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A Delayed Vaccination Model for Rotavirus Infection

Florence A. Adongo[1], Lawrence O. Onyango[2,*], Job Bonyo[3], G.O. Lawi[4], Ogada A. Elisha[5]

[2,5] *Mathematics Department, Faculty of Science, Egerton University, Nakuru, Kenya*
[1,3] *Mathematics Department, Faculty of Science, Maseno University, Kisumu, Kenya*
[4] *Mathematics Department, Faculty of Science, Masinde Muliro University of Science and Technology, Kakamega, Kenya*

Abstract. In this work, a mathematical model for rotavirus infection incorporating delay differential equations has been formulated. Stability analysis of the model has been performed. The result shows that the Disease Free Equilibrium is globally asymptotically stable and the Endemic Equilibrium undergoes a Hopf bifurcation. Numerical analysis has been performed to validate the analysis.

2020 Mathematics Subject Classifications: 34C60, 34xx, 37Nxx

Key Words and Phrases: Rotavirus, Hopf Bifurcation, Global asymptotic stability, Endemic Equilibrium

1. Introduction

This work is an extension of the work done by Onyango et.al [8]. In their work, they assumed that the effects of vaccines are immediate. This has not been the case since there must be time lapse. It is therefore necessary to investigate how this time lapse impact on the effectiveness of the vaccine. For the literature review, proof of existence of both disease free and endemic equilibrium, the establishment of basic reproduction number of the model, see [8].
This work is organized as follows. The model is formulated in section 2, in section 3, the model is analyzed. In section 4, the numerical simulation and discussion is performed. Conclusion and discussion is done in section 5.

*Corresponding author.
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Email addresses: florenceeadongo@gmail.com (F.A. Adongoi), lawionyi@gmail.com (O.L. Onyango), jobbonyo@maseno.ac.ke (J. Bonyo), achiengelisha@gmail.com (E.A. Ogada), glawi@mmust.ac.ke (G.Lawi)

2. Model description and formulation.

We achieve the objective of this study, by formulating a mathematical model based on a system of delay differential equation for rota-virus incorporating time delay in the effects of vaccination. The total human population size understudy, N(t), at any time is subdivided into classes such as susceptible S, infectious with rotavirus I, vaccinated V and recovered R. The total population N(t) = S(t) + V(t) + I(t) + R(t). Assuming that the mass action incidence transmission is defined by βSI, where β is the effective contact rate for disease transmission and the initial conditions are such that the parameter S, V, I, R remain non-negative for all time $t \geq 0$. Stability analysis of the model is done to determine the conditions for the spread of disease in a given population. Rotavirus spreads by contact with infected faeces and might also be transmitted through faecally-contaminated; food, water and respiratory droplets [1]. Since the incubation period is very short [8], we assume that the probability of survival till the infectious state for the individuals exposed to rotavirus is unity and therefore exclude the exposure stage. The individuals infected with rotavirus include both symptomatic and asymptomatic cases because they are capable of infecting others [9]. The recovery class comprises of those who have been removed from the scene of infection by such means as infection acquired immunity and death. It is possible children can develop some level of immunity to rotavirus from maternal antibody due to breastfeeding but this immunity does not last for long hence we consider the effect of vaccination at birth and vaccination of susceptibles [8]. The human population is not assumed to be constant, since birth, immigration, emigration and death occur. Assumed a constant recruitment ρ out of which $(1-\rho)\Lambda$ is into susceptible class and $\rho\Lambda$ is into the vaccinated class. Susceptibles are vaccinated at the rate γ and the vaccine efficacy which has been shown to wane is assumed to take place at the of ω [6]. The parameter $0 \leq 1-\epsilon < 1$ models the decrease in the risk of infection as a result of vaccination. Disease mortality takes place at the rate δ and recovery from infection takes place at the rate κ, it therefore natural that after a single natural infection immunity is developed, subsequent infections are less severe [8]. The population decreases due to natural deaths at a rate μ. Most vaccines take time in the body to become effective, this is because immunity has to be developed to protect the body against infection. The time the vaccine is administered and the time it becomes effective is defined as time delay denoted by τ. These parameter values are summarized in Table 1 below.

The flow chart for the proposed model is shown in Fig.1 Finally, from the above definition and assumptions, the proposed mathematical model and the parameters are described below:

$$\begin{aligned}
\frac{dS}{dt} &= (1-\rho)\Lambda - \beta SI - \gamma S + \omega V - \mu S, \\
\frac{dV}{dt} &= \rho\Lambda + \gamma S - (1-\epsilon)\beta V(t-\tau)I - (\omega+\mu)V, \\
\frac{dI}{dt} &= \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta+\kappa+\mu)I,
\end{aligned}$$

Table 1: Parameter values

Parameter	Symbol
Recruitment rate into susceptible	$(1-\rho)\Lambda$
Recruitment rate into vaccination	$\rho\Lambda$
Vaccination rate of susceptible	γ
Vaccine efficacy waning rate	ω
Expected decrease in the risk of infection	ϵ
Rate of flow into the removed class	κ
Transmission rate	β
Natural death rate of human	μ
Rotavirus induced deaths	δ
Vaccinated individual	ρ
Delay time in vaccination	τ

$$\frac{dR}{dt} = \kappa I - \mu R \tag{1}$$

We set the initial conditions for system (1) as $S(\theta) = \phi_1(\theta)$, $V(\theta) = \phi_2(\theta)$, $I(\theta) = \phi_3(\theta)$, $R(\theta) = \phi_4(\theta)$, where $\phi_i(\theta) \geq 0$, $\theta \in [-\tau, 0]$, $\phi(0) > 0$, for $i = 1, 2, 3 \cdots$ such that $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)$ are defined in the Banach space of continuous functions mapping in the interval $[-\tau, 0] \Rightarrow \mathbb{R}^4$.

3. Model analysis

Since the model has been analysed by Onyango et.al [8] when delay has not been incorporated, it is in order that we analyse only the effect of delay on both the disease free equilibrium and local stability of the endemic equilibrium.

3.1. The Global Stability of Disease Free Equilibrium

To prove the global stability, we use R_v as derived and explained by Onyango et.al, see [8]. The global stability of equilibrium is globally asymptotically stable if $R_v \leq 1$. We use the technique by Castillo Chavez [4]. We write system (1) in the form; $\frac{dX}{dt}$=$H(X, Z)$ $\frac{dZ}{dt}$=$G(X, Z)$, $G(X, 0) = 0$ Where $X \in R^2$ denotes uninfected compartments (S,V) and $Z \in R^1$ denotes infected compartment (I). The disease free equilibrium is now denoted as $E_1^0 = (X^0, 0)$, $X^0 = \left(\frac{\omega\Lambda+(1-\rho)\mu\Lambda}{\mu(\omega+\gamma+\mu)}, \frac{(\gamma+\mu\rho)\Lambda}{\mu(\mu+\omega+\gamma)}\right)$

The technique stipulates that the following conditions H1 and H2 must be met to guarantee global asymptotically stability:

H1: For $\frac{dX}{dt}$=$H(X, 0)$, X^0 is globally asymptotically stable.

H2: $G(X, Z) = PZ - \widehat{G}(X, Z), \widehat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$,

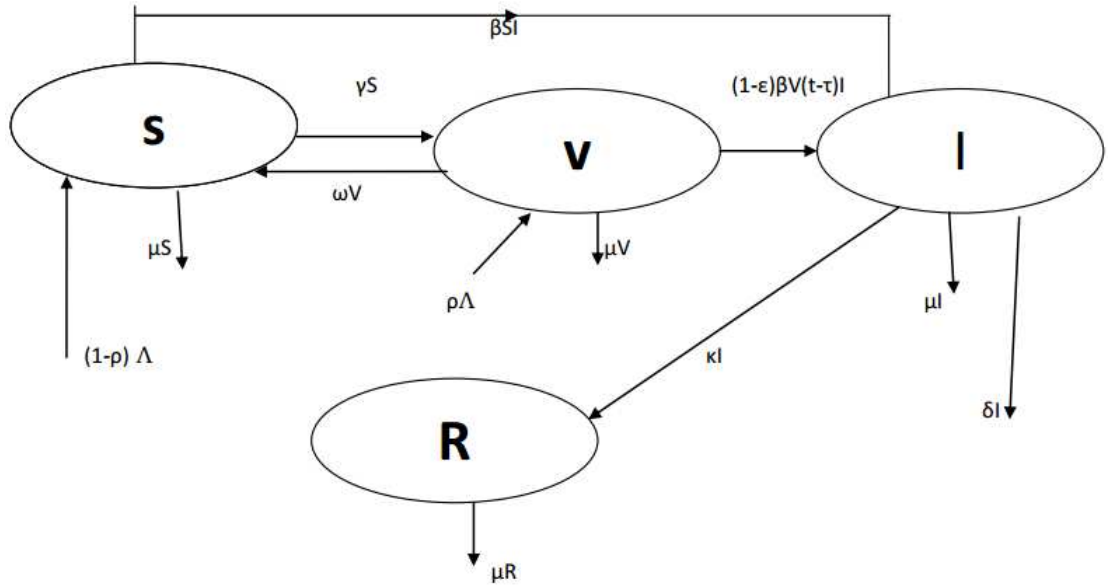

Figure 1: Model Flow Chart

where X^0 is the disease free equilibrium, $P = D_z G(X, 0)$ is an M-matrix (the off-diagonal element of P are non-negative) and Ω is the region where the model (1) is biologically feasible.

Theorem 1. *The disease free equilibrium E^0 of system (1) is globally stable if $R_v < 1$ and unstable whenever $R_v > 1$, provided that the conditions H1 and H2 above are satisfied.*

Proof. From system (1), we can clearly see that

$$H(X, 0) = \begin{pmatrix} (1-\rho)\Lambda - (\gamma + \mu)S + \omega V \\ \rho\Lambda + \gamma S - (\omega + \mu)V \end{pmatrix}$$

and

$$G(X, Z) = PZ - \widehat{G}(X, Z)$$

Differentiating the right hand side of equation 3 of system (1) with respect to I, we obtain

$$P = \beta S + (1-\epsilon)\beta V(t-\tau) - (\delta + \kappa + \mu).$$

Therefore

$$PZ = \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I$$

and

$$\begin{aligned} \widehat{G}Z &= PZ - GZ \\ &= \beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I - (\beta SI + (1-\epsilon)\beta V(t-\tau)I - (\delta + \kappa + \mu)I) \\ &= 0 \end{aligned}$$

Since conditions H1 and H2 are satisfied, the disease free equilibrium is therefore globally asymptotically stable when $R_v < 1$ and unstable whenever $R_v > 1$.

3.2. The Local Stability of Endemic Equilibrium (E.E.)

The Jacobian matrix at the endemic equilibrium E^* can be expressed as

$$J = \begin{pmatrix} a_1 & a_2 & a_3 \\ a_4 & a_5e^{-\lambda\tau} + a_6 & a_7 \\ a_8 & a_5e^{-\lambda\tau} & a_9 \end{pmatrix}$$

where,

$$\begin{aligned} a_1 &= -(\beta I^* + \gamma + \mu) \\ a_2 &= \omega \\ a_3 &= -\beta S^* \\ a_4 &= \gamma \\ a_5 &= -(1-\epsilon)\beta I^* \\ a_6 &= -(\omega + \mu) \\ a_7 &= (1-\epsilon)\beta V^*(t-\tau) \\ a_8 &= \beta I^* \\ a_9 &= \beta S^* + (1-\epsilon)V^*(t-\tau) - (\delta + \kappa + \mu) \end{aligned}$$

To find the characteristic equation of the linearized system (1) at steady states, we compute the eigenvalues of the following matrix

$$\begin{vmatrix} \lambda - a_1 & a_2 & a_3 \\ a_4 & \lambda - [a_5e^{-\lambda\tau} + a_6] & a_7 \\ a_8 & a_5e^{-\lambda\tau} & \lambda - a_9 \end{vmatrix} = 0$$

this gives

$$\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0 + (N_2\lambda^2 + N_1\lambda + N_0)e^{-\lambda\tau} = 0, \tag{2}$$

where

$$\begin{aligned} M_2 &= -(a_1 + a_6 + a_9) \\ M_1 &= (a_6a_9 + a_1a_6 + a_1a_9 - a_2a_4 - a_3a_8) \\ M_0 &= (-a_1a_6a_9 - a_2a_4a_9 - a_2a_7a_8 + a_3a_6a_8) \\ N_2 &= -a_5 \\ N_1 &= (a_5a_9 - a_5a_7 + a_1a_5) \\ N_0 &= (a_1a_5a_7 - a_1a_5a_9 + a_3a_4a_5 + a_3a_5a_8). \end{aligned}$$

Multiplying both sides of equation (2) by $e^{\lambda\tau}$, we obtain

$$(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0)e^{\lambda\tau} + N_2\lambda^2 + N_1\lambda + N_0 = 0 \tag{3}$$

When $\tau = 0$, equation (3) can be expressed as

$$\lambda^3 + M_{02}\lambda^2 + M_{01}\lambda + M_{00} = 0, \tag{4}$$

where

$$\begin{aligned} M_{02} =& (M_2 + N_2) \\ M_{01} =& (M_1 + N_1) \\ M_{00} =& (M_0 + N_0). \end{aligned}$$

Based on Routh Hurwitz theorem [10], it can be concluded that all the roots of equation (4) are in the open left half plane if and only if the following condition holds:
$C1 : M_{02} > 0, M_{00} > 0$ and $M_{02}M_{01} > M_{00}$. If $\tau = 0$ and $C1$ holds then equation (2) is locally asymptotically stable.
For $\tau > 0$, we let $\lambda = iw$, for $w > 0$ be a root of equation (3). Substituting $\lambda = iw$ into (2) we obtain

$$(-iw^3 - M_2w^2 + iM_1w + M_0)((cos(w\tau) + isin(w\tau)) - N_2w^2 + iN_1w + N_0 = 0 \qquad (5)$$

On separating the real and imaginary parts of equation (5) gives

$$\begin{aligned} p_1(w)cos(w\tau) - p_2(w)sin(w\tau) &= p_3(w) \\ P_4(w)sin(w\tau) + p_5(w)cos(w\tau) &= p_6(w), \end{aligned} \qquad (6)$$

where

$$\begin{aligned} p_1(w) &= -M_2w^2 + M_0 \\ P_2(w) &= M_1w - w^3 \\ p_3(w) &= N_2w^2 - N_0 \\ p_4(w) &= M_0 - M_2w^2 \\ p_5(w) &= M_1w - w^3 \\ p_6(w) &= -N_1w \end{aligned}$$

Solving equation (6), we obtain

$$\begin{aligned} cos(w\tau) &= \frac{p_{01}(w)}{p_{00}(w)} \\ sin(w\tau) &= \frac{p_{02}(w)}{p_{00}(w)}, \end{aligned} \qquad (7)$$

where

$$\begin{aligned} p_{00} &= M_2w^4 - (2M_0M_2 - M_1^2)w^2 - w^6 + M_0 + 2M_1w^4 \\ p_{01} &= (M_0N_2 + N_0M_2 - M_1N_1)w^2 - (M_2N_2 - N_1)w^4 - N_0M_0 \\ P_{02} &= (M_1N_2 - N_0)w^3 - N_2w^5 - N_0M_1w \end{aligned}$$

Squaring and adding the two equations in equation (7), we get

$$p_{01}^2(w) + p_{02}^2(w) - p_{00}^2(w) = 0 \qquad (8)$$

Suppose that C2: equation (8) has at least one positive root, w_0, then equation (4) will definitely have pure imaginary roots $\pm iw_0$. For w_0 we obtain the critical value of time delay as shown below

$$\tau_0 = \frac{1}{w_0} arccos\left\{\frac{p_{01}(w_0)}{p_{00}(w_0)}\right\} \tag{9}$$

Differentiating equation (3) implicitly with respect to τ we obtain

$$\left(3\lambda^2 + 2M_2\lambda + M_1\right)e^{\lambda\tau}\frac{d\lambda}{d\tau} + \left(\lambda + \tau\frac{d\lambda}{d\tau}\right)\left(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0\right)e^{\lambda\tau} + (2N_2\lambda + N_1)\frac{d\lambda}{d\tau} = 0, \tag{10}$$

which can be arranged in the form of

$$\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{Q_1(\lambda)}{Q_2(\lambda)} - \frac{\tau}{\lambda}, \tag{11}$$

where

$$\begin{aligned} Q_1 &= \left(3\lambda^2 + 2M_2\lambda + M_1\right)e^{\lambda\tau} + 2N_2\lambda + N_1 \\ Q_2 &= \lambda\left(\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0\right)e^{\lambda\tau} \end{aligned}$$

Taking real component of $\left(\frac{d\lambda}{d\tau}\right)^{-1}$ at $\tau = \tau_0$, with $\lambda = iw$, we have

$$Re\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_0} = \frac{B_R N_R + B_I N_I}{N_R^2 + N_I^2},$$

where

$$\begin{aligned} B_R &= 3w^2 cos\tau_0 w_0 - 2M_2 w^2 cos\tau_0 w_0 - M_1 sin\tau_0 w_0 - 2N_2 w^2 - \tau w^4 cos\tau_0 w_0 - M_2 w^2 cos\tau_0 w_0 \\ &\quad + M_2 w^3 sin\tau_0 w_0 - M_0 w sin\tau_0 w_0; \\ B_I &= 3w^3 cos\tau_0 w_0 + 2M_2 w^2 sin\tau_0 w_0 - M_1 w cos\tau_0 w_0 - N_1 w + \tau w^4 sin\tau_0 w_0 + M_2 w^3 cos\tau_0 w_0 \\ &\quad + M_w^2 sin\tau_0 w_0 - M_0 w cos\tau_0 w_0; \\ N_R &= -w^5 sin\tau_0 w_0 + M_2 w^4 cos\tau_0 w_0 + M_1 w^3 sin\tau_0 w_0 - M_0 cos\tau_0 w_0 \\ N_I &= w^5 cos\tau_0 w_0 + M_2 w^4 sin\tau_0 w_0 - M_1 w^3 cos\tau_0 w_0 - M_0 w^2 sin\tau_0 w_0 \end{aligned}$$

Observe that if $C3 : B_R N_R + B_I N_I \neq 0$ holds, then $Re\left[\frac{d\lambda}{d\tau}\right]^{-1}_{\tau=\tau_0} \neq 0$. Following the workings above and the Hopf bifurcation theory in [2, 3, 5, 7], we have the theorem below

Theorem 2. . *If conditions $C1 - C3$ hold, then the endemic equilibrium $E^*(S^*, V^*, I^*)$ of the system* (1) *is locally asymptotically stable when $\tau \in [0, \tau_0]$; the system undergoes a Hopf bifurcation at $E^*(S^*, V^*, I^*)$ when $\tau = \tau_0$ and a family of periodic solutions bifurcate from $E^*(S^*, V^*, I^*)$.*

4. Numerical simulations and Discussions

In this section we have carried out the simulations to validate the analytical findings and illustrate the long term dynamics of system (1). The parameter values are the same as the ones used in [8] with only τ being varied with time as indicated in the figures. Figure (2) shows that the disease free equilibrium is globally asymptotically stable when $R_v = 0.7692$ which is clearly less than unity. From the figure, it can be clearly seen that $I^0 = 0$. Figure (3) shows that the endemic equilibrium $E^*(35.7321, 45.5913, 6.3217)$

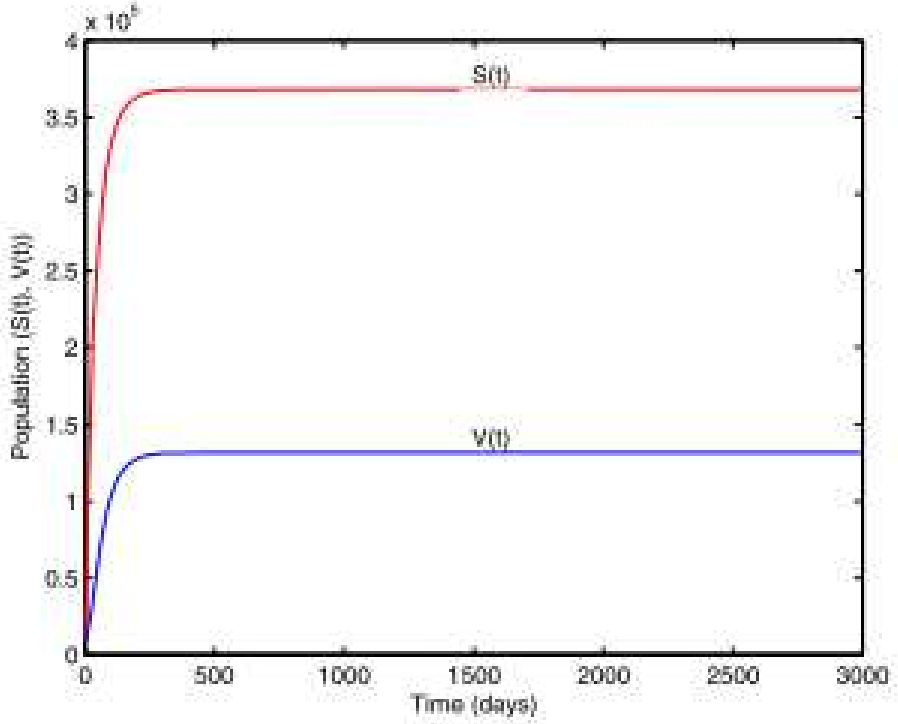

Figure 2: Simulation of system (1) shows the global stability of the disease-free equilibrium when $R_v = 0.7692$

is locally asymptotically stable when $\tau \in [0, \tau_0 = 31.1725]$. This is in line with Theorem 2 above.

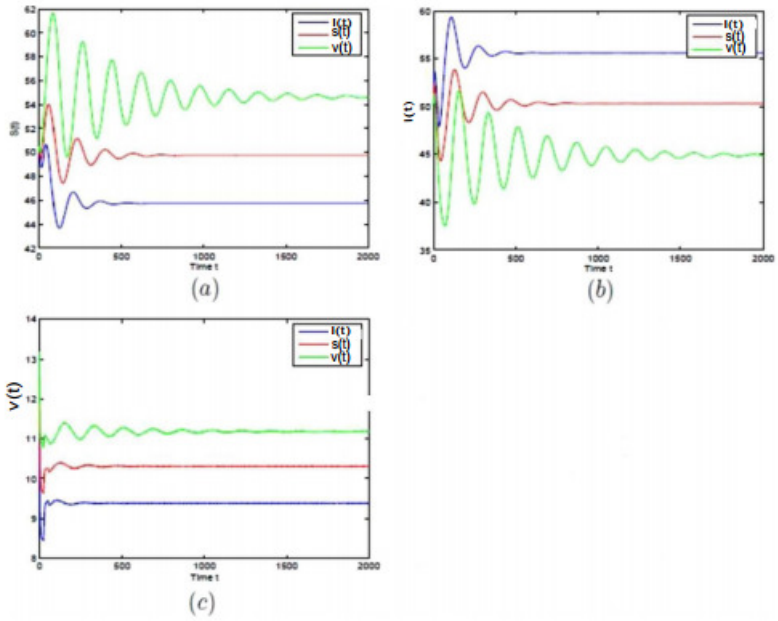

Figure 3: The effects of ϵ on all classes with (a) $\epsilon = 0.0127$, $\tau = 5.76$ and $R_v = 4.5672$, (b) $\epsilon = 0.91855, \tau = 1.257, R_V = 1.7261$ and (c) $\epsilon = 0.4123, \tau = 3.1267, R_V = 3.1672$.

In Figure (3)(a), we can clearly see that when $\epsilon = 0.0127$, $\tau = 5.76$ and $R_v = 4.5672$, the rate of infectives are quite high as compared to Figures (3)(b) and (c) when $\epsilon = 0.91855, \tau = 1.257, R_V = 1.7261$ and $\epsilon = 0.4123, \tau = 3.1267, R_V = 3.1672$ respectively. This is a proof enough that rotavirus infections can be easily contained by introducing very strong vaccines and reducing the vaccine delay time.

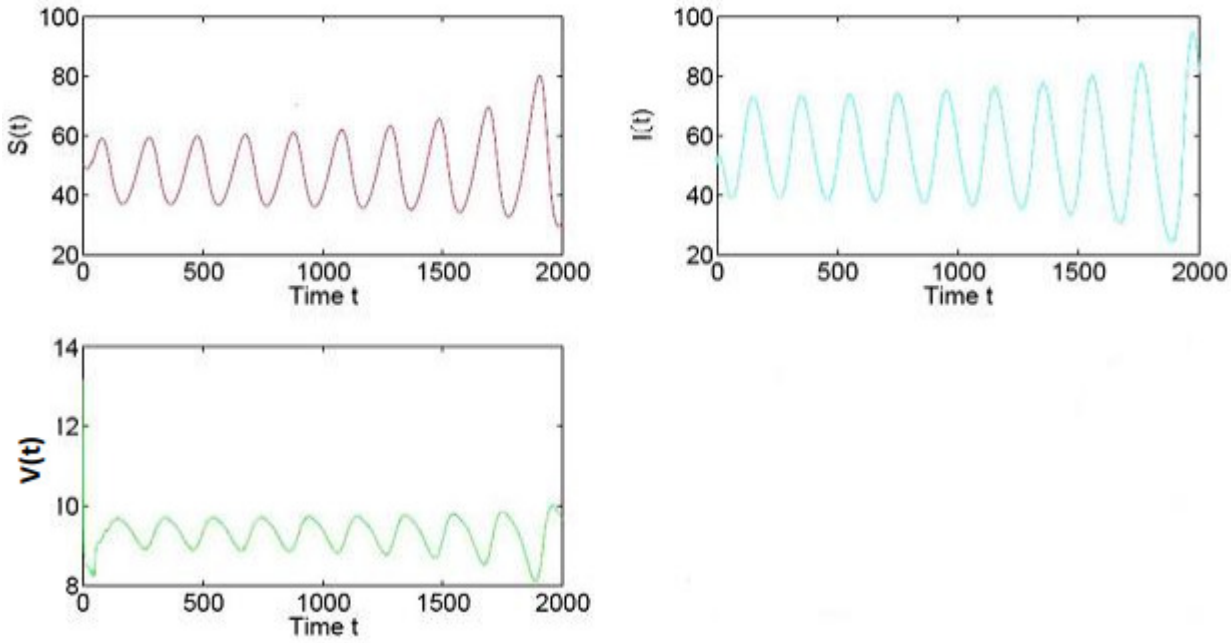

Figure 4: Time plots of S, V and I with $\tau = 36.125 > \tau_0 = 31.1725$

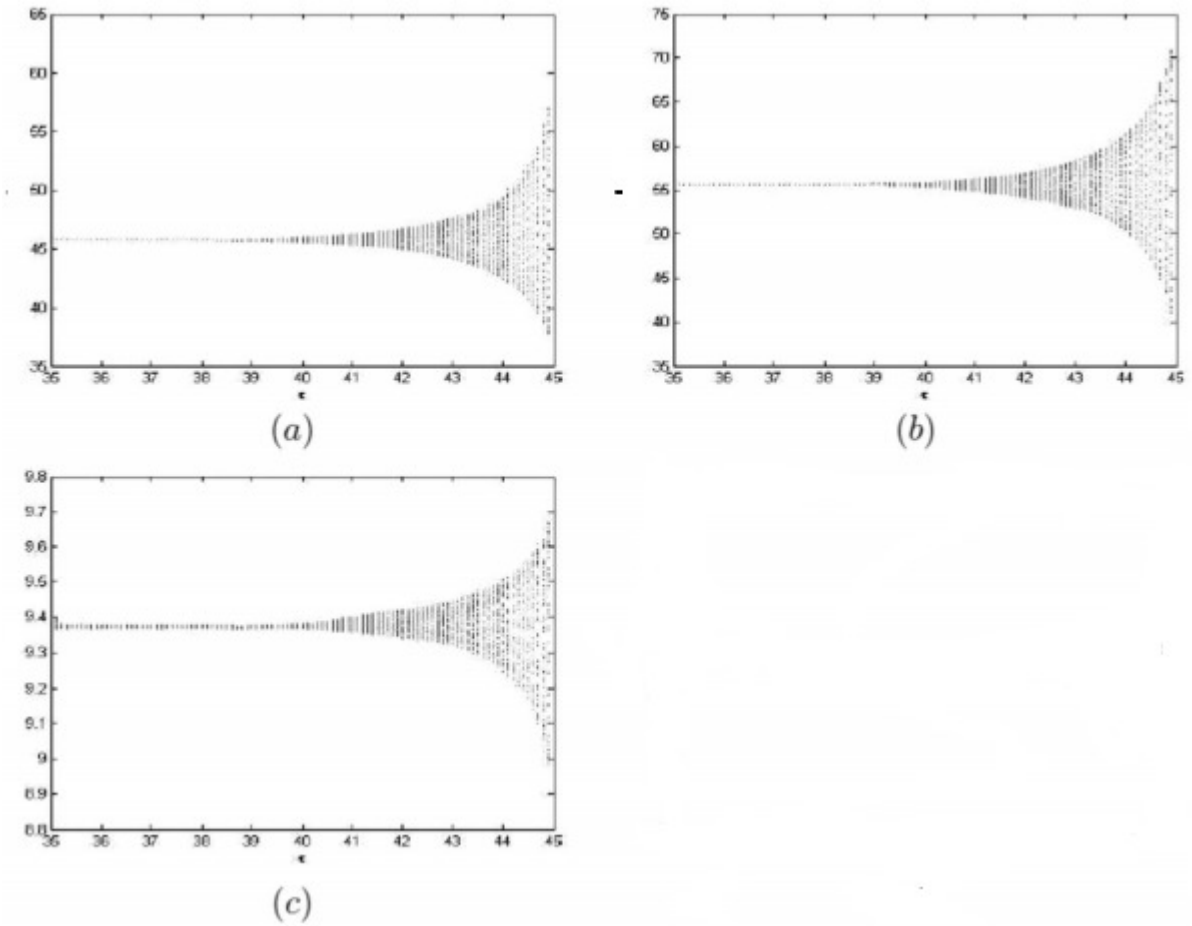

Figure 5: Bifurcation diagrams of system (1) with respect to τ (a)S, (b) V and (c) I

Figure 4 that a family of periodic solutions bifurcate at $E^*(35.7321, 45.5913, 6.3217)$. This phenomenon is also illustrated by Figure 5

5. Conclusion and Recommendation

In this work, we have formulated a mathematical model for rotavirus incorporating time delay in vaccination. The disease free equilibrium has been proved to be globally stable. The endemic equilibria is proved to be locally stable whenever $\tau = 0$ and undergoes a Hopf bifurcation if $\tau > 0$. From the analytical and simulation results, we recommend that a strong vaccine with a short delay time should be introduced in order to effectively control rotavirus infections. As a future work, we propose that the stability and directions of Hopf bifurcations derived in this work should be established.

6. Declarations

6.1. Competing interests

The authors declare that they have no competing interests.

6.2. Authorial Contribution

The authors have contributed as follows:

(i) Florence Adongo: Formulated the model

(ii) Lawrence Onyango: analyzed the model

(iii) Job Bonyo : Performed numerical Analysis

(iv) : Ogada A. Elisha: performed numerical simulations

(v) George Lawi: proof read the manuscript

6.3. Source of data

The data used to perform numerical simulation is from Onyango et.al [8]

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