equations of system (10) we get

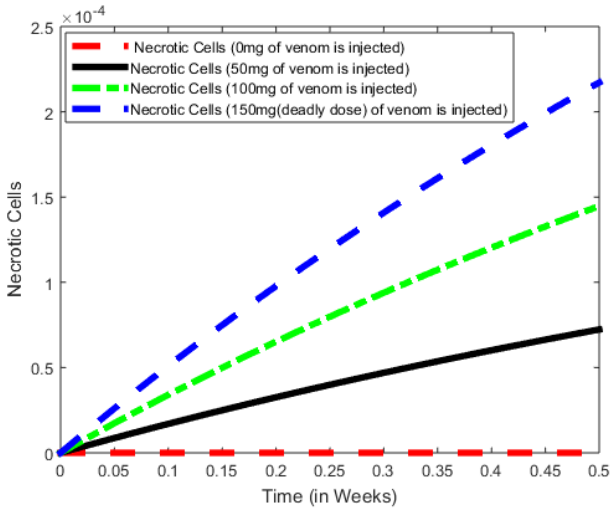
$$\frac{dP_1}{dt} = \gamma_T T\left(1 - \frac{T}{K_T}\right) - \mu_1 P_1. \tag{16}$$

It follows that

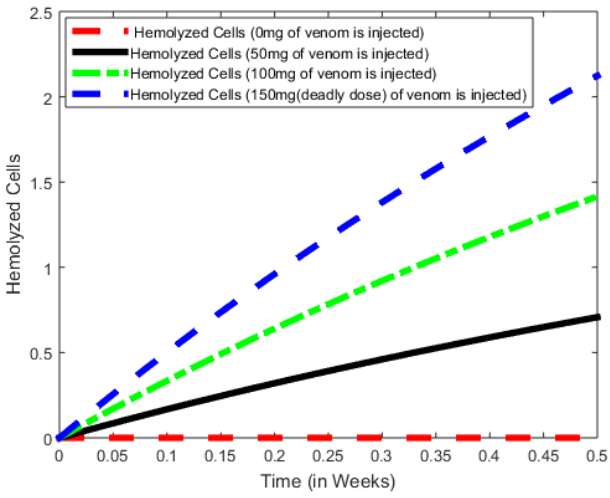
$$\frac{dP_1}{dt} \leq \gamma_T K_T - \mu_1 P_1.$$

Applying comparison theorem [73] it can be shown that

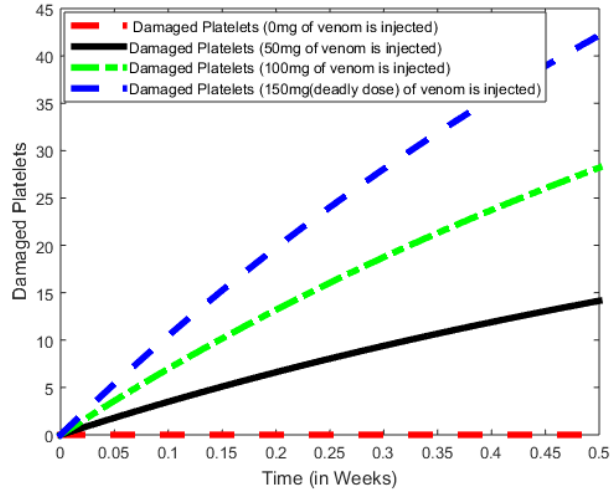
$$P_1(t) \leq P_1(0)e^{-\mu_1 t} + \frac{\gamma_T K_T}{\mu_1}\left[1 - e^{-\mu_1 t}\right].$$



(a)



(b)



(c)

Figure 3. Simulations showing the effects of varying the initial amount of Russell's Viper venom injected on **(a)** tissue cells **(b)** red blood cells **(c)** Platelets. The red dashed, black solid, green dashed, and blue dashed lines denote the quantities of damaged tissue, red blood and platelet cells when $0mg, 50mg, 100mg$ and $150mg$ of venom are injected, respectively.

Thus, $\limsup_{t\to\infty} P_1(t) \leq \frac{\gamma_T K_T}{\mu_1}$.

Similarly, let P_2 denotes the total quantity of healthy and damaged red blood cells (hemolyzed). Thus, $P_2 = R + H$ and $\frac{dP_2}{dt} = \frac{dR}{dt} + \frac{dH}{dt}$. Now, adding the second and seventh equations of system (10) we obtain

$$\frac{dP_2}{dt} = \gamma_R R\left(1 - \frac{R}{K_R}\right) - \mu_2 P_2. \tag{17}$$

It follows that

$$\frac{dP_2}{dt} \leq \gamma_R K_R - \mu_2 P_2.$$

Applying comparison theorem [73] it can be shown that

$$P_2(t) \leq P_2(0)e^{-\mu_2 t} + \frac{\gamma_R K_R}{\mu_2}\left[1 - e^{-\mu_2 t}\right].$$

Thus, $\limsup_{t\to\infty} P_2(t) \leq \frac{\gamma_R K_R}{\mu_2}$. In the same manner let P_3 denotes the total quantity of healthy and damaged platelets. Thus, $P_3 = P + D$ and $\frac{dP_3}{dt} = \frac{dP}{dt} + \frac{dD}{dt}$. Now, adding the third and eighth equations of system (10) we get

$$\frac{dP_3}{dt} = \gamma_P P\left(1 - \frac{P}{K_P}\right) - \mu_3 P_3. \tag{18}$$

It follows that

$$\frac{dP_3}{dt} \leq \gamma_P K_P - \mu_3 P_3.$$

Applying comparison theorem [73] it can be shown that

$$P_3(t) \leq P_3(0)e^{-\mu_3 t} + \frac{\gamma_P K_P}{\mu_3}\left[1 - e^{-\mu_3 t}\right].$$

Thus, $\limsup_{t\to\infty} P_3(t) \leq \frac{\gamma_P K_P}{\mu_3}$. Finally, taking the ninth equation of

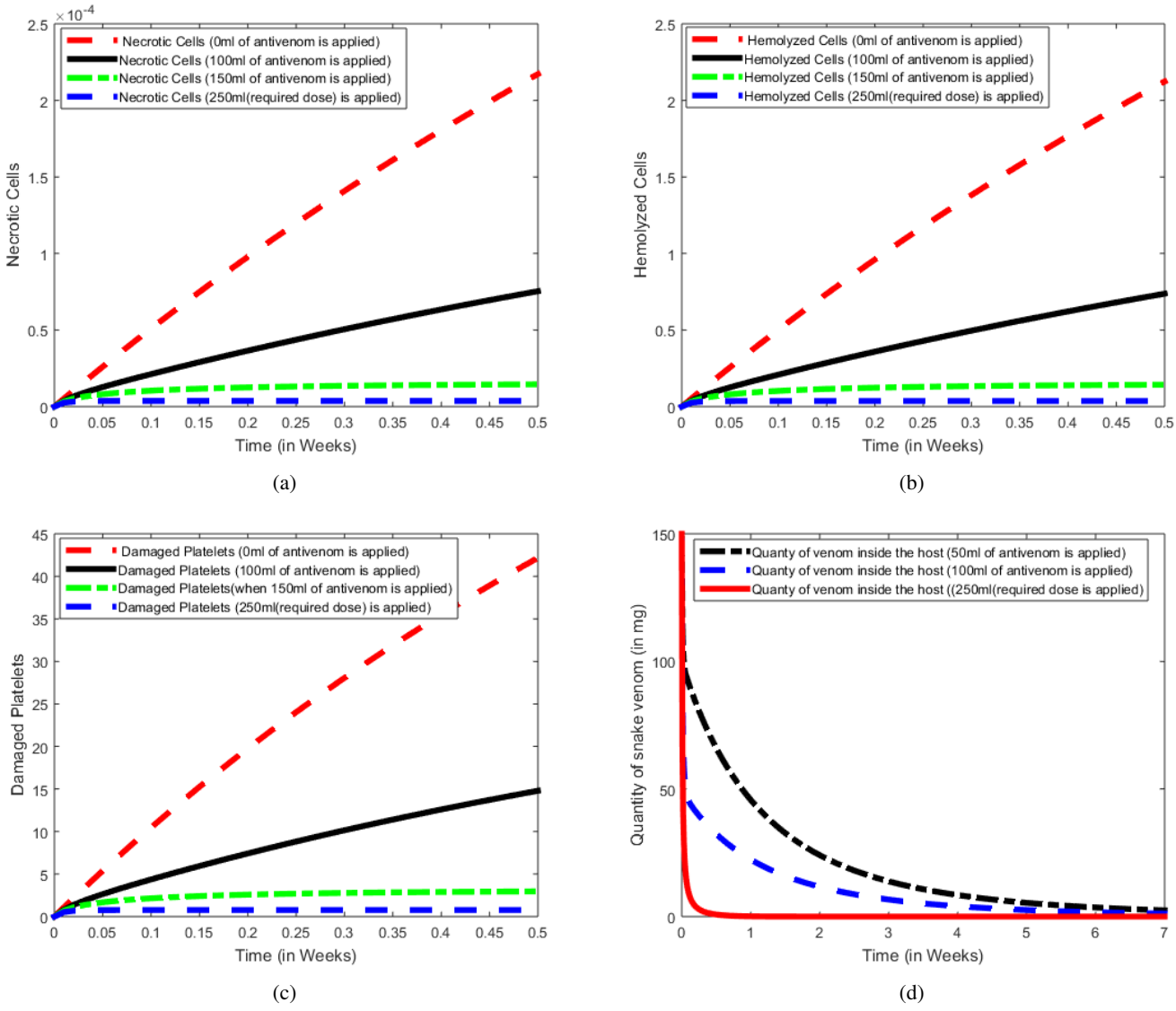


Figure 4. Simulations showing the effects of varying the initial dose of snake antivenom in averting damaged **(a)** tissue cells **(b)** red blood cells **(c)** Platelets and **(d)** deactivating venom inside the host body. In Figures 4a, 4b and 4c, the red dashed, black solid, green dashed, and blue dashed lines represent the quantities of necrotic, hemolyzed and damaged platelet cells when $0ml$, $100ml$, $150ml$ and $250ml$ of antivenom are administered, respectively. While in Figure 4d, the black dashed, blue dashed and red solid lines represent the quantities of venom inside the host body when $50ml$, $100ml$ and $250ml$ of antivenom are administered, respectively.

system (10) and using $V(t) \leq V_0, A(t) \leq A_0$ we have

$$\frac{dC}{dt} \leq \beta_4 A_0 V_0 - \mu_C C. \tag{19}$$

Consequently, using the comparison theorem in conjunction with the integrating factor technique of solving first order linear differential equations, we have

$$C(t) \leq C(0)e^{-\mu_C t} + \frac{\beta_4 A_0 V_0}{\mu_C}\left[1 - e^{-\mu_C t}\right].$$

Thus, $\limsup_{t\to\infty} C(t) \leq \frac{\beta_4 A_0 V_0}{\mu_C}$. Hence, Ω is positively invariant, meaning that, all the solutions starting in Ω stay in Ω for $t > 0$. Thus, it is established that Ω is an attracting set. □

Since, the region Ω is positively invariant, it suffice to investigate the dynamics of the model equations given by (10) in Ω, where the usual existence, uniqueness, continuation of solutions hold.

4. Results and Discussion

4.1. Equilibrium Points of the Model

To obtain the equilibrium points of the model equations given by system (10) the right hand side of each equation in system (10), is set to zero and solves for the associated state variables. The model equations have two non-negative equilibrium points, viz; the trivial and the venom free equilibrium points, denoted

by ε_0 and ε_1 correspondingly. The results obtained are presented in the following subsections.

4.1.1. Trivial Equilibrium Point

The trivial equilibrium point is presented as follows:
$\varepsilon_0 = \left(T^0, R^0, P^0, V^0, A^0, N^0, H^0, D^0, C^0\right) = (0,0,0,0,0,0,0,0,0)$.
It is important to note that this equilibrium point is biologically not feasible. However, its qualitative analysis is of interest.

4.1.2. Venom Free Equilibrium Point

The venom free equilibrium point of the model is given by:

$$\begin{aligned}\varepsilon_1 &= (T^*, R^*, P^*, V^*, A^*, N^*, H^*, D^*, C^*)\\ &= \left(\frac{K_T(\gamma_T-\mu_T)}{\gamma_T}, \frac{K_R(\gamma_R-\mu_R)}{\gamma_R}, \frac{K_P(\gamma_P-\mu_P)}{\gamma_P}, 0,0,0,0,0,0\right).\end{aligned} \tag{20}$$

This equilibrium point is biologically and mathematical feasible. It describes the healthy state of tissue, red blood cells and platelets. Observe that if $\gamma_T = \mu_T, \gamma_R = \mu_R$ and $\gamma_P = \mu_P$ then the equilibrium point ε_1 reduces to ε_0. Therefore, for the equilibrium point ε_1 to be positive we must have $\gamma_T > \mu_T, \gamma_R > \mu_R$ and $\gamma_P > \mu_P$.

4.1.3. Global Stability of Equilibrium Points of the Model

Here we shall use Lyapunov function theory in conjunction with La-Salle's invariance principle to establish the global asymptotic stability of the trivial and venom free equilibrium points.

4.1.4. Global Stability of Trivial Equilibrium Point

Theorem 4.1. *The trivial equilibrium point (ε_0) of model (10), is globally asymptotically stable in* Ω.

Proof. The stability analysis of (ε_0) is simplified by defining a perturbation

$$W = X - \varepsilon_0, \quad X = (T,R,P,V,A,N,H,D,C). \tag{21}$$

Therefore, model (10) is expressed as:

$$\frac{dW}{dt} = B(W)W, \tag{22}$$

where $W = W_i^T (i = 1, ..., 9)$ and $B(W)$ is a matrix of coefficients of the system (10) with the variables $W_i (i = 1, ..., 9)$, this is presented as follows: where, $Z_{11} = \frac{(\gamma_T-\beta_1W_4-\mu_T)K_T-2\gamma_TW_1}{K_T}$, $Z_{22} = \frac{(\gamma_R-\beta_2W_4-\mu_R)K_R-2\gamma_RR}{K_R}$,
$Z_{33} = \frac{(\gamma_P-\beta_3W_4-\mu_P)K_P-2\gamma_PP}{K_P}$, $Z_{44} = -\beta_1W_1 - \beta_2W_2 - \beta_3W_3 - \beta_4W_5 - \mu_V$.
Observe that $\varepsilon_W = (0,0,0,0,0,0,0,0,0)$, is the only equilibrium point of equation (22). Furthermore, we consider the following Lypunov function as applied in the following studies [74, 75, 76] and references therein.

$$V(W) = \langle Y, W\rangle, \quad Y = (1,1,1,1,1,1,1,1,1) > 0. \tag{24}$$

$$\begin{aligned}V'(W) &= \langle Y, B(W)W\rangle,\\ &= Z_{11}W_1 + Z_{22}W_2 + Z_{33}W_3\\ &\quad - (W_1\beta_1 + W_2\beta_2 + W_3\beta_3 + W_5\beta_4 + \mu_V)W_4\\ &\quad - (W_4\beta_4 + \mu_A)W_5 - \mu_NW_6 - \mu_HW_7 - \mu_DW_8 - \mu_CW_9,\\ &= \left(\gamma_T\left(1-\frac{W_1}{K_T}\right) - \frac{\gamma_TW_1}{K_T} - \beta_1W_4 - \mu_T\right)W_1\\ &\quad + \left(\gamma_R\left(1-\frac{W_2}{K_R}\right) - \frac{\gamma_RW_2}{K_R} - \beta_2W_4 - \mu_R\right)W_2\\ &\quad + \left(\gamma_P\left(1-\frac{W_3}{K_P}\right) - \frac{\gamma_PW_3}{K_P} - \beta_3W_4 - \mu_P\right)W_3\\ &\quad - (\beta_1W_1 + \beta_2W_2 + \beta_3W_3 + \beta_4W_5 + \mu_V)W_4\\ &\quad - (\beta_4W_4 + \mu_A)W_5 - \mu_NW_6 - \mu_HW_7 - \mu_DW_8 - \mu_DW_9.\end{aligned} \tag{25}$$

Consider the following conditions:

$$W_1 \le K_T, \quad W_2 \le K_R, \quad W_3 \le K_P. \tag{26}$$

Therefore, applying the conditions given in (26) in equation (25) we obtain

$$\begin{aligned}V'(W) \le &-\left(\frac{\gamma_TW_1}{K_T} + \beta_1W_4 + \mu_T\right)W_1 - \left(\frac{\gamma_RW_2}{K_R} + \beta_2W_4 + \mu_R\right)W_2\\ &- \left(\frac{\gamma_PW_3}{K_P} + \beta_3W_4 + \mu_P\right)W_3\\ &- (\beta_1W_1 + \beta_2W_2 + \beta_3W_3 + \beta_4W_5 + \mu_V)W_4\\ &- (\beta_4W_4 + \mu_A)W_5 - \mu_NW_6 - \mu_HW_7 - \mu_DW_8 - \mu_CW_9.\end{aligned} \tag{27}$$

Thus, $V'(W) \le 0$ with $V'(W) = 0$, if and only if $W_i = 0, (i = 1, 2, ..., 9)$. Hence, $V(W)$ is Lypunov function in Ω. Further, since, Ω is an invariant and attracting set as established in Lemma (3.1) it follows from La-Salle's invariance principle in [77] that the maximum invariant set contained in $\{V/V'(W) = 0\}$ is ε_W. Consequently, the transformed equilibrium point ε_W, is globally asymptotically stable in Ω. Hence, the trivial equilibrium, ε_0, is also globally asymptotically stable in Ω. □

4.1.5. Global Stability of Venom Free Equilibrium Point

Theorem 4.2. *The venom free equilibrium point (ε_1) of model (10), is globally asymptotically stable in* Ω.

Proof. Consider the following linear Lyapunov function given by:

$$\mathcal{W}(t) = a_1V(t) + a_2N(t) + a_3H(t) + a_4D(t) + a_5C(t), \tag{28}$$

where $a_i, i = 1, ...5$ are positive constants to be chosen later. The time derivative of the Lyapunov function along the solutions of model (10) is given as;

$$\begin{aligned}\dot{\mathcal{W}}(t) &= a_1\dot{V}(t) + a_2\dot{N}(t) + a_3\dot{H}(t) + a_4\dot{D}(t) + a_5\dot{C}(t),\\ &= a_1\left[-\beta_1TV - \beta_2RV - \beta_3AV - \mu_VV\right] + a_2\left[\beta_1TV - \mu_NN\right]\\ &+ a_3\left[\beta_2RV - \mu_HH\right] + a_4\left[\beta_3PV - \mu_DD\right] + a_5\left[\beta_4AV - \mu_CC\right].\end{aligned} \tag{29}$$

$$B(W) = \begin{bmatrix} Z_{11} & 0 & 0 & -\beta_1 W_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & Z_{22} & 0 & -\beta_2 W_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & Z_{33} & -\beta_3 W_3 & 0 & 0 & 0 & 0 & 0 \\ -\beta_1 W_4 & -\beta_2 W_4 & -\beta_3 W_4 & Z_{44} & -\beta_4 W_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\beta_4 W_5 & -\beta_4 W_4 - \mu_A & 0 & 0 & 0 & 0 \\ \beta_1 W_4 & 0 & 0 & \beta_1 W_1 & 0 & -\mu_N & 0 & 0 & 0 \\ 0 & \beta_2 W_4 & 0 & \beta_2 W_2 & 0 & 0 & -\mu_H & 0 & 0 \\ 0 & 0 & \beta_3 W_4 & \beta_3 W_3 & 0 & 0 & 0 & -\mu_D & 0 \\ 0 & 0 & 0 & \beta_4 W_5 & \beta_4 W_4 & 0 & 0 & 0 & -\mu_C \end{bmatrix}, \quad (23)$$

$$\dot{\mathcal{W}} = (a_1 - a_2)\beta_1 TV + (a_1 - a_3)\beta_2 RV + (a_1 - a_4)\beta_3 PV + (a_1 - a_5)\beta_4 AV - a_1\mu_V V - a_2\mu_N N - a_3\mu_H H - a_4\mu_D D - a_5\mu_C C. \quad (30)$$

Choosing $a_i = \frac{1}{\mu_V\mu_N\mu_H\mu_D\mu_C}$ for $(i = 1, ...5)$ and applying it in equation (30) we obtain

$$\dot{\mathcal{W}} = -\left[\left(\frac{1}{\mu_N\mu_H\mu_D\mu_C}\right)V + \left(\frac{1}{\mu_V\mu_H\mu_D\mu_C}\right)N + \left(\frac{1}{\mu_V\mu_N\mu_D\mu_C}\right)H\right] - \left[\left(\frac{1}{\mu_V\mu_N\mu_H\mu_C}\right)D + \left(\frac{1}{\mu_V\mu_N\mu_H\mu_D}\right)C\right]. \quad (31)$$

Consequently, using equation (31), it follows that $\dot{\mathcal{W}} < 0$ unconditionally, since all the model parameters are positive in Ω. For $\dot{\mathcal{W}} = 0$ we must have $V = N = H = D = C = 0$. Following the claim that Ω is invariant and attracting set, it follows that the largest possible invariant set in Ω is the singleton ε_1. According to La-Salle's invariance principle [77], ε_1 is globally attractive. Therefore, the venom free equilibrium, ε_1, is globally asymptotically stable. □

4.2. Numerical Simulation

In this section, some numerical simulations were performed using the values of the model parameters in Table 3. According to Bawaskar in [79], the deadly dose of Russell's viper venom is $V_0 = 150mg$ and the initial dose of antivenom needed to neutralize the venom is $A_0 = 250ml$. The numerical simulation results are shown in Figures 2, 3, 4, 5 and 6.

4.2.1. Effects of venom toxins on target cells with and without antivenom

Figure 2a shows the deleterious effects of toxins inside the Russell's viper venom on the tissue cells. It can be observed that the quantity of damaged tissue cells is on the increase when antivenom is not administered (red dot line). On the other hand, a negligible quantity of damaged tissue cells is noticed when antivenom is administered (blue line). Also, in Figures 2b and 2c

Table 3. Values of parameter used in numerical simulation.

Parameter	Values	Reference
γ_T	0.009 week^{-1}	Estimated
γ_R	$\frac{1}{17.143}$week^{-1}	[71, 72]
γ_P	$\frac{1}{1.429}$week^{-1}	[78]
$K_i(i = T, R, P)$	80000, 10000, 5000	Estimated
μ_T	$\frac{1}{3}$week^{-1}	Estimated
μ_R	$\frac{1}{17.143}$week^{-1}	[71, 72]
μ_P	$\frac{1}{1.429}$week^{-1}	[78]
$\mu_i(i = V, A, N)$	0.1, 0.013, 0.001	Estimated
$\mu_i(i = H, D, C)$	0.0012, 0.00013, 0.0002	Estimated
$\beta_i(i = 1, 2)$	$7.1 \times 10^{-11}, 5.1 \times 10^{-06}$	Estimated
$\beta_i(i = 3, 4)$	$3.7 \times 10^{-04}, 0.87$	Estimated

we notice a significant amount of damaged red blood cells and platelets in the absence of antivenom to neutralize the circulating venom. However, an insignificant number of damaged red blood cells and platelets are observed when snake antivenom is administered.

4.2.2. Effects of varying initial quantity of venom on the target cells

The dynamical effect of increasing the initial dose of venom on the target cells is depicted in Figure 3. The outcome reveals that the amounts of injured tissue, red blood cells, and platelet cells increase as the initial dose of venom increases. This result suggests that the magnitude of damage to be inflicted by venom toxins on the target cells depends on the initial quantity of venom injected by the offending snake. Therefore, determining the amount of venom injected by the offending snake is crucial in the management of snakebite patients.

4.2.3. Effects of varying initial dose of antivenom on the damaged cells and the venom

The simulations in Figures 4a, 4b and 4c demonstrate the effect of varying antivenom doses in preventing damaged cells as a result of venom toxins. It is obvious that the application of the re-

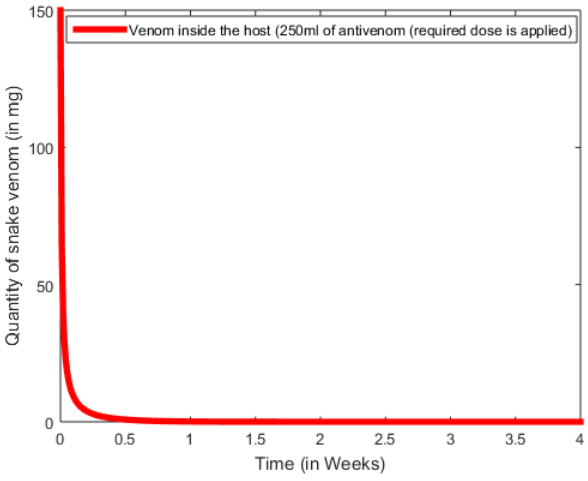


Figure 5. Simulation showing the effect of using adequate dose of antivenom in decreasing the quantity of venom inside the host.

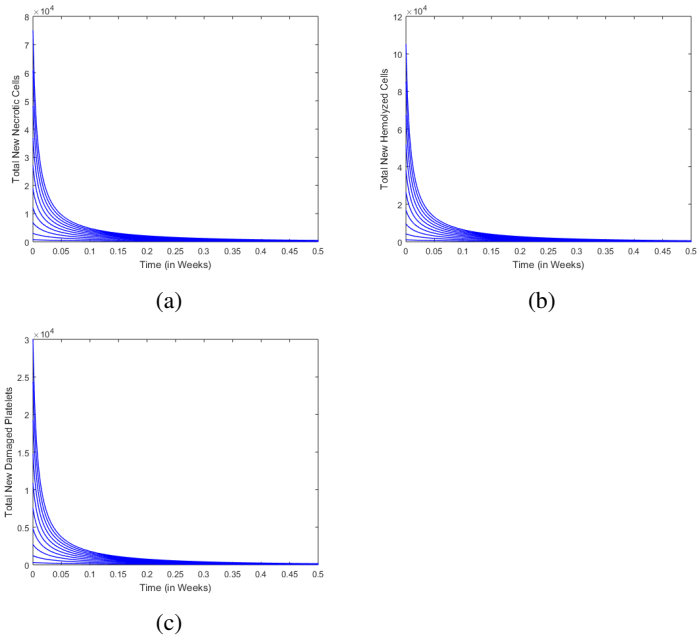


Figure 6. Simulation results showing total quantity of damaged **(a)** tissue cells **(b)** red blood cells **(c)** platelets. In all the cases different initial conditions were used to illustrate the result of global asymptotic stability of the venom free equilibrium point.

quired dose of antivenom is more effective in terms of averting damaged cells. Also, the dynamics of varying the initial dose of antivenom in deactivating venom toxins inside the host body is depicted in Figure 4d. It is evident that when a lower-than-required amount of antivenom is administered, it takes longer time to neutralize the quantity of venom inside the host. On the other hand, when the required amount of antivenom is applied, it takes less time to neutralize the venom toxins. This finding supports the need for administering an adequate dose of antivenom in order to enhance the time of neutralizing the lethal dose of venom within the host.

4.2.4. Effect of adequate dose of antivenom in decreasing the quantity of venom inside the host body

According to the simulation result shown in Figure 5, application of adequate dose of antivenom leads to the elimination of a deadly dose of Russell viper venom within one week. This result is in line with the recovery time for snakebite envenoming in Treatment and Research Hospital, Katungo, Gombe state, as reported in [80]. This finding supports the use of the recommended dose of antivenom in the treatment of snakebites envenoming, since it will not only prevent harm to the cells but also speed up recovery time. It is worth mentioning that the epidemiological implication of the numerical results provided in Figures 2, 3, 4 and 5 is that whenever snakebite envenomation is confirmed, the required doses of antivenom therapy should be administered as soon as possible to avoid the potential damage that venom toxins will inflict on target cells. As a result, envenomation-related deaths and disabilities will be avoided.

4.2.5. Numerical illustration of global asymptotic stability of the venom free equilibrium point

The results in Figures 6a, 6b and 6c illustrate the convergence of solutions to the venom free equilibrium point which uphold the result of global asymptotic stability of venom free equilibrium point presented in Theorem 4.2.

5. Conclusions

In this work, we developed and analyzed an in-host model of snakebite envenoming. The model was used to study some toxic effects of snake venom on tissue, red blood, and platelet cells of humans under the influence of snake antivenom. The basic properties of the model in terms of positvity and boundedness of solutions were explored. The qualitative study of the model reveals that the model has two non-negative equilibrium points, namely, trivial and venom- free. The equilibrium points were shown to be globally asymptotically stable and numerical simulations were used to illustrate the result of the global asymptotic stability of the venom free equilibrium point as established in Theorem 4.2. Furthermore, numerical simulations also revealed the importance of antivenom therapy in preventing the deleterious effects of snake venom on target cells. It is also shown through simulation that the application of required dose of antivenom can lead to the elimination of venom toxins within one week. The public health implication of the simulation results in Figures 2, 3, 4 and 5 in terms of managing snakebite envenomation is that determining the quantity of venom injected by the offending snake is crucial. In addition, the required dose of antivenom should be administered as soon as possible so that envenomation-related deaths and disabilities can be prevented. Some of the numerical findings in this study provide some useful insights into the management and control of snakebite envenoming patients, such as determining the initial quantity of venom injected by the offending snake and applying the required dose of antivenom to neutralize the venom toxins. This work is limited to the effect of cytotoxic and hemotoxic venoms on the tissue, red blood, and platelet

cells of humans under the influence of snake antivenom. In the future, we intend to use delay differential equations to model the impact of early and late treatment. Future studies may also be directed towards modeling the effects of other types of snake venom toxins, such as neurotoxins and anticoagulant toxins, on their target cells.

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