STABILITY ANALYSIS OF ROTAVIRUS MODEL WITH CO-INFECTION AND CONTROL MEASURES

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Abstract

A mathematical model of the spread of rotavirus diarrhea based on a continuous time ordinary differential equation modeled two viral strains of influenza is presented. The existing influenza models is extended to include the case of co-infection when a single individual is infected with both strains of rotavirus and to explore the effects of maternal antibodies, vaccination and seasonality. The model exhibits two equilibria, disease-free equilibrium (DFE) and the endemic equilibrium (EE). Equilibrium analysis is conducted in the case with constant controls for both epidemic and endemic dynamics. By the use of Lyapunov function, it is shown that if the effective reproduction number, $\Re_0^c < 1$*, the DFE is globally asymptotically stable and in such a case, the EE is unstable. Moreover, if* $\Re_0^c > 1$*, the endemic equilibrium is globally asymptotically stable.*

Keywords: Co-infection, Maternal Antibodies, Rotavirus, Rotarix, Viral Strains, Seasonality, Vaccination.

Introduction

Rotavirus is the most common cause of gastroenteritis in children 6 months to 2 years of age (Parashar *et al*., 2006). Approximately 55,000 children are hospitalized each year with rotavirus in the United States and about 611,000 children die from the disease worldwide. Rotavirus also causes gastroenteritis in adults and is associated with as many as 36% of cases of traveler's diarrhea (Sheridan *et al*., 1981). Immunity after a rotavirus infection is incomplete. After initial exposure children are more susceptible to diarrheal illnesses of any kind (Reves *et al*, 1989), but repeat infections with rotavirus tend to be less severe than the original infection. Severe cases of diarrhea are reported more often with the first infection than with secondary infections. Even serotype specific immunity from rotaviral diarrhea is incomplete (Reves *et al*., 1989; Yuan *et al*., 2004).

Rotavirus infects almost all children in both developed and developing countries by age 5 years, but severe, dehydrating gastroenteritis occurs primarily among children aged 3 - 35 months. Rotavirus illness can range in severity from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death (Kang, 2006; Rodriguez *et al*., 1987). The incubation period lasts 1 - 3 days. Illness is characterized by vomiting followed by fever and diarrhea. Up to one-third of patients have a temperature of *>* 102^{o}F (*>* 39^{o}C). Gastrointestinal symptoms generally resolve in 3-7 days.

Rotavirus is shed in high concentrations in the stools of infected children and is transmitted primarily by the fecal-oral route, both through close person-to-person contact and through contact with inanimate objects which have become infected with the disease. It is

hypothesized that rotavirus is also transmitted through respiratory droplets, in the same manner as influenza (Parashar, 1998; Widdowson, 2004).

Co-infection is the concurrent infection with more than one strain of rotavirus in a single individual. It is during co-infection that reassortments of rotavirus can arise. Rotavirus is ubiquitous in the environment, so rotavirus has not mutated to the extent that the influenza virus has. Most often these reassortants occur between different human strains. Because recombination can occur between human and animal strains of influenza, it is hypothesized that this type of recombination can occur with different strains of rotavirus as well (Dennehy, 2007; De Grazia *et al*., 2007).

There are only a few published models of rotavirus transmission in existence. Knowledge of the transmission cycle of rotavirus is the main factor restricting growth in this field. In light of the uncertainty regarding the modes of transmission, it is hypothesized that the only means to control the spread of rotavirus is to create an inexpensive and effective vaccine.

Mathematical models, in general, have become important tools in predicting the behavior of epidemics and in evaluating prevention measures. Modeling is a quantitative measure that can be used to guide public health policy by providing conceptual results like threshold measures and contact rates. Modeling can also help to clarify certain parameters, variables, and assumptions (Brauer and Castillo-Chavez, 2000; Castillo-Chavez *et al*., 2001).

White *et al.* (1997) created a model of rotavirus transmission and observed the levels of cross-immunity necessary to suppress similar strains. They addressed the issue of heterogeneity among strains of the same pathogen. Another study of rotavirus by Shim *et al*. (2006a) examined the role of maternal antibodies in age-structured models with and without vaccination. Shim's models delve further into the dynamics of passive immunity and consider only one strain of rotavirus. In another development, Shim *et al*. (2006b) examined the role of seasonality of rotavirus infection with its vaccination. Ortega (2008) formulated a model of the spread of rotavirus diarrhea based on a continuous time ordinary differential equations model of two viral strains of influenza. He expanded this influenza model to include the case of co-infection and further to explore the effects of vaccination.

The objective of this paper is to test the role of maternal antibodies, seasonality and vaccination on rotavirus transmission both theoretically and through analytical simulations by including the possibility of co-infection with both circulating strains of rotavirus.

Model Formulation

The new model for the transmission dynamics of rotavirus, in the presence of two co-circulating strains and co-infection, within a population, is formulated by divided the total population at time t (denoted by $N(t)$) into twelve sub-populations of susceptible $S(t)$, breastfeeding $M(t)$, latently infected $L(t)$, infectious with rotavirus strain 1 $Y_1(t)$, infectious with rotavirus strain 2 $Y_2(t)$, recovered from infection with rotavirus strain 1 $Z_1(t)$, recovered from infection with rotavirus strain 2 $Z_2(t)$, infectious with rotavirus strain 1 after already being infected with strain 2 $I_1(t)$, infectious with rotavirus strain 2 after already being infected with strain 1 $I_2(t)$, infectious with both strains of rotavirus simultaneously $C(t)$, recovered from both strains of rotavirus $W(t)$, and vaccinated $V(t)$, so that

$$N(t)=S(t)+M(t)+L(t)+Y_1(t)+Y_2(t)+Z_1(t)+Z_2(t)+I_1(t)+I_2(t)+C(t)+W(t)+V(t) \quad (1)$$

It is assumed that the total population, $N(t)$ is constant. This is appropriate since demographic changes and rotavirus-induced mortality are negligible under the temporal scale consideration.

We also assume the protection role of maternal antibodies provided by breastfeeding. Therefore, the infection rate among infants who are breastfed is assumed to be reduced by factor ε where $0<\varepsilon<1$ over a short window in time.

In fact, it is assumed that only the proportion q of newborns per unit time is breastfed with an average effective immune period to rotavirus infection (due to breastfeeding) of $\frac{1}{\rho}$. The average life span of an individual is $\frac{1}{\mu}$. The total death rate $\mu(S+M+L+Y_1+Y_2+Z_1+Z_2+I_1+I_2+C+W+V)$ is assumed to be equal to total birth rate μN; $\frac{1}{(\alpha_1+\alpha_2+\alpha_c+\mu)}$ is the average effective latent period; β is the transmission rate per infective and is assumed to depend on the season and consequently, it is modeled by

$$\beta(t)=\beta_0(1+\beta_1\cos(2\pi(t-\tau))), \quad (2)$$

where β_0 is the mean transmission rate, β_1 its amplitude and τ the lag-associated with seasonal transmission.

In this study, we consider two vaccines namely, neonatal vaccine (given to infants immediately after birth) and Rotarix (given to infants at two months and four months of age). It is assumed that the neonatal vaccine is applied only to the proportion λ of non-breast-fed newborns $(1-q)\mu$ per unit time and that the vaccine effectiveness wanes after an average period of $\frac{1}{\in}$. It is further assumed that infants who are neither breastfed nor vaccinated enter directly the susceptible class and that vaccination provides 100% protection until it wanes. We consider vaccinating (with Rotarix) individuals from susceptible class at the rate ϕ.

Using these definitions and assumptions we arrive at the following non-autonomous nonlinear system of equations that models the transmission dynamics of rotavirus infections in a homogeneously mixing population:

$$\frac{dS}{dt}=((1-\lambda)(1-q)-S)\mu-(\lambda_1+\lambda_2+\beta_cC)S+\rho M+\in V-\phi S+\delta W \quad (3)$$

$$\frac{dM}{dt}=(q-M)\mu-\varepsilon(\lambda_1+\lambda_2+\beta_cC)M-\rho M \quad (4)$$

$$\frac{dL}{dt}=(\lambda_1+\lambda_2+\beta_cC)S+\varepsilon(\lambda_1+\lambda_2+\beta_cC)M-(\alpha_1+\alpha_2+\alpha_c+\mu)L \quad (5)$$

$$\frac{dY_1}{dt} = \alpha_1 L - (\gamma_1 + \mu)Y_1 \tag{6}$$

$$\frac{dY_2}{dt} = \alpha_2 L - (\gamma_2 + \mu)Y_2 \tag{7}$$

$$\frac{dZ_1}{dt} = \gamma_1 Y_1 - (\sigma_2 \lambda_2 + \mu)Z_1 \tag{8}$$

$$\frac{dZ_2}{dt} = \gamma_2 Y_2 - (\sigma_1 \lambda_1 + \mu)Z_2 \tag{9}$$

$$\frac{dI_1}{dt} = \sigma_1 \lambda_1 Z_2 - (\gamma_1 + \mu)I_1 \tag{10}$$

$$\frac{dI_2}{dt} = \sigma_2 \lambda_2 Z_1 - (\gamma_2 + \mu)I_2 \tag{11}$$

$$\frac{dC}{dt} = \alpha_c L - (\gamma_c + \mu)C \tag{12}$$

$$\frac{dW}{dt} = \gamma_1 I_1 + \gamma_2 I_2 + \gamma_c C - (\delta + \mu)W \tag{13}$$

$$\frac{dV}{dt} = \lambda(1-q)\mu + \phi S - (\in + \mu)V, \tag{14}$$

where

$\lambda_1 = \beta(Y_1 + I_1)$, $\lambda_2 = \beta(Y_2 + I_2)$ and $\beta_c = a\beta$

The initial conditions are:

$$\begin{aligned} &S(0) = S_0, \quad M(0) = M_0, \quad L(0) = L_0, \quad Y_1(0) = Y_{10}, \quad Y_2(0) = Y_{20}, \quad Z_1(0) = Z_{10}, \\ &Z_2(0) = Z_{20}, \quad I_1(0) = I_{10}, \quad I_2(0) = I_{20}, \quad C(0) = C_0, \quad W(0) = W_0, \quad V(0) = V_0 \end{aligned} \tag{15}$$

Basic Properties of Model

For the special case when the transmission rate per infective β is a positive constant, i.e. $\beta > 0$, we will examine the positivity and invariant region of the solutions of equations (3) – (15).

Positivity of solution

Since the model monitors human population, we need to show that all the state variables remain non-negative for all times.

Theorem 1: Let $\theta = \left\{ \begin{array}{l} (S, M, L, Y_1, Y_2, Z_1, Z_2, I_1, I_2, C, W, V) \in \Re_+^{12} : S(0) > 0, M(0) > 0, \\ L(0) > 0, Y_1(0) > 0, Y_2(0) > 0, Z_1(0) > 0, Z_2(0) > 0, I_1(0) > 0, I_2(0) > 0, \\ C(0) > 0, W(0) > 0, V(0) > 0 \end{array} \right\}$ then the solutions $(S(t), M(t), L(t), Y_1(t), Y_2(t), Z_1(t), Z_2(t), I_1(t), I_2(t), C(t), W(t), V(t))$ of the system of equations (3) – (15) are positive for all $t \geq 0$.

Proof: Consider equation (3)

$$\frac{dS}{dt} = ((1-\lambda)(1-q) - S)\mu - (\lambda_1 + \lambda_2 + \beta_c C)S + \rho M + \in V - \phi S + \delta W \tag{16}$$

i.e.

$$\frac{dS}{dt} \geq (1-\lambda)(1-q)\mu - (\phi + \mu)S \tag{17}$$

$$\frac{dS}{dt} + (\phi + \mu)S = (1-\lambda)(1-q)\mu \tag{18}$$

Solving, we have

$$S(t) = \frac{(1-\lambda)(1-q)\mu}{(\phi + \mu)}\left(1 - e^{-(\phi+\mu)t}\right) + ce^{-(\phi+\mu)t} \tag{19}$$

Taking initial condition, we get

$$S(t) = \frac{(1-\lambda)(1-q)\mu}{(\phi + \mu)} + \left(S_0 - \frac{(1-\lambda)(1-q)\mu}{(\phi + \mu)}\right)e^{-(\phi+\mu)t} \geq 0 \tag{20}$$

Consider (4)

$$\frac{dM}{dt} = (q - M)\mu - \varepsilon(\lambda_1 + \lambda_2 + \beta_c C)M - \rho M \tag{21}$$

i.e.

$$\frac{dM}{dt} \geq q\mu - (\rho + \mu)M \tag{22}$$

$$\frac{dM}{dt} + (\rho + \mu)M = q\mu \tag{23}$$

Solving, we have

$$M(t) = \frac{q\mu}{(\rho + \mu)}\left(1 - e^{-(\rho+\mu)t}\right) + ce^{-(\rho+\mu)t} \tag{24}$$

Taking initial condition, we get

$$M(t) = \frac{q\mu}{(\rho + \mu)} + \left(M_0 - \frac{q\mu}{(\rho + \mu)}\right)e^{-((\rho+\mu))t} \geq 0 \tag{25}$$

Similarly, it can be shown that

$$\begin{array}{l} L(t) = L_0 e^{-(\alpha_1+\alpha_2+\alpha_c+\mu)t} \geq 0, \quad Y_1(t) = Y_{10}e^{-(\gamma_1+\mu)t} \geq 0, \quad Y_2(t) = Y_{20}e^{-(\gamma_2+\mu)t} \geq 0, \\ Z_1(t) = Z_{10}e^{-\mu t} \geq 0, \quad Z_2(t) = Z_{20}e^{-\mu t} \geq 0, \quad I_1(t) = I_{10}e^{-(\gamma_1+\mu)t} \geq 0, \quad I_2(t) = I_{20}e^{-(\gamma_2+\mu)t} \geq 0, \\ C(t) = C_0 e^{-(\gamma_c+\mu)t} \geq 0, \quad W(t) = W_0 e^{-(\delta+\mu)t} \geq 0, \\ V(t) = \dfrac{\lambda(1-q)\mu}{(\in +\mu)} + \left(V_0 - \dfrac{\lambda(1-q)\mu}{(\in +\mu)}\right)e^{-(\in+\mu)t} \geq 0 \end{array} \tag{26}$$

for all time $t \geq 0$.

Invariant region

Theorem 2: Let $(S(t), M(t), L(t), Y_1(t), Y_2(t), Z_1(t), Z_2(t), I_1(t), I_2(t), C(t), W(t), V(t))$ be the solution of system (3) – (14) with initial conditions $(S_0, M_0, L_0, Y_{10}, Y_{20}, Z_{10}, Z_{20}, I_{10}, I_{20}, C_0, W_0, V_0)$. The compact set, $\varphi = \{(S, M, L, Y_1, Y_2, Z_1, Z_2, I_1, I_2, C, W, V) \in \Re_+^{12}, W_H \leq 1\}$ is positively invariant and attract all solution in $\Re_+^{12}$.

Proof: We follow the proof given in Mushanyu *et al.* (2018). Consider,

$$W(t) = (W_H) = (S + M + L + Y_1 + Y_2 + Z_1 + Z_2 + I_1 + I_2 + C + W + V). \quad (27)$$

The time derivative of $W(t)$ is given by

$$\frac{dW(t)}{dt} = \left(\frac{dW_H}{dt}\right) = \left(\frac{dS}{dt} + \frac{dM}{dt} + \frac{dL}{dt} + \frac{dY_1}{dt} + \frac{dY_2}{dt} + \frac{dZ_1}{dt} + \frac{dZ_2}{dt} + \frac{dI_1}{dt} + \frac{dI_2}{dt} + \frac{dC}{dt} + \frac{dW}{dt} + \frac{dV}{dt}\right) = (\mu - \mu W_H) \quad (28)$$

This gives

$$\frac{dW_H}{dt} = \mu + \mu W_H \leq 0 \qquad \text{for} \qquad W_H \geq 1 \quad (29)$$

From (29), we have $\frac{dW}{dt} \leq 0$ which implies that ϕ is a positive invariant set. We also note that by solving (29), we have

$$0 \leq W_H \leq \left(1 + W_H(0) e^{-\mu t}\right) \quad (30)$$

where $W_H(0)$ is the initial condition of $W_H(t)$. Thus, $0 \leq W_H \leq 1$ as $t \to \infty$ and hence φ is an attractive set.

Model Analysis

The model system (3) – (14) is analysed qualitatively to get insights into its dynamical features which give better understanding of the impact of control strategies on the transmission dynamics of Rotavirus.

Disease free equilibrium (DFE)

The disease-free equilibrium of model system (3) – (14) is obtained by setting

$$\frac{dS}{dt} = \frac{dM}{dt} = \frac{dL}{dt} = \frac{dY_1}{dt} = \frac{dY_2}{dt} = \frac{dZ_1}{dt} = \frac{dZ_2}{dt} = \frac{dI_1}{dt} = \frac{dI_2}{dt} = \frac{dC}{dt} = \frac{dW}{dt} = \frac{dV}{dt} = 0, \quad (31)$$

and in the absence of disease, $L = Y_1 = Y_2 = I_1 = I_2 = C = 0$ so that:

$$\left.\begin{aligned} S^0 &= \frac{((\rho+\mu)(\in+\mu) - q\mu(\in+\mu) - \lambda\mu(1-q)(\rho+\mu))}{(\rho+\mu)(\in+\phi+\mu)} \\ M^0 &= \frac{q\mu}{(\rho+\mu)} \\ V^0 &= \frac{\lambda\mu(1-q) + \phi S^0}{(\in+\mu)} \end{aligned}\right\} \quad (32)$$

Hence DFE is

$$\left(S^0, M^0, L^0, Y_1^0, Y_2^0, Z_1^0, Z_2^0, I_1^0, I_2^0, C^0, W^0, V^0\right)=$$
$$\left(\frac{((\rho+\mu)(\in+\mu)-q\mu(\in+\mu)-\lambda\mu(1-q)(\rho+\mu))}{(\rho+\mu)(\in+\phi+\mu)}, \frac{q\mu}{(\rho+\mu)}, 0,0,0,0,0,0,0,0,0, \frac{\lambda\mu(1-q)+\phi S^0}{(\in+\mu)}\right) \quad (33)$$

Basic reproduction number, $\Re_0$

The basic reproduction number denoted by $\Re_0$ is the average number of secondary infections caused by an infectious individual during his or her entire period of infectiousness (Diekman *et al.*, 1990). The basic reproduction number is an important non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies. Thus, whether a disease becomes persistent or dies out in a community depends on the value of the reproduction number, $\Re_0$. Furthermore, stability of equilibria can be analysed using $\Re_0$. If $\Re_0 < 1$ it means that every infectious individual will cause less than one secondary infection and hence the disease will die out and when $\Re_0 > 1$, every infectious individual will cause more than one secondary infection and hence the disease will invade the population. A large number of $\Re_0$ may indicate the possibility of a major epidemic. For the case of a model with a single infected class, $\Re_0$ is simply the product of the infection rate and the mean duration of the infection.

Since the infection components in this model are L, Y_1, Y_2, I_1, I_2 and C, then from equation (5) and (12)

$$F_i = \begin{pmatrix} \beta(Y_1 + I_1 + Y_2 + I_2 + aC)(S + \varepsilon M) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (34)$$

Partial differentiation of F_i with respect to L, Y_1, Y_2, I_1, I_2 and C gives the new infection matrix

$$F = \begin{pmatrix} 0 & \beta(S^0 + \varepsilon M^0) & \beta(S^0 + \varepsilon M^0) & \beta(S^0 + \varepsilon M^0) & \beta(S^0 + \varepsilon M^0) & a\beta(S^0 + \varepsilon M^0) \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad (35)$$

On the other hand,

$$V_i = \begin{pmatrix} (\alpha_1 + \alpha_2 + \alpha_c + \mu)I \\ -\alpha_1 L + (\gamma_1 + \mu)Y_1 \\ -\alpha_2 L + (\gamma_2 + \mu)Y_2 \\ (\gamma_1 + \mu)I_1 \\ (\gamma_2 + \mu)I_2 \\ -\alpha_c L + (\gamma_c + \mu)C \end{pmatrix} \quad (36)$$

Partial differentiation of V_i with respect to L, Y_1, Y_2, I_1, I_2 and C gives the transition matrix

$$V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_1 & k_2 & 0 & 0 & 0 & 0 \\ -\alpha_2 & 0 & k_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & k_3 & 0 \\ -\alpha_c & 0 & 0 & 0 & 0 & k_4 \end{pmatrix} \tag{37}$$

It follows that

$$V^{-1} = \begin{pmatrix} \frac{1}{k_1} & 0 & 0 & 0 & 0 & 0 \\ \frac{\alpha_1}{k_1 k_2} & \frac{1}{k_2} & 0 & 0 & 0 & 0 \\ \frac{\alpha_2}{k_1 k_3} & 0 & \frac{1}{k_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{k_2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{k_3} & 0 \\ \frac{\alpha_c}{k_1 k_4} & 0 & 0 & 0 & 0 & \frac{1}{k_4} \end{pmatrix} \tag{38}$$

It follows that the next generation matrix is given by

$$FV^{-1} = \begin{pmatrix} b & a_1 & a_2 & a_1 & a_2 & aa_3 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{39}$$

where

$$k_1 = \alpha_1 + \alpha_2 + \alpha_c + \mu, \quad k_2 = \gamma_1 + \mu, \quad k_3 = \gamma_2 + \mu, \quad k_4 = \gamma_c + \mu,$$

$$a_1 = \frac{\beta\left(S^0 + \varepsilon M^0\right)}{k_2}, \quad a_2 = \frac{\beta\left(S^0 + \varepsilon M^0\right)}{k_3}, \quad a_3 = \frac{\beta\left(S^0 + \varepsilon M^0\right)}{k_4}, \quad b = \frac{\alpha_1}{k_1} a_1 + \frac{\alpha_2}{k_1} a_2 + \frac{a\alpha_c}{k_1} a_3$$

The spectral radius for FV^{-1} gives the effective reproduction number (basic reproduction number with controls) denoted by $\Re_0^c$ which is given by

$$\Re_0^c = \left(\frac{\alpha_1}{k_2} + \frac{\alpha_2}{k_3} + \frac{a\alpha_c}{k_4} \right) \frac{\beta\left(S^0 + \varepsilon M^0\right)}{k_1} = \Re_{0Y_1}^c + \Re_{0Y_2}^c + \Re_{0C}^c \tag{40}$$

which provides a measurement for the disease risk during rotavirus transmission. The first term in $\Re_0^c$ comes from rotavirus strain 1, the second term comes from rotavirus strain 2, and the third term represents the contribution from both strains.

Endemic equilibrium (EE)

We now analyse the equilibria of the system (3) – (14) which will provide essential information regarding the long-term dynamics of the disease. Let $(S, M, L, Y_1, Y_2, Z_1, Z_2, I_1, I_2, C, W, V)$ be an equilibrium of model (3) – (14), which satisfies the following equations

$$\left.\begin{aligned}
(1-\lambda)(1-q)\mu - \beta(Y_1 + I_1 + Y_2 + I_2 + aC)S + \rho M + \in V + \delta W - (\phi + \mu)S = 0 \\
q\mu - \varepsilon\beta(Y_1 + I_1 + Y_2 + I_2 + aC)M - (\rho + \mu)M = 0 \\
\beta(Y_1 + I_1 + Y_2 + I_2 + aC)(S + \varepsilon M) - (\alpha_1 + \alpha_2 + \alpha_c + \mu)L = 0 \\
\alpha_1 L - (\gamma_1 + \mu)Y_1 = 0 \\
\alpha_2 L - (\gamma_2 + \mu)Y_2 = 0 \\
\gamma_1 Y_1 - (\sigma_2\beta(Y_2 + I_2) + \mu)Z_1 = 0 \\
\gamma_2 Y_2 - (\sigma_1\beta(Y_1 + I_1) + \mu)Z_2 = 0 \\
\sigma_1\beta(Y_1 + I_1)Z_2 - (\gamma_1 + \mu)I_1 = 0 \\
\sigma_2\beta(Y_2 + I_2)Z_1 - (\gamma_2 + \mu)I_2 = 0 \\
\alpha_c L - (\gamma_c + \mu)C = 0 \\
\gamma_1 I_1 + \gamma_2 I_2 + \gamma_c C - (\delta + \mu)W = 0 \\
\lambda(1-q)\mu + \phi S - (\in + \mu)V = 0
\end{aligned}\right\} \quad (41)$$

Theorem 3: A unique positive endemic equilibrium exists for the system (41) if and only if $\Re_0^c > 1$.

Proof: Solving the equations (41) at the endemic steady-state gives:

$$Y_1^* = \frac{\alpha_1 L^*}{(\gamma_1 + \mu)}, \quad Y_2^* = \frac{\alpha_2 L^*}{(\gamma_2 + \mu)}, \quad C^* = \frac{\alpha_c L^*}{(\gamma_c + \mu)}, \quad I_1^* = \frac{-A_5 \pm \sqrt{A_5^2 + 4A_4A_6}}{2A_4},$$

$$I_2^* = \frac{-A_2 \pm \sqrt{A_2^2 + 4A_1A_3}}{2A_1}, \qquad Z_1^* = \frac{(\gamma_2 + \mu)I_2^*}{\sigma_2\beta(Y_2^* + I_2^*)}, \qquad Z_2^* = \frac{(\gamma_1 + \mu)I_1^*}{\sigma_1\beta(Y_1^* + I_1^*)},$$

$$M^* = \frac{q\mu}{(\varepsilon\beta(Y_1^* + I_1^* + Y_2^* + I_2^* + aC^*) + (\rho + \mu))}, \qquad W^* = \frac{(\gamma_1 I_1^* + \gamma_2 I_2^* + \gamma_c C^*)}{(\delta + \mu)},$$

$$S^* = \frac{\left(A + \frac{\in \lambda(1-q)\mu}{(\in + \mu)} + \frac{\rho q\mu}{(\varepsilon\beta(Y_1^* + I_1^* + Y_2^* + I_2^* + aC^*) + (\rho + \mu))} + \frac{\delta(\gamma_1 I_1^* + \gamma_2 I_2^* + \gamma_c C^*)}{(\delta + \mu)}\right)}{\left(\beta(Y_1^* + I_1^* + Y_2^* + I_2^* + aC^*) + (\phi + \mu) - \frac{\in \phi}{(\in + \mu)}\right)},$$

$$L^* = \frac{\beta(Y_1^* + I_1^* + Y_2^* + I_2^* + aC^*)(S^* + \varepsilon M^*)}{(\alpha_1 + \alpha_2 + \alpha_c + \mu)}, \qquad V^* = \frac{\lambda(1-q)\mu + \phi S^*}{(\in + \mu)}$$

where

$$A = (1-\lambda)(1-q)\mu, \qquad A_1 = \sigma_2\beta(\gamma_2 + \mu), \qquad A_2 = \sigma_2\beta(\gamma_2 + \mu)Y_2^* + \mu(\gamma_2 + \mu) - \sigma_2\beta\gamma_1 Y_1^*$$

$$, A_3 = \sigma_2\beta\gamma_1 Y_1^* Y_2^*, \qquad A_4 = \sigma_1\beta(\gamma_1 + \mu), \qquad A_5 = \sigma_1\beta(\gamma_1 + \mu)Y_1^* + \mu(\gamma_1 + \mu) - \sigma_1\beta\gamma_2 Y_2^*$$

$$, A_6 = \sigma_1\beta\gamma_2 Y_1^* Y_2^*$$

Therefore, a unique positive endemic equilibrium for the system (3) – (14) is
$$E^* = \left(S^*, M^*, L^*, Y_1^*, Y_2^*, Z_1^*, Z_2^*, I_1^*, I_2^*, C^*, W^*, V^*\right) \tag{42}$$

Global Asymptotic Stability

Here, we investigate the global stability of the disease-free equilibrium point, $E^0 = \left(S^0, M^0, L^0, Y_1^0, Y_2^0, Z_1^0, Z_2^0, I_1^0, I_2^0, C^0, W^0, V^0\right)$ and endemic equilibrium point, $E^* = \left(S^*, M^*, L^*, Y_1^*, Y_2^*, Z_1^*, Z_2^*, I_1^*, I_2^*, C^*, W^*, V^*\right)$.

Theorem 4: If $\Re_0^c < 1$, the disease-free equilibrium (DFE) point E^0 of the dynamical system (3) – (14) is globally asymptotically stable.

Proof: Define a Lyapunov function:
$$F = \int_N^S \left(1 - \frac{S^0}{x}\right)dx + \int_N^M \left(1 - \frac{M^0}{x}\right)dx + \Re_0^c L \tag{43}$$
Then, the derivative of F along solutions of system (3) – (14) is
$$\frac{dF}{dt} = \left(1 - \frac{S^0}{S}\right)\frac{dS}{dt} + \left(1 - \frac{M^0}{M}\right)\frac{dM}{dt} + \Re_0^c \frac{dI}{dt} \tag{44}$$
$$= \left(1 - \frac{S^0}{S}\right)\left((1-\lambda)(1-q)\mu - \beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)S + \rho M + \in V + \delta W - (\phi + \mu)S\right) +$$
$$\left(1 - \frac{M^0}{M}\right)\left(q\mu - \varepsilon\beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)M - (\rho + \mu)M\right) +$$
$$\Re_0^c\left(\beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)(S + \varepsilon M) - (\alpha_1 + \alpha_2 + \alpha_c + \mu)L\right)$$
$$= \left(\Re_0^c - 1\right)\left(\beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)(S + \varepsilon M)\right) + (1 - \lambda - \lambda q) + \left(1 - \frac{S^0}{S}\right)(\in V + \delta W) - (\phi + \mu)S -$$
$$\left(\mu + \frac{\rho S^0}{S}\right)M + \left((\phi + \mu) - \frac{(1-\lambda)(1-q)\mu}{S}\right)S^0 + \beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)\left(S^0 + \varepsilon M^0\right) +$$
$$\left((\rho + \mu) - \frac{q\mu}{M}\right)M^0 - \Re_0^c(\alpha_1 + \alpha_2 + \alpha_c + \mu)L$$
That is
$$\frac{dF}{dt} \le \left(\Re_0^c - 1\right)\left(\beta\left(Y_1 + I_1 + Y_2 + I_2 + aC\right)(S + \varepsilon M)\right)$$
If $\Re_0^c < 1$, we get $\frac{dF}{dt} < 0$ which implies that the disease-free equilibrium E^0 of system (3) – (14) is globally asymptotically stable.

Theorem 5: If $\Re_0^c > 1$, the endemic equilibrium (EE) point E^* of the dynamical system (3) – (14) is globally asymptotically stable.

Proof: We let $A = Y_1 + I_1$ and $B = Y_2 + I_2$ and define a Lyapunov function:
$$F = \int_{S^*}^S \left(1 - \frac{S^*}{x}\right)dx + \int_{M^*}^M \left(1 - \frac{M^*}{x}\right)dx + \int_{L^*}^L \left(1 - \frac{L^*}{x}\right)dx + \frac{\beta\left(S^* + \varepsilon M^*\right)A^*}{\alpha_1 L^*}\int_{A^*}^A \left(1 - \frac{A^*}{x}\right)dx +$$
$$\frac{\beta\left(S^* + \varepsilon M^*\right)B^*}{\alpha_2 L^*}\int_{B^*}^B \left(1 - \frac{B^*}{x}\right)dx + \frac{\beta\left(S^* + \varepsilon M^*\right)aC^*}{\alpha_c L^*}\int_{C^*}^C \left(1 - \frac{C^*}{x}\right)dx \tag{45}$$
Then, the derivative of F along solutions of system (3) – (14) is

$$\frac{dF}{dt}=\left(1-\frac{S^*}{S}\right)\frac{dS}{dt}+\left(1-\frac{M^*}{M}\right)\frac{dM}{dt}+\left(1-\frac{L^*}{L}\right)\frac{dL}{dt}+\frac{\beta\left(S^*+\varepsilon M^*\right)A^*}{\alpha_1 L^*}\left(1-\frac{A^*}{A}\right)\frac{dA}{dt}+$$
$$\frac{\beta\left(S^*+\varepsilon M^*\right)B^*}{\alpha_2 L^*}\left(1-\frac{B^*}{B}\right)\frac{dB}{dt}+\frac{\beta\left(S^*+\varepsilon M^*\right)aC^*}{\alpha_c L^*}\left(1-\frac{C^*}{C}\right)\frac{dC}{dt} \quad (46)$$

By direct calculations, we have that:

$$\left(1-\frac{S^*}{S}\right)\frac{dS}{dt}=\beta S^*A^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SA}{S^*A^*}\right)+\beta S^*B^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SB}{S^*B^*}\right)+$$
$$a\beta S^*C^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SC}{S^*C^*}\right)-\frac{(\phi+\mu)}{S}\left(S^*-S\right)^2-\rho M^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{M}{M^*}\right)-$$
$$\in V^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{V}{V^*}\right)-\delta W^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{W}{W^*}\right)\le\beta S^*A^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SA}{S^*A^*}\right)+$$
$$\beta S^*B^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SB}{S^*B^*}\right)+a\beta S^*C^*\left(1-\frac{S^*}{S}\right)\left(1-\frac{SC}{S^*C^*}\right)$$
$$\left(1-\frac{M^*}{M}\right)\frac{dM}{dt}=\varepsilon\beta M^*A^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MA}{M^*A^*}\right)+\varepsilon\beta M^*B^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MB}{M^*B^*}\right)+$$
$$a\varepsilon\beta M^*C^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MC}{M^*C^*}\right)-\frac{(\rho+\mu)}{M}\left(M^*-M\right)^2\le\varepsilon\beta M^*A^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MA}{M^*A^*}\right)+$$
$$\varepsilon\beta M^*B^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MB}{M^*B^*}\right)+a\varepsilon\beta M^*C^*\left(1-\frac{M^*}{M}\right)\left(1-\frac{MC}{M^*C^*}\right)$$
$$\left(1-\frac{L^*}{L}\right)\frac{dL}{dt}=\beta S^*A^*\left(1-\frac{L^*}{L}\right)\left(\frac{SA}{S^*A^*}-\frac{L}{L^*}\right)+\beta S^*B^*\left(1-\frac{L^*}{L}\right)\left(\frac{SB}{S^*B^*}-\frac{L}{L^*}\right)+$$
$$a\beta S^*C^*\left(1-\frac{L^*}{L}\right)\left(\frac{SC}{S^*C^*}-\frac{L}{L^*}\right)+\varepsilon\beta M^*A^*\left(1-\frac{L^*}{L}\right)\left(\frac{MA}{M^*A^*}-\frac{L}{L^*}\right)+$$
$$\varepsilon\beta M^*B^*\left(1-\frac{L^*}{L}\right)\left(\frac{MB}{M^*B^*}-\frac{L}{L^*}\right)+a\varepsilon\beta M^*C^*\left(1-\frac{L^*}{L}\right)\left(\frac{MC}{M^*C^*}-\frac{L}{L^*}\right)$$

and

$$\frac{\beta\left(S^*+\varepsilon M^*\right)A^*}{\alpha_1 L^*}\left(1-\frac{A^*}{A}\right)\frac{dA}{dt}=\beta\left(S^*+\varepsilon M^*\right)A^*\left(1-\frac{A^*}{A}\right)\left(\frac{L}{L^*}-\frac{A}{A^*}\right)$$
$$\frac{\beta\left(S^*+\varepsilon M^*\right)B^*}{\alpha_2 L^*}\left(1-\frac{B^*}{B}\right)\frac{dB}{dt}=\beta\left(S^*+\varepsilon M^*\right)B^*\left(1-\frac{B^*}{B}\right)\left(\frac{L}{L^*}-\frac{B}{B^*}\right)$$
$$\frac{\beta\left(S^*+\varepsilon M^*\right)aC^*}{\alpha_c L^*}\left(1-\frac{C^*}{C}\right)\frac{dC}{dt}=a\beta\left(S^*+\varepsilon M^*\right)A^*\left(1-\frac{C^*}{C}\right)\left(\frac{L}{L^*}-\frac{C}{C^*}\right)$$

As a result, we get

$$\frac{dF}{dt} \le \beta S^* A^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SA}{S^*A^*}\right) + \beta S^* B^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SB}{S^*B^*}\right) + a\beta S^* C^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SC}{S^*C^*}\right)$$

$$+ \varepsilon\beta M^* A^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MA}{M^*A^*}\right) + \varepsilon\beta M^* B^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MB}{M^*B^*}\right) +$$

$$a\varepsilon\beta M^* C^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MC}{M^*C^*}\right) + \beta S^* A^* \left(1-\frac{L^*}{L}\right)\left(\frac{SA}{S^*A^*}-\frac{L}{L^*}\right) + \beta S^* B^* \left(1-\frac{L^*}{L}\right)\left(\frac{SB}{S^*B^*}-\frac{L}{L^*}\right) +$$

$$a\beta S^* C^* \left(1-\frac{L^*}{L}\right)\left(\frac{SC}{S^*C^*}-\frac{L}{L^*}\right) + \varepsilon\beta M^* A^* \left(1-\frac{L^*}{L}\right)\left(\frac{MA}{M^*A^*}-\frac{L}{L^*}\right) +$$

$$\varepsilon\beta M^* B^* \left(1-\frac{L^*}{L}\right)\left(\frac{MB}{M^*B^*}-\frac{L}{L^*}\right) + a\varepsilon\beta M^* C^* \left(1-\frac{L^*}{L}\right)\left(\frac{MC}{M^*C^*}-\frac{L}{L^*}\right) +$$

$$\beta\left(S^* + \varepsilon M^*\right)A^* \left(1-\frac{A^*}{A}\right)\left(\frac{L}{L^*}-\frac{A}{A^*}\right) + \beta\left(S^* + \varepsilon M^*\right)B^* \left(1-\frac{B^*}{B}\right)\left(\frac{L}{L^*}-\frac{B}{B^*}\right) +$$

$$a\beta\left(S^* + \varepsilon M^*\right)A^* \left(1-\frac{C^*}{C}\right)\left(\frac{L}{L^*}-\frac{C}{C^*}\right)$$

For the function $v(x) = 1 - x + \ln x$, we know that $x > 0$ leads to $v(x) \le 0$. And if $x = 1$, then $v(x) = 0$. Note that:

$$\beta S^* A^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SA}{S^*A^*}\right) + \beta S^* A^* \left(1-\frac{L^*}{L}\right)\left(\frac{SA}{S^*A^*}-\frac{L}{L^*}\right) \le \beta S^* A^* \left(\frac{A}{A^*} - \ln\left(\frac{A}{A^*}\right) - \frac{L}{L^*} + \ln\left(\frac{L}{L^*}\right)\right)$$

Moreover, we can obtain

$$\beta S^* B^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SB}{S^*B^*}\right) + \beta S^* B^* \left(1-\frac{L^*}{L}\right)\left(\frac{SB}{S^*B^*}-\frac{L}{L^*}\right) \le \beta S^* B^* \left(\frac{B}{B^*} - \ln\left(\frac{B}{B^*}\right) - \frac{L}{L^*} + \ln\left(\frac{L}{L^*}\right)\right)$$

$$a\beta S^* C^* \left(1-\frac{S^*}{S}\right)\left(1-\frac{SC}{S^*C^*}\right) + a\beta S^* C^* \left(1-\frac{L^*}{L}\right)\left(\frac{SC}{S^*C^*}-\frac{L}{L^*}\right) \le$$

$$a\beta S^* C^* \left(\frac{C}{C^*} - \ln\left(\frac{C}{V^*}\right) - \frac{L}{L^*} + \ln\left(\frac{L}{L^*}\right)\right)$$

$$\varepsilon\beta M^* A^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MA}{M^*A^*}\right) + \varepsilon\beta M^* A^* \left(1-\frac{L^*}{L}\right)\left(\frac{MA}{M^*A^*}-\frac{L}{L^*}\right) \le$$

$$\varepsilon\beta M^* A^* \left(\frac{A}{A^*} - \ln\left(\frac{A}{A^*}\right) - \frac{L}{L^*} + \ln\left(\frac{L}{L^*}\right)\right)$$

$$\varepsilon\beta M^* B^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MB}{M^*B^*}\right) + \varepsilon\beta M^* B^* \left(1-\frac{L^*}{L}\right)\left(\frac{MB}{M^*B^*}-\frac{L}{L^*}\right) \le$$

$$\varepsilon\beta M^* B^* \left(\frac{B}{B^*} - \ln\left(\frac{B}{B^*}\right) - \frac{L}{L^*} + \ln\left(\frac{L}{L^*}\right)\right)$$

$$a\varepsilon\beta M^* C^* \left(1-\frac{M^*}{M}\right)\left(1-\frac{MC}{M^* C^*}\right)+a\varepsilon\beta M^* C^* \left(1-\frac{L^*}{L}\right)\left(\frac{MC}{M^* C^*}-\frac{L}{L^*}\right)\leq$$

$$a\varepsilon\beta M^* C^* \left(\frac{C}{C^*}-\ln\left(\frac{C}{V^*}\right)-\frac{L}{L^*}+\ln\left(\frac{L}{L^*}\right)\right)$$

$$\beta\left(S^*+\varepsilon M^*\right)A^* \left(1-\frac{A^*}{A}\right)\left(\frac{L}{L^*}-\frac{A}{A^*}\right)\leq \beta\left(S^*+\varepsilon M^*\right)A^* \left(\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\frac{A}{A^*}+\ln\left(\frac{A}{A^*}\right)\right)$$

$$\beta\left(S^*+\varepsilon M^*\right)B^* \left(1-\frac{B^*}{B}\right)\left(\frac{L}{L^*}-\frac{B}{B^*}\right)\leq \beta\left(S^*+\varepsilon M^*\right)B^* \left(\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\frac{B}{B^*}+\ln\left(\frac{B}{B^*}\right)\right)$$

$$a\beta\left(S^*+\varepsilon M^*\right)C^* \left(1-\frac{C^*}{C}\right)\left(\frac{L}{L^*}-\frac{C}{C^*}\right)\leq a\beta\left(S^*+\varepsilon M^*\right)C^* \left(\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\frac{C}{C^*}+\ln\left(\frac{C}{C^*}\right)\right)$$

Consequently, we gain

$$\frac{dF}{dt}\leq \beta\left(S^*+\varepsilon M^*\right)A^* \left(\frac{A}{A^*}-\ln\left(\frac{A}{A^*}\right)-\frac{L}{L^*}+\ln\left(\frac{L}{L^*}\right)\right)+\beta\left(S^*+\varepsilon M^*\right)B^* \left(\begin{array}{l}\frac{B}{B^*}-\ln\left(\frac{B}{B^*}\right)-\\ \frac{L}{L^*}+\ln\left(\frac{L}{L^*}\right)\end{array}\right)+$$

$$a\beta\left(S^*+\varepsilon M^*\right)C^* \left(\frac{C}{C^*}-\ln\left(\frac{C}{C^*}\right)-\frac{L}{L^*}+\ln\left(\frac{L}{L^*}\right)\right)+\beta\left(S^*+\varepsilon M^*\right)A^* \left(\begin{array}{l}\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\\ \frac{A}{A^*}+\ln\left(\frac{A}{A^*}\right)\end{array}\right)+$$

$$\beta\left(S^*+\varepsilon M^*\right)B^* \left(\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\frac{B}{B^*}+\ln\left(\frac{B}{B^*}\right)\right)+a\beta\left(S^*+\varepsilon M^*\right)C^* \left(\begin{array}{l}\frac{L}{L^*}-\ln\left(\frac{L}{L^*}\right)-\\ \frac{C}{C^*}+\ln\left(\frac{C}{C^*}\right)\end{array}\right)=0$$

One can see that the largest invariant subset, where $\frac{dF}{dt}=0$, is E^*. By LaSalle's Invariance Principle [7], E^* is globally asymptotically stable when $\Re_0^c>1$.

Results and Discussion

There are only a few published models of rotavirus transmission in existence. Based on this, we have proposed a model to investigate the role of maternal antibodies, seasonality and vaccination on rotavirus transmission theoretically by including the possibility of co-infection with both circulating strains of rotavirus. The model proposed is a twelve-dimensional system that describes the time evolution of the susceptible, breastfeeding, latently infected, infectious with rotavirus strain 1, infectious with rotavirus strain 2, recovered from infection with rotavirus strain 1, recovered from infection with rotavirus strain 2, infectious with rotavirus strain 1 after already being infected with strain 2, infectious with rotavirus strain 2 after already being infected with strain 1, infectious with both strains of rotavirus simultaneously, recovered from both strains of rotavirus and recovered human hosts, and the vaccinated.

In the mathematical sense, the model is much easier to analyse and the results are standard, namely, the disease dynamics are completely determined by the basic reproduction number:

if $\Re_0^c \leq 1$ then rotavirus dies out; otherwise, the disease persists. That is, the model exhibits regular threshold dynamics.
Regardless, our current study provides a modelling framework to investigate the complex rotavirus transmission under the impact of maternal antibodies and vaccination, and the findings from model confirm the positive effect of maternal antibodies and vaccination in lowering the infection risk and reducing the disease prevalence. That is, maternal antibodies and vaccination can help to reduce the prevalence of rotavirus.

Conclusion

We have conducted an analysis on the global asymptotic stability of the disease-free equilibrium and endemic equilibrium. Essentially, these stability results establish $\Re_0^c = 1$ as a forward transcritical bifurcation point, or, a sharp threshold for disease dynamics, and indicate that reducing $\Re_0^c$ to values at or below unity will be sufficient to eradicate the disease. In other words, the cholera model (3) – (14) exhibits regular threshold dynamics.

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